methacetin-fitting

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Load all important libraries

```
library(dMod)
library(stringr) # Um bequem mit strings zu arbeiten
library(tidyverse) # Viele Funktionen, u.a. für data.frames und ggplot2 für schöne plots
library(magrittr) # der Pipe-operator %>%: z.B: x = a; y=f(x); z=g(y); wird zu z= a %>% f %>% g
library(conveniencefunctions)
library(libSBML)
```

Model setup

Read the model

This is basically copied from a libSBML-example

```
filename <- "/home/denial/Promotion/Projects/methacetin_fitting/model/met13_pkpd_7.xml" # Attention: ti
d <-  readSBML(filename)

m <- SBMLDocument_getModel(d)
# errors   = SBMLDocument_getNumErrors(d);
# SBMLDocument_printErrors(d);


level   = SBase_getLevel  (d);
version = SBase_getVersion(d);

cat("File: ",filename," (Level ",level,", version ",version,")\n");
```

```
## File:  /home/denial/Promotion/Projects/methacetin_fitting/model/met13_pkpd_7.xml  (Level  3 , versio
```

```
cat("  model id: ", ifelse(Model_isSetId(m), Model_getId(m) ,"(empty)"),"\n");
```

```
##   model id:  met13_pkpd_7
```

```
cat( "functionDefinitions: ", Model_getNumFunctionDefinitions(m) ,"\n" );
```

```
## functionDefinitions:  0
```

```
cat( "    unitDefinitions: ", Model_getNumUnitDefinitions    (m) ,"\n" );
```

```
##     unitDefinitions:  17
```

```
cat( "   compartmentTypes: ", Model_getNumCompartmentTypes   (m) ,"\n" );
```

```
##    compartmentTypes:  0
```

```
cat( "        specieTypes: ", Model_getNumSpeciesTypes       (m) ,"\n" );
```

```
##         specieTypes:  0
```

```
cat( "       compartments: ", Model_getNumCompartments       (m) ,"\n" );
```

```
##        compartments:  11
```

```
cat( "            species: ", Model_getNumSpecies            (m) ,"\n" );
```

```
##             species:  48
```

```
cat( "         parameters: ", Model_getNumParameters         (m) ,"\n" );
```

```
##          parameters:  200
```

```
cat( " initialAssignments: ", Model_getNumInitialAssignments (m) ,"\n" );
```

```
##  initialAssignments:  12
```

```
cat( "              rules: ", Model_getNumRules              (m) ,"\n" );
```

```
##               rules:  101
```

```
cat( "        constraints: ", Model_getNumConstraints        (m) ,"\n" );
```

```
##         constraints:  0
```

```
cat( "          reactions: ", Model_getNumReactions          (m) ,"\n" );
```

```
##           reactions:  88
```

```
cat( "             events: ", Model_getNumEvents             (m) ,"\n" );
```

```
##              events:  0
```

```
cat( "\n" );
```

Einschub: der Pipe-Operator %>%

```
# Mit dem Pipe-Operator kann man Funktionen verketten
# Standardmäßig wird das vorherige Ergebnis als erstes Argument von der nächsten Funktion eingesetzt. w

f <- function(x) x^2;
g <- function(x,y) x-y;

2 %>% f # f(2)
```

```
## [1] 4
```

```
2 %>% f %>% g(3) # g(f(2),3) = 4-3 = 1
```

```
## [1] 1
```

```
2 %>% f %>% g(3,.) # g(3,f(2)) = 3-4 = -1
```

```
## [1] -1
```

```
# Man kann auch Funktionen definieren, die mit . losgehen, was dann das Argument für die Funktion ist.
h <- . %>% sqrt %>% add(5)
h(4)
```

```
## [1] 7
```

```r
# Das ist besonders nützlich in lapply, sapply und so weiter, wo man über eine liste(oder einen vektor)
sapply(1:4, function(i) i^2 +5)
```

```
## [1]  6  9 14 21
```

```r
sapply(1:4 , . %>% raise_to_power(2) %>% add(5) ) # dassselbe
```

```
## [1]  6  9 14 21
```

Assignment Rules

1. Get the assignment rules as string
2. Apply the assignment rules onto themselves with str_replace. This is for assigments that convert parameters into other parameters

```r
# get rules
nrules <- Model_getNumRules(m)
lrules <- Model_getListOfRules(m)
rules <- structure(sapply(0:(nrules-1), . %>% ListOfRules_get(lrules,.) %>% Rule_getFormula),
                   names = sapply(0:(nrules-1), . %>% ListOfRules_get(lrules,.) %>% Rule_getId))
rulenames <- names(rules)

# "Cure" rules: Since I do a parameter trafo for the units, I don't want to have any unit conversions v
# A "bad" rule would be eg "QC = CO*3600/100", since I take care of the Units later. Therefore, the rul
rules <- rules %>% str_replace_all(c("1000" = "1", "3600" = "1", "\\b60\\b" = 1)) %>% set_names(rulenam



# Apply the rules onto themselves to insert parameter transformations
# Final goal is to have a named vector where
  # names are the "inner" parameters that are used within the model
  # values are functions of "outer" parameters that are fed into the model

# apply rules 1st time
rules <- paste0("(", rules, ")") %>% set_names(paste0("\\b", rulenames, "\\b"))
rules <- str_replace_all(rules, rules) %>% set_names(rulenames)

# apply rules 2nd time
rules <- paste0("(", rules, ")") %>% set_names(paste0("\\b", rulenames, "\\b"))
rules <- str_replace_all(rules, rules) %>% set_names(rulenames)

# check if any of the rules are functions of other rules
indices <- rules %>% sapply(. %>% str_detect(paste0("\\b",rulenames, "\\b")) %>% any)
rules %>% extract(indices) %>% sapply(. %>% str_detect(paste0("\\b",rulenames, "\\b")) %>% extract(rule
```

```
## named list()
```

```r
# print(rules)

# getSymbols(rules) # These are the "outer" parameters
```

Reactions

```
# get reactions
nreactions <- Model_getNumReactions(m)
lreactions <- Model_getListOfReactions(m)
reactions <- lapply(0:(nreactions-1), function(i) {

  reaction <-  ListOfReactions_get(lreactions,i)

  nreactants <- reaction %>% Reaction_getNumReactants()
  if (nreactants > 0) {
    lreactants <- reaction %>% Reaction_getListOfReactants()
    myreactant_stoichiometries <- lapply(0:(nreactants-1), . %>% ListOfSpeciesReferences_get(lreactants
    myreactant_IDs <- lapply(0:(nreactants-1), . %>% ListOfSpeciesReferences_get(lreactants,.) %>% Simpl
    from = paste0(paste0("(", myreactant_stoichiometries, "*", myreactant_IDs, ")"), collapse = "+")
  } else {
    from = ""
  }

  nproducts <- reaction %>% Reaction_getNumProducts()
  if (nproducts > 0) {
    lproducts <- reaction %>% Reaction_getListOfProducts()
    myproduct_stoichiometries <- lapply(0:(nproducts-1), . %>% ListOfSpeciesReferences_get(lproducts,.)
    myproduct_IDs <- lapply(0:(nproducts-1), . %>% ListOfSpeciesReferences_get(lproducts,.) %>% SimpleSp
    to = paste0(paste0("(", myproduct_stoichiometries, "*", myproduct_IDs, ")"), collapse = "+")
  } else {
    to = ""
  }

  # Apply rules to rate expressions
  myrules <- rules
  mynames <- names(myrules)
  absorption_indices <- str_detect(myrules, "Absorption")
  absorption_rules <- myrules[absorption_indices] %>% structure(names = mynames[absorption_indices])
  myrules <- structure(myrules[!str_detect(myrules, "Absorption")], names = paste0("\\b", mynames[!str_

  rate <-  reaction %>% Reaction_getKineticLaw() %>% KineticLaw_getFormula() %>% str_replace_all(myrules

  description <- reaction %>% Reaction_getId()

  # Incorporate the absorption:
  # For this I add another reaction which absorbs the oral dose, e.g. D_apap_sul
  if(description %>% str_detect("Absorption")) {
    from[2] <- names(absorption_rules)[absorption_rules %>% str_detect(paste0(description, "\\)*$"))]
    to[2] <- ""
    rate[2] <- rate
    description[2] <- description
  }
  # print(i)

  return(data.frame(from = from, to  = to, rate = rate, description = description, stringsAsFactors = F
}) %>% do.call(rbind,.) # make one big data.frame out of it


# Build the dMod-object "eqnlist", which stores the reactions and stoichiometries
```

```
el <- eqnlist()
for(i in 1:nrow(reactions)) el <- addReaction(el, reactions$from[i], reactions$to[i], reactions$rate[i]


# Convert to "eqnvec", which is basically a named vector of the ODEs and the names denote the states
f <- el %>% as.eqnvec()

# This is the full ODE when every rule is applied
# print(f)
```

Parameters

```
# get the parameters from the definition
nsbml_parameters <- m %>% Model_getNumParameters()
lsbml_parameters <- m %>% Model_getListOfParameters()
sbml_parameters <- structure(sapply(0:(nsbml_parameters-1), . %>% ListOfParameters_get(lsbml_parameters

# unit conversion
sbml_parameter_units <- structure(sapply(0:(nsbml_parameters-1), . %>% ListOfParameters_get(lsbml_parame
# The factors to bring each parameter to the units seconds, grams, litres
multiplication_factors <- sapply(0:(nsbml_parameters-1), . %>%
         ListOfParameters_get(lsbml_parameters,.) %>%
         Parameter_getDerivedUnitDefinition %>%
         {myunitdef <- .
           nunits <- UnitDefinition_getNumUnits(myunitdef)
         lunits <- UnitDefinition_getListOfUnits(myunitdef)
         lapply(0:(nunits-1), . %>%
                  ListOfUnits_get(lunits,.) %>%
                  {(Unit_getMultiplier(.) * 10^(Unit_getScale(.)))^Unit_getExponent(.)}) %>% Reduce("*"
         } %>%
         {.}
       )
sbml_parameters <- sbml_parameters * multiplication_factors


# Initial assignments
niass <- m %>% Model_getNumInitialAssignments()
liass <- m %>% Model_getListOfInitialAssignments()
iass <- structure(sapply(0:(niass-1), . %>% ListOfInitialAssignments_get(liass,.) %>% print %>%  str_spl
```

```
## [1] "<initialAssignment symbol=\"Ave_apap_sul\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\
## [1] "<initialAssignment symbol=\"D_apap_sul\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">\
## [1] "<initialAssignment symbol=\"Ave_apap\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">\n
## [1] "<initialAssignment symbol=\"D_apap\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">\n
## [1] "<initialAssignment symbol=\"Ave_metc13\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">
## [1] "<initialAssignment symbol=\"D_metc13\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">\n
## [1] "<initialAssignment symbol=\"Ave_apap_cys\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\
## [1] "<initialAssignment symbol=\"D_apap_cys\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">
## [1] "<initialAssignment symbol=\"Ave_apap_glu\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\
## [1] "<initialAssignment symbol=\"D_apap_glu\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">
## [1] "<initialAssignment symbol=\"Ave_co2c13\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">
## [1] "<initialAssignment symbol=\"D_co2c13\">\n  <math xmlns=\"http://www.w3.org/1998/Math/MathML\">\n
```

```r
nspecies <- Model_getNumSpecies(m)
lspecies <- Model_getListOfSpecies(m)
species <- lapply(0:(nspecies-1), . %>% {ListOfSpecies_get(lspecies,.)} %>% Species_getId()) %>% do.cal

inits <- structure(sapply(0:(nspecies-1), . %>% ListOfSpecies_get(lspecies,.) %>% Species_getInitialAmo
inits[names(iass)] <- sbml_parameters[iass]

# All parameters combined, more than actually needed, because many of them have been replaced due to Ru
all_pars <- c(sbml_parameters, inits) # all possible parameters

# To check if the unit conversion worked
data.frame(par = names(sbml_parameters), value = sbml_parameters, original_unit= sbml_parameter_units,
```

```
##                   par        value      original_unit
## 1                  BW 7.000000e+04                 kg
## 2                  CO 1.083300e-01            ml_per_s
## 3                  QC 1.083300e+05          litre_per_h
## 4                FVre 9.049000e-04         litre_per_kg
## 5                FVgu 1.710000e-05         litre_per_kg
## 6                FVki 4.400000e-06         litre_per_kg
## 7                FVli 2.100000e-05         litre_per_kg
## 8                FVlu 7.600000e-06         litre_per_kg
## 9                FVsp 2.600000e-06         litre_per_kg
## 10               FVve 5.140000e-05         litre_per_kg
## 11               FVar 2.570000e-05         litre_per_kg
## 12               FVpl 4.240000e-05         litre_per_kg
## 13               FQgu 1.464620e-01       dimensionless
## 14               FQki 1.900000e-01       dimensionless
## 15                FQh 2.153850e-01       dimensionless
## 16               FQlu 1.000000e+00       dimensionless
## 17               FQsp 1.723100e-02       dimensionless
## 18               FQre 5.946150e-01       dimensionless
## 19              MPPGL 4.500000e-02            mg_per_g
## 20         D_apap_sul 0.000000e+00                  mg
## 21    IVDOSE_apap_sul 0.000000e+00                  mg
## 22    PODOSE_apap_sul 0.000000e+00                  mg
## 23        Ka_apap_sul 6.944444e-04               per_h
## 24         F_apap_sul 1.000000e+00       dimensionless
## 25       fup_apap_sul 1.000000e+00       dimensionless
## 26        BP_apap_sul 1.000000e+00       dimensionless
## 27     fumic_apap_sul 1.000000e+00       dimensionless
## 28   CLrenal_apap_sul 2.666667e-03          litre_per_h
## 29      Kpsp_apap_sul 1.000000e+00       dimensionless
## 30      Kpgu_apap_sul 1.000000e+00       dimensionless
## 31      Kpre_apap_sul 8.000000e-01       dimensionless
## 32      Kpki_apap_sul 1.000000e+00       dimensionless
## 33      Kplu_apap_sul 1.000000e+00       dimensionless
## 34      Kpli_apap_sul 1.000000e+00       dimensionless
## 35             D_apap 0.000000e+00                  mg
## 36        IVDOSE_apap 0.000000e+00                  mg
## 37        PODOSE_apap 0.000000e+00                  mg
## 38            Ka_apap 6.944444e-04               per_h
## 39             F_apap 8.700000e-01       dimensionless
## 40           fup_apap 1.000000e+00       dimensionless
```

```
## 41            BP_apap 1.000000e+00      dimensionless
## 42          fumic_apap 1.000000e+00      dimensionless
## 43       CLrenal_apap 1.983333e-04        litre_per_h
## 44          Kpsp_apap 1.000000e+00      dimensionless
## 45          Kpgu_apap 1.000000e+00      dimensionless
## 46          Kpre_apap 8.000000e-01      dimensionless
## 47          Kpki_apap 1.000000e+00      dimensionless
## 48          Kplu_apap 1.000000e+00      dimensionless
## 49          Kpli_apap 1.000000e+00      dimensionless
## 50           D_metc13 0.000000e+00                 mg
## 51      IVDOSE_metc13 1.000000e-01                 mg
## 52      PODOSE_metc13 0.000000e+00                 mg
## 53          Ka_metc13 6.944444e-04              per_h
## 54           F_metc13 1.000000e+00      dimensionless
## 55         fup_metc13 1.000000e+00      dimensionless
## 56          BP_metc13 1.000000e+00      dimensionless
## 57       fumic_metc13 1.000000e+00      dimensionless
## 58     CLrenal_metc13 0.000000e+00        litre_per_h
## 59        Kpsp_metc13 1.000000e+00      dimensionless
## 60        Kpgu_metc13 1.000000e+00      dimensionless
## 61        Kpre_metc13 3.000000e-01      dimensionless
## 62        Kpki_metc13 1.000000e+00      dimensionless
## 63        Kplu_metc13 1.000000e+00      dimensionless
## 64        Kpli_metc13 1.000000e+00      dimensionless
## 65         D_apap_cys 0.000000e+00                 mg
## 66    IVDOSE_apap_cys 0.000000e+00                 mg
## 67    PODOSE_apap_cys 0.000000e+00                 mg
## 68        Ka_apap_cys 6.944444e-04              per_h
## 69         F_apap_cys 1.000000e+00      dimensionless
## 70       fup_apap_cys 1.000000e+00      dimensionless
## 71        BP_apap_cys 1.000000e+00      dimensionless
## 72     fumic_apap_cys 1.000000e+00      dimensionless
## 73   CLrenal_apap_cys 6.933333e-03        litre_per_h
## 74      Kpsp_apap_cys 1.000000e+00      dimensionless
## 75      Kpgu_apap_cys 1.000000e+00      dimensionless
## 76      Kpre_apap_cys 8.000000e-01      dimensionless
## 77      Kpki_apap_cys 1.000000e+00      dimensionless
## 78      Kplu_apap_cys 1.000000e+00      dimensionless
## 79      Kpli_apap_cys 1.000000e+00      dimensionless
## 80         D_apap_glu 0.000000e+00                 mg
## 81    IVDOSE_apap_glu 0.000000e+00                 mg
## 82    PODOSE_apap_glu 0.000000e+00                 mg
## 83        Ka_apap_glu 6.944444e-04              per_h
## 84         F_apap_glu 1.000000e+00      dimensionless
## 85       fup_apap_glu 1.000000e+00      dimensionless
## 86        BP_apap_glu 1.000000e+00      dimensionless
## 87     fumic_apap_glu 1.000000e+00      dimensionless
## 88   CLrenal_apap_glu 2.333333e-03        litre_per_h
## 89      Kpsp_apap_glu 1.000000e+00      dimensionless
## 90      Kpgu_apap_glu 1.000000e+00      dimensionless
## 91      Kpre_apap_glu 8.000000e-01      dimensionless
## 92      Kpki_apap_glu 1.000000e+00      dimensionless
## 93      Kplu_apap_glu 1.000000e+00      dimensionless
## 94      Kpli_apap_glu 1.000000e+00      dimensionless
```

```
## 95           D_co2c13 0.000000e+00                mg
## 96       IVDOSE_co2c13 0.000000e+00                mg
## 97       PODOSE_co2c13 0.000000e+00                mg
## 98           Ka_co2c13 5.555556e-04             per_h
## 99            F_co2c13 1.000000e+00      dimensionless
## 100         fup_co2c13 1.000000e+00      dimensionless
## 101          BP_co2c13 1.000000e+00      dimensionless
## 102       fumic_co2c13 1.000000e+00      dimensionless
## 103     CLrenal_co2c13 0.000000e+00        litre_per_h
## 104        Kpsp_co2c13 1.000000e+00      dimensionless
## 105        Kpgu_co2c13 1.000000e+00      dimensionless
## 106        Kpre_co2c13 5.000000e-01      dimensionless
## 107        Kpki_co2c13 1.000000e+00      dimensionless
## 108        Kplu_co2c13 1.000000e+00      dimensionless
## 109        Kpli_co2c13 1.000000e+00      dimensionless
## 110                Qgu          NaN        litre_per_h
## 111                Qki          NaN        litre_per_h
## 112                 Qh          NaN        litre_per_h
## 113                Qha          NaN        litre_per_h
## 114                Qlu          NaN        litre_per_h
## 115                Qsp          NaN        litre_per_h
## 116                Qre          NaN        litre_per_h
## 117     Abody_apap_sul          NaN                 mg
## 118    Cpl_ve_apap_sul          NaN       mg_per_litre
## 119 Cli_free_apap_sul          NaN       mg_per_litre
## 120 Cki_free_apap_sul          NaN       mg_per_litre
## 121      Car_apap_sul          NaN       mg_per_litre
## 122      Csp_apap_sul          NaN       mg_per_litre
## 123      Cgu_apap_sul          NaN       mg_per_litre
## 124      Cre_apap_sul          NaN       mg_per_litre
## 125      Cki_apap_sul          NaN       mg_per_litre
## 126      Clu_apap_sul          NaN       mg_per_litre
## 127      Cli_apap_sul          NaN       mg_per_litre
## 128      Cve_apap_sul          NaN       mg_per_litre
## 129        Abody_apap          NaN                 mg
## 130       Cpl_ve_apap          NaN       mg_per_litre
## 131     Cli_free_apap          NaN       mg_per_litre
## 132     Cki_free_apap          NaN       mg_per_litre
## 133          Car_apap          NaN       mg_per_litre
## 134          Csp_apap          NaN       mg_per_litre
## 135          Cgu_apap          NaN       mg_per_litre
## 136          Cre_apap          NaN       mg_per_litre
## 137          Cki_apap          NaN       mg_per_litre
## 138          Clu_apap          NaN       mg_per_litre
## 139          Cli_apap          NaN       mg_per_litre
## 140          Cve_apap          NaN       mg_per_litre
## 141      Abody_metc13          NaN                 mg
## 142     Cpl_ve_metc13          NaN       mg_per_litre
## 143   Cli_free_metc13          NaN       mg_per_litre
## 144   Cki_free_metc13          NaN       mg_per_litre
## 145        Car_metc13          NaN       mg_per_litre
## 146        Csp_metc13          NaN       mg_per_litre
## 147        Cgu_metc13          NaN       mg_per_litre
## 148        Cre_metc13          NaN       mg_per_litre
```

```
## 149        Cki_metc13          NaN       mg_per_litre
## 150        Clu_metc13          NaN       mg_per_litre
## 151        Cli_metc13          NaN       mg_per_litre
## 152        Cve_metc13          NaN       mg_per_litre
## 153    Abody_apap_cys          NaN                 mg
## 154   Cpl_ve_apap_cys          NaN       mg_per_litre
## 155 Cli_free_apap_cys          NaN       mg_per_litre
## 156 Cki_free_apap_cys          NaN       mg_per_litre
## 157      Car_apap_cys          NaN       mg_per_litre
## 158      Csp_apap_cys          NaN       mg_per_litre
## 159      Cgu_apap_cys          NaN       mg_per_litre
## 160      Cre_apap_cys          NaN       mg_per_litre
## 161      Cki_apap_cys          NaN       mg_per_litre
## 162      Clu_apap_cys          NaN       mg_per_litre
## 163      Cli_apap_cys          NaN       mg_per_litre
## 164      Cve_apap_cys          NaN       mg_per_litre
## 165    Abody_apap_glu          NaN                 mg
## 166   Cpl_ve_apap_glu          NaN       mg_per_litre
## 167 Cli_free_apap_glu          NaN       mg_per_litre
## 168 Cki_free_apap_glu          NaN       mg_per_litre
## 169      Car_apap_glu          NaN       mg_per_litre
## 170      Csp_apap_glu          NaN       mg_per_litre
## 171      Cgu_apap_glu          NaN       mg_per_litre
## 172      Cre_apap_glu          NaN       mg_per_litre
## 173      Cki_apap_glu          NaN       mg_per_litre
## 174      Clu_apap_glu          NaN       mg_per_litre
## 175      Cli_apap_glu          NaN       mg_per_litre
## 176      Cve_apap_glu          NaN       mg_per_litre
## 177      Abody_co2c13          NaN                 mg
## 178     Cpl_ve_co2c13          NaN       mg_per_litre
## 179   Cli_free_co2c13          NaN       mg_per_litre
## 180   Cki_free_co2c13          NaN       mg_per_litre
## 181        Car_co2c13          NaN       mg_per_litre
## 182        Csp_co2c13          NaN       mg_per_litre
## 183        Cgu_co2c13          NaN       mg_per_litre
## 184        Cre_co2c13          NaN       mg_per_litre
## 185        Cki_co2c13          NaN       mg_per_litre
## 186        Clu_co2c13          NaN       mg_per_litre
## 187        Cli_co2c13          NaN       mg_per_litre
## 188        Cve_co2c13          NaN       mg_per_litre
## 189   MET2APAP_HLM_CL 3.333333e-04 mulitre_per_min_mg
## 190       MET2APAP_Km 8.000000e-02       mg_per_litre
## 191    MET2APAP_CLliv          NaN        litre_per_h
## 192    APAPGLU_HLM_CL 3.200000e-03 mulitre_per_min_mg
## 193        APAPGLU_Km 8.000000e-02       mg_per_litre
## 194     APAPGLU_CLliv          NaN        litre_per_h
## 195    APAPSUL_HLM_CL 1.333333e-03 mulitre_per_min_mg
## 196        APAPSUL_Km 8.000000e-02       mg_per_litre
## 197     APAPSUL_CLliv          NaN        litre_per_h
## 198    APAPCYS_HLM_CL 6.666667e-05 mulitre_per_min_mg
## 199        APAPCYS_Km 8.000000e-02       mg_per_litre
## 200     APAPCYS_CLliv          NaN        litre_per_h
##     multiplication_factor original_value
## 1            1.000000e+03    7.00000e+01
```

```
## 2           1.000000e-03    1.08330e+02
## 3           2.777778e-04    3.89988e+08
## 4           1.000000e-03    9.04900e-01
## 5           1.000000e-03    1.71000e-02
## 6           1.000000e-03    4.40000e-03
## 7           1.000000e-03    2.10000e-02
## 8           1.000000e-03    7.60000e-03
## 9           1.000000e-03    2.60000e-03
## 10          1.000000e-03    5.14000e-02
## 11          1.000000e-03    2.57000e-02
## 12          1.000000e-03    4.24000e-02
## 13          1.000000e+00    1.46462e-01
## 14          1.000000e+00    1.90000e-01
## 15          1.000000e+00    2.15385e-01
## 16          1.000000e+00    1.00000e+00
## 17          1.000000e+00    1.72310e-02
## 18          1.000000e+00    5.94615e-01
## 19          1.000000e-03    4.50000e+01
## 20          1.000000e-03    0.00000e+00
## 21          1.000000e-03    0.00000e+00
## 22          1.000000e-03    0.00000e+00
## 23          2.777778e-04    2.50000e+00
## 24          1.000000e+00    1.00000e+00
## 25          1.000000e+00    1.00000e+00
## 26          1.000000e+00    1.00000e+00
## 27          1.000000e+00    1.00000e+00
## 28          2.777778e-04    9.60000e+00
## 29          1.000000e+00    1.00000e+00
## 30          1.000000e+00    1.00000e+00
## 31          1.000000e+00    8.00000e-01
## 32          1.000000e+00    1.00000e+00
## 33          1.000000e+00    1.00000e+00
## 34          1.000000e+00    1.00000e+00
## 35          1.000000e-03    0.00000e+00
## 36          1.000000e-03    0.00000e+00
## 37          1.000000e-03    0.00000e+00
## 38          2.777778e-04    2.50000e+00
## 39          1.000000e+00    8.70000e-01
## 40          1.000000e+00    1.00000e+00
## 41          1.000000e+00    1.00000e+00
## 42          1.000000e+00    1.00000e+00
## 43          2.777778e-04    7.14000e-01
## 44          1.000000e+00    1.00000e+00
## 45          1.000000e+00    1.00000e+00
## 46          1.000000e+00    8.00000e-01
## 47          1.000000e+00    1.00000e+00
## 48          1.000000e+00    1.00000e+00
## 49          1.000000e+00    1.00000e+00
## 50          1.000000e-03    0.00000e+00
## 51          1.000000e-03    1.00000e+02
## 52          1.000000e-03    0.00000e+00
## 53          2.777778e-04    2.50000e+00
## 54          1.000000e+00    1.00000e+00
## 55          1.000000e+00    1.00000e+00
```

```
## 56           1.000000e+00    1.00000e+00
## 57           1.000000e+00    1.00000e+00
## 58           2.777778e-04    0.00000e+00
## 59           1.000000e+00    1.00000e+00
## 60           1.000000e+00    1.00000e+00
## 61           1.000000e+00    3.00000e-01
## 62           1.000000e+00    1.00000e+00
## 63           1.000000e+00    1.00000e+00
## 64           1.000000e+00    1.00000e+00
## 65           1.000000e-03    0.00000e+00
## 66           1.000000e-03    0.00000e+00
## 67           1.000000e-03    0.00000e+00
## 68           2.777778e-04    2.50000e+00
## 69           1.000000e+00    1.00000e+00
## 70           1.000000e+00    1.00000e+00
## 71           1.000000e+00    1.00000e+00
## 72           1.000000e+00    1.00000e+00
## 73           2.777778e-04    2.49600e+01
## 74           1.000000e+00    1.00000e+00
## 75           1.000000e+00    1.00000e+00
## 76           1.000000e+00    8.00000e-01
## 77           1.000000e+00    1.00000e+00
## 78           1.000000e+00    1.00000e+00
## 79           1.000000e+00    1.00000e+00
## 80           1.000000e-03    0.00000e+00
## 81           1.000000e-03    0.00000e+00
## 82           1.000000e-03    0.00000e+00
## 83           2.777778e-04    2.50000e+00
## 84           1.000000e+00    1.00000e+00
## 85           1.000000e+00    1.00000e+00
## 86           1.000000e+00    1.00000e+00
## 87           1.000000e+00    1.00000e+00
## 88           2.777778e-04    8.40000e+00
## 89           1.000000e+00    1.00000e+00
## 90           1.000000e+00    1.00000e+00
## 91           1.000000e+00    8.00000e-01
## 92           1.000000e+00    1.00000e+00
## 93           1.000000e+00    1.00000e+00
## 94           1.000000e+00    1.00000e+00
## 95           1.000000e-03    0.00000e+00
## 96           1.000000e-03    0.00000e+00
## 97           1.000000e-03    0.00000e+00
## 98           2.777778e-04    2.00000e+00
## 99           1.000000e+00    1.00000e+00
## 100          1.000000e+00    1.00000e+00
## 101          1.000000e+00    1.00000e+00
## 102          1.000000e+00    1.00000e+00
## 103          2.777778e-04    0.00000e+00
## 104          1.000000e+00    1.00000e+00
## 105          1.000000e+00    1.00000e+00
## 106          1.000000e+00    5.00000e-01
## 107          1.000000e+00    1.00000e+00
## 108          1.000000e+00    1.00000e+00
## 109          1.000000e+00    1.00000e+00
```

```
## 110          2.777778e-04           NaN
## 111          2.777778e-04           NaN
## 112          2.777778e-04           NaN
## 113          2.777778e-04           NaN
## 114          2.777778e-04           NaN
## 115          2.777778e-04           NaN
## 116          2.777778e-04           NaN
## 117          1.000000e-03           NaN
## 118          1.000000e-03           NaN
## 119          1.000000e-03           NaN
## 120          1.000000e-03           NaN
## 121          1.000000e-03           NaN
## 122          1.000000e-03           NaN
## 123          1.000000e-03           NaN
## 124          1.000000e-03           NaN
## 125          1.000000e-03           NaN
## 126          1.000000e-03           NaN
## 127          1.000000e-03           NaN
## 128          1.000000e-03           NaN
## 129          1.000000e-03           NaN
## 130          1.000000e-03           NaN
## 131          1.000000e-03           NaN
## 132          1.000000e-03           NaN
## 133          1.000000e-03           NaN
## 134          1.000000e-03           NaN
## 135          1.000000e-03           NaN
## 136          1.000000e-03           NaN
## 137          1.000000e-03           NaN
## 138          1.000000e-03           NaN
## 139          1.000000e-03           NaN
## 140          1.000000e-03           NaN
## 141          1.000000e-03           NaN
## 142          1.000000e-03           NaN
## 143          1.000000e-03           NaN
## 144          1.000000e-03           NaN
## 145          1.000000e-03           NaN
## 146          1.000000e-03           NaN
## 147          1.000000e-03           NaN
## 148          1.000000e-03           NaN
## 149          1.000000e-03           NaN
## 150          1.000000e-03           NaN
## 151          1.000000e-03           NaN
## 152          1.000000e-03           NaN
## 153          1.000000e-03           NaN
## 154          1.000000e-03           NaN
## 155          1.000000e-03           NaN
## 156          1.000000e-03           NaN
## 157          1.000000e-03           NaN
## 158          1.000000e-03           NaN
## 159          1.000000e-03           NaN
## 160          1.000000e-03           NaN
## 161          1.000000e-03           NaN
## 162          1.000000e-03           NaN
## 163          1.000000e-03           NaN
```

```
## 164          1.000000e-03           NaN
## 165          1.000000e-03           NaN
## 166          1.000000e-03           NaN
## 167          1.000000e-03           NaN
## 168          1.000000e-03           NaN
## 169          1.000000e-03           NaN
## 170          1.000000e-03           NaN
## 171          1.000000e-03           NaN
## 172          1.000000e-03           NaN
## 173          1.000000e-03           NaN
## 174          1.000000e-03           NaN
## 175          1.000000e-03           NaN
## 176          1.000000e-03           NaN
## 177          1.000000e-03           NaN
## 178          1.000000e-03           NaN
## 179          1.000000e-03           NaN
## 180          1.000000e-03           NaN
## 181          1.000000e-03           NaN
## 182          1.000000e-03           NaN
## 183          1.000000e-03           NaN
## 184          1.000000e-03           NaN
## 185          1.000000e-03           NaN
## 186          1.000000e-03           NaN
## 187          1.000000e-03           NaN
## 188          1.000000e-03           NaN
## 189          1.666667e-05   2.00000e+01
## 190          1.000000e-03   8.00000e+01
## 191          2.777778e-04           NaN
## 192          1.666667e-05   1.92000e+02
## 193          1.000000e-03   8.00000e+01
## 194          2.777778e-04           NaN
## 195          1.666667e-05   8.00000e+01
## 196          1.000000e-03   8.00000e+01
## 197          2.777778e-04           NaN
## 198          1.666667e-05   4.00000e+00
## 199          1.000000e-03   8.00000e+01
## 200          2.777778e-04           NaN
```

```
  # filter(par %in% c("MET2APAP_HLM_CL", "fumic_metc13", "MPPGL", "BW", "FVli"))  #%>% summarise(prod(m
  # filter(par %in% c("CO", "QC"))
# rules[str_detect(rules, "MET2APAP")]
# rules[str_detect(rules, "CO")]
```

C-Code

the odemodel() command takes a while because sensitivity equations are calculated for derivatives and then the whole system is compiled into c-code.

```
# myodemodel <- odemodel(f, modelname = "methacetin") # this compiles the ode into a c-file. you can co
# save(myodemodel, file = "methacetin.rda")

load("methacetin.rda")
```

Prediction function

Make a prediction function from the odemodel. x will be a function x(times, pars)

```
x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

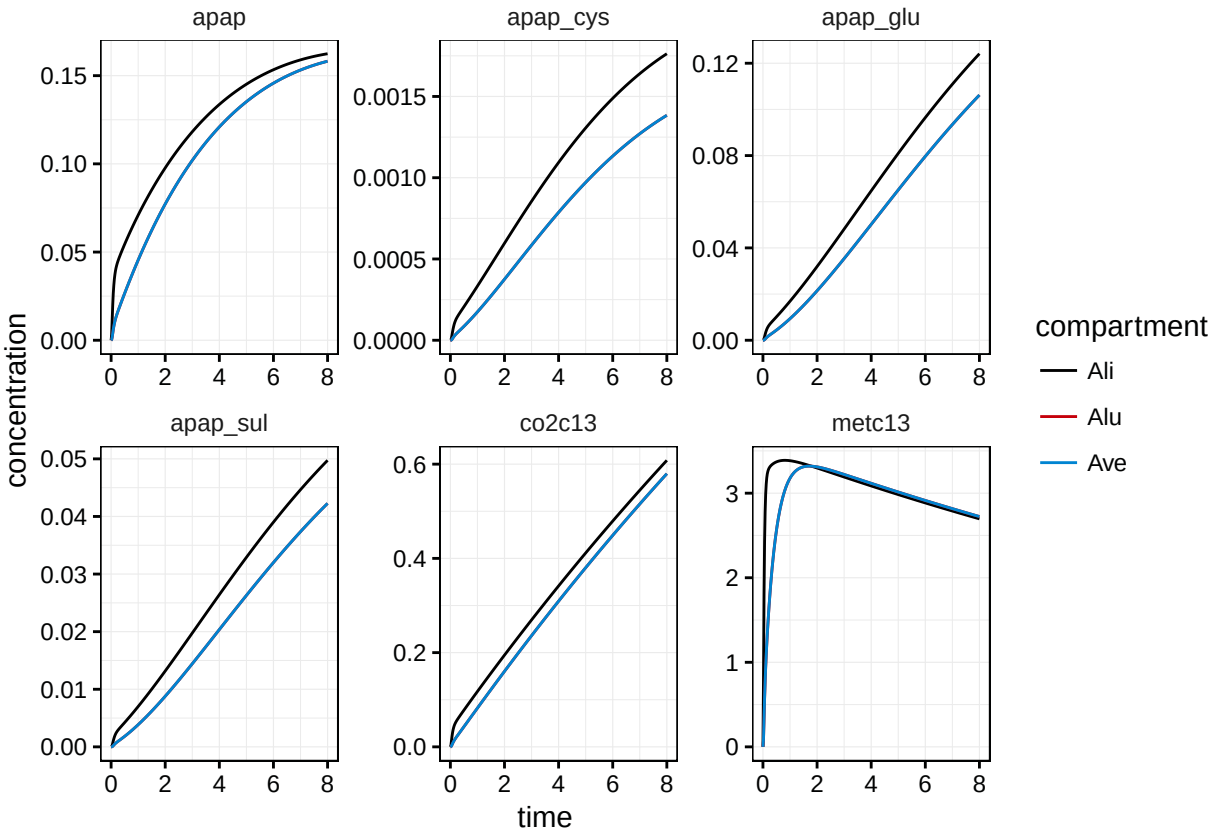
```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]
```

Example plot

This plot is supposed to be the first plot from chunk 3 of the html-file that you sent me via email.

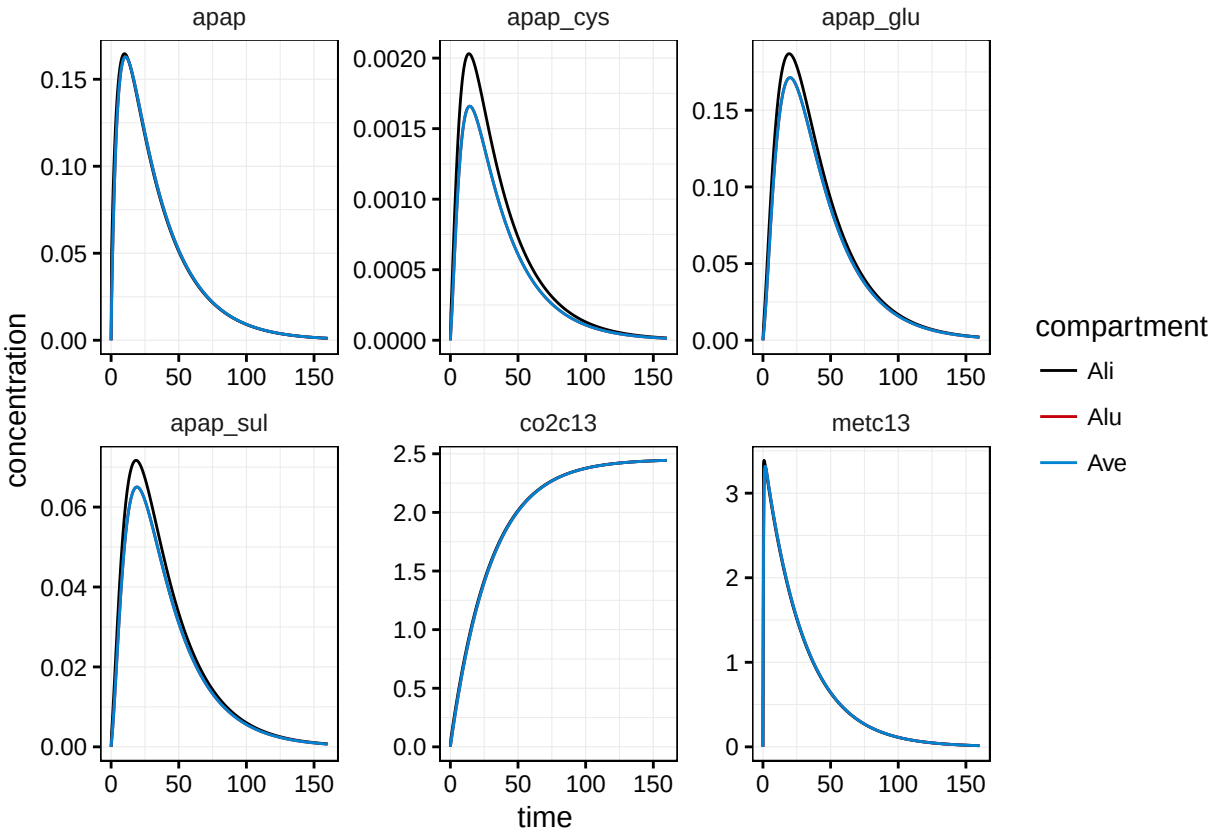
```
pars["Ave_metc13"] <- 0
pars["D_metc13"] <- 0.1 #100mg

mytimes = seq(0,8*3600, length.out = 400) #8 hours

# pred <- (g*x)(0:50, mypars, deriv = F, conditions = rownames(attr(data, "cond")))
prediction <- (x)(times = mytimes, pars = pars, deriv = F, conditions = "c1")

# Compute the volumes in litres for each state
volumes <- lapply(0:(nspecies-1), . %>% {ListOfSpecies_get(lspecies,.)} %>% Species_getCompartment()) %
myrules <- rules %>% set_names(paste0("\\b", rulenames, "\\b"))
volumes <- str_replace_all(volumes, myrules) %>% set_names(species)
vol_fun <- funC0(volumes)
vol <- do.call(vol_fun, as.list(pars)) %>% t %>% {data.frame(volume=., name = rownames(.), stringsAsFac

# Plot
plot_fun <- function(pred) pred %>%
  wide2long() %>%
  full_join(vol,by= "name") %>%
  mutate(value = value * 1000, time = time/3600, concentration = value/volume) %>% # scale g to mg, s t
  separate(col = name, into = c("compartment", "substance"), sep = "_", extra = "merge") %>%
  filter(compartment %in% c("Ali", "Ave", "Alu")) %>% # plot only liver, venuous and lung (as in the ht
  ggplot(aes(x= time, y = concentration)) +
  geom_line(aes(color = compartment)) +
  facet_wrap(~substance, scales = "free") +
  theme_dMod() + scale_color_dMod()

save(f, file = "~/Promotion/Projects/methacetin_fitting/R/f.rda")

plot_fun(prediction)
```

```
## Warning: Column `name` joining factor and character vector, coercing into
## character vector
```



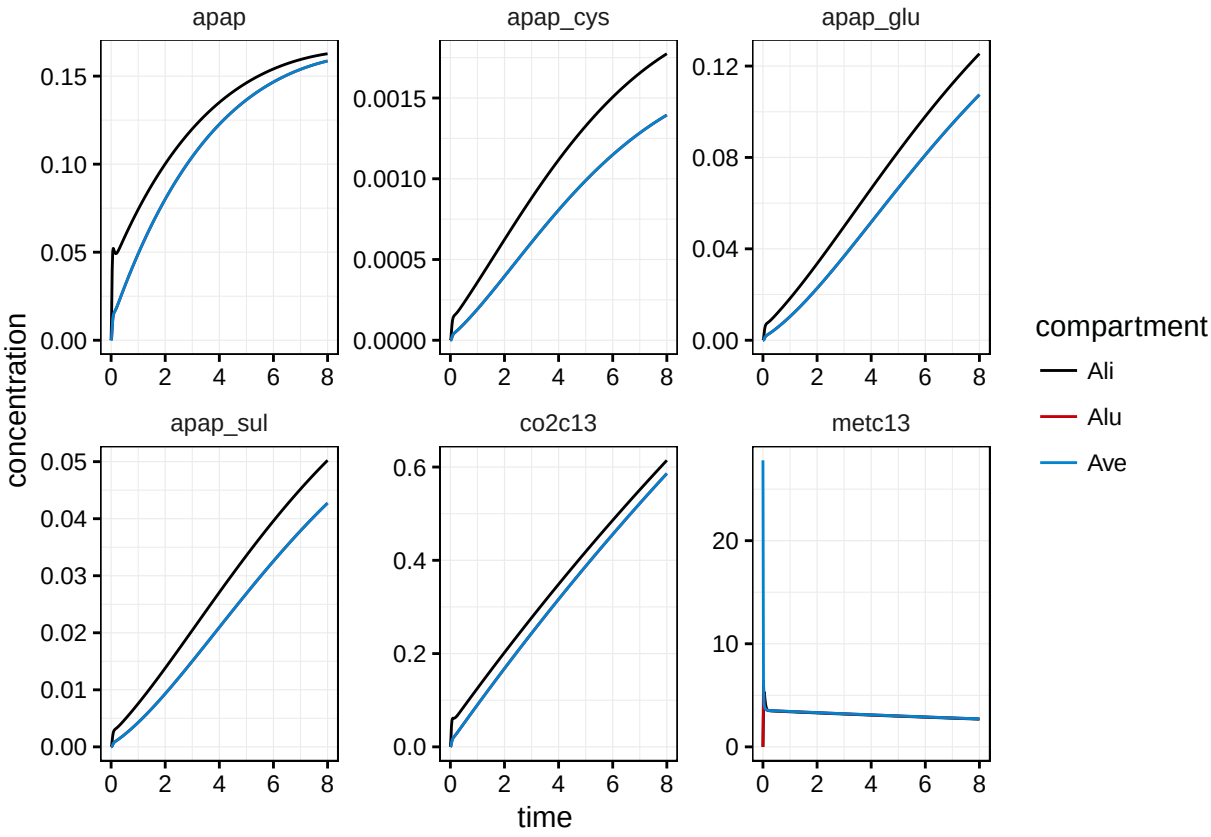

```
prediction_long <- (x)(times = mytimes*20,pars = pars, deriv = F, conditions = "c1")
plot_fun(prediction_long)
```

```
## Warning: Column `name` joining factor and character vector, coercing into
## character vector
```




```
# Second plot from chunk 3
pars <- all_pars[getParameters(x)]
pars["Ave_metc13"] <- 0.1
pars["D_metc13"] <- 0 #100mg
# pars["Kplu_metc13"] <- 1
# pars["FVlu"] <- 7.6*10^(-6) * 10

prediction_second_plot <- (x)(times = mytimes,pars = pars, deriv = F, conditions = "c1")
plot_fun(prediction_second_plot)
```

```
## Warning: Column `name` joining factor and character vector, coercing into
## character vector
```



Modelling

Reduce the model complexity by inserting the fixed parameter values

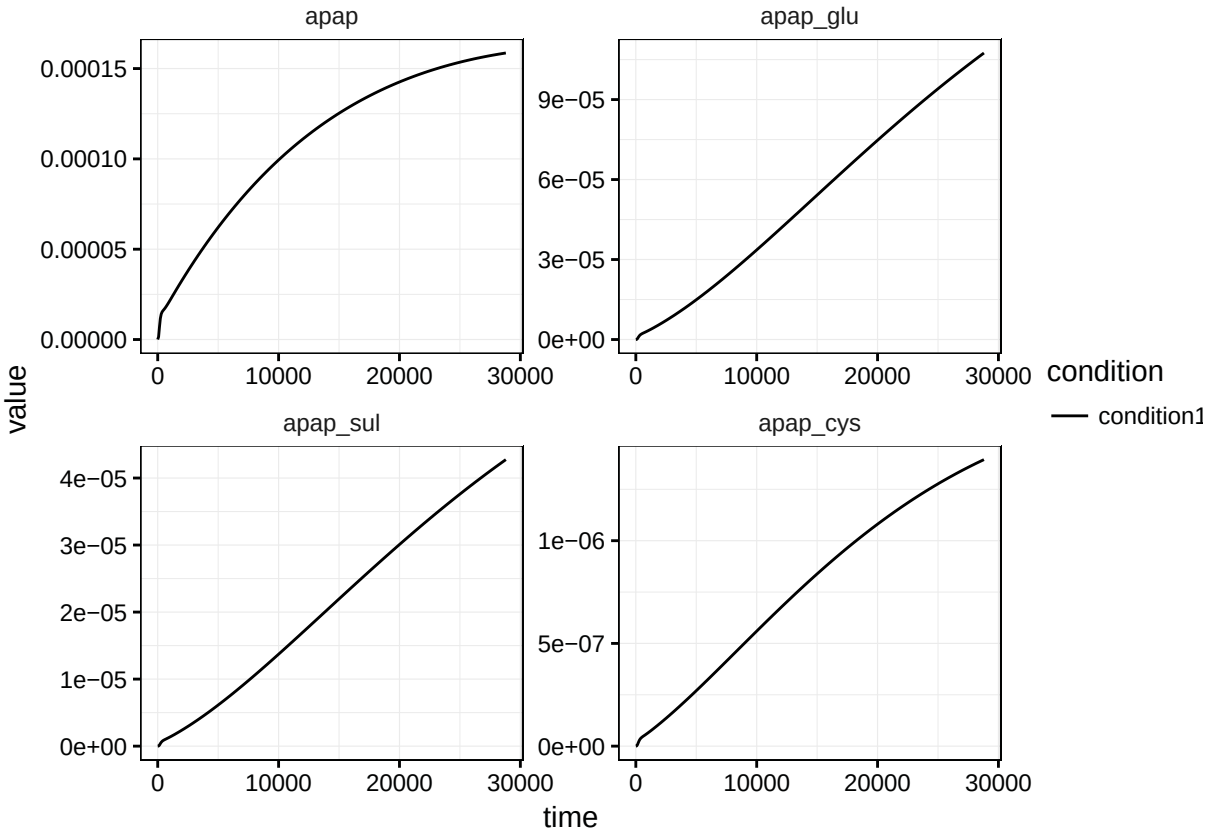
```
free_parameters <- c("APAPGLU_HLM_CL",  # Vmax value
                     "APAPGLU_Km",  # Km value
                     "APAPSUL_HLM_CL",  # Vmax value
                     "APAPGLU_Km",  # Km value
                     "APAPCYS_HLM_CL",  # Vmax value
                     "APAPCYS_Km"  # Km value
                     )


fixed_parameters <- pars[!(names(pars)%in%c(free_parameters,names(f)[1]))] %>% names


myodemodel <- odemodel(f, modelname = "methacetin_reduced", fixed = fixed_parameters)

x <- Xs(myodemodel)
```

Observation function

```
observables <- c(apap = "Ave_apap/(BW*FVve)",
                 apap_glu = "Ave_apap_glu/(BW*FVve)",
```

```
                  apap_sul = "Ave_apap_sul/(BW*FVve)",
                  apap_cys = "Ave_apap_cys/(BW*FVve)"
                  )

g <- Y(observables, x, parameters = free_parameters)
```

```
(g*x)(mytimes, pars) %>% set_names("condition1") %>% plotPrediction(name %in% names(observables))
```

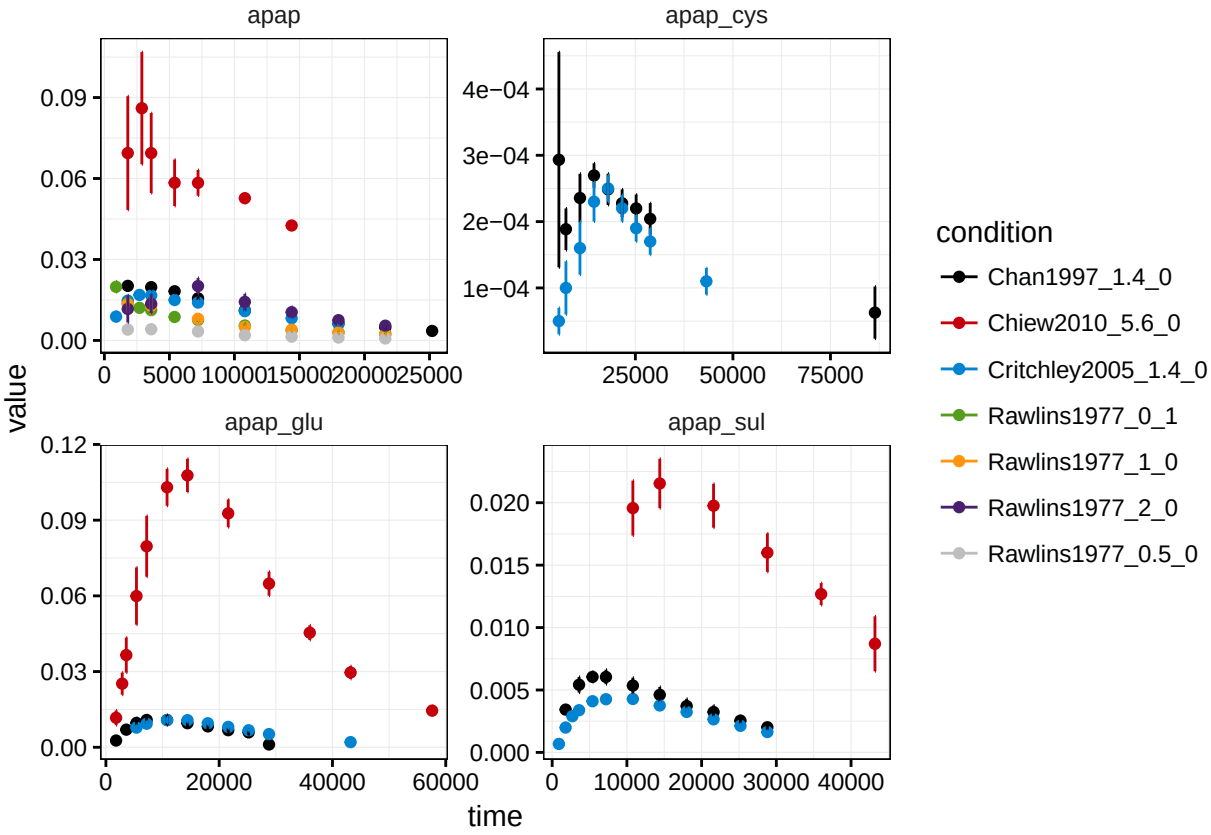


Data

Load the data and transform it

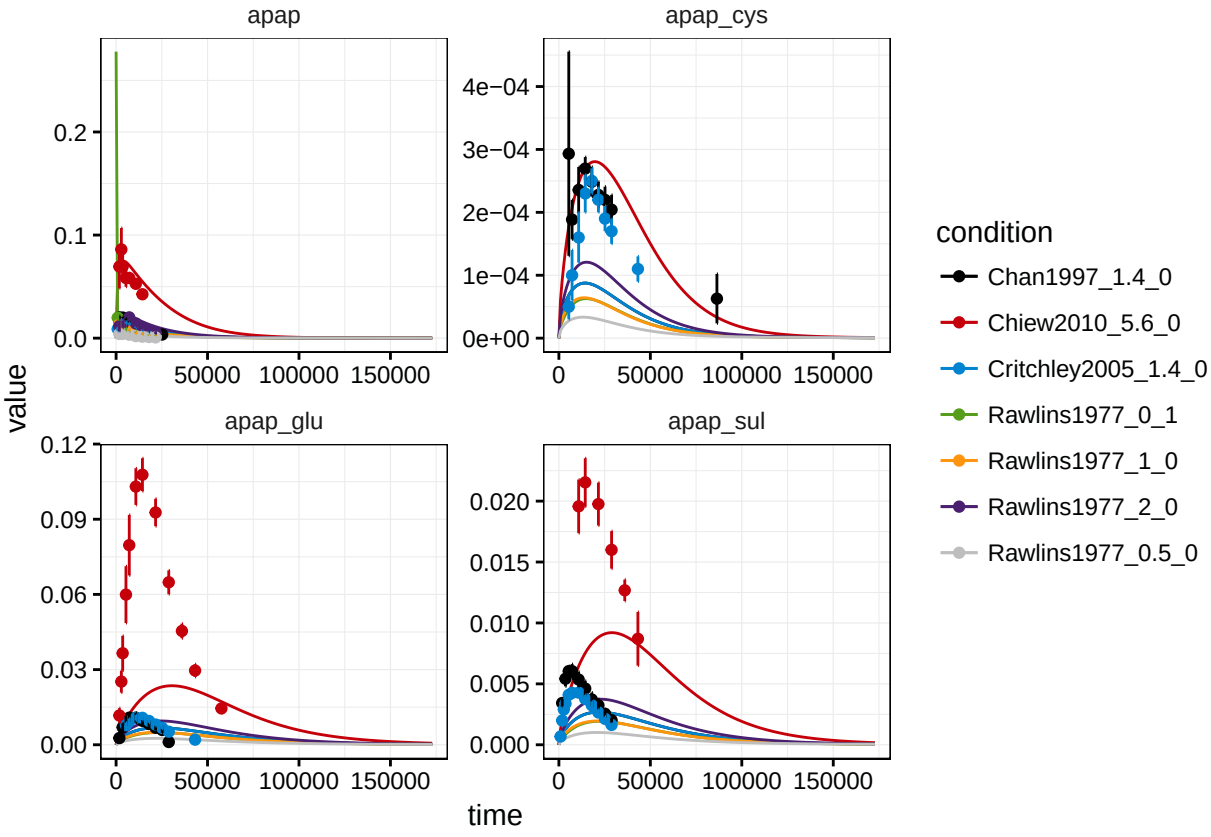
```
myfiles <- list.files("~/Promotion/Projects/methacetin_fitting/data/", full.names = T)


raw_data <- myfiles %>% lapply(. %>% read.table(header = T, sep = "\t", stringsAsFactors = F))


data <-
  raw_data %>%
  lapply(. %>%
           select(-contains("_mol")) %>%
           gather("name_std", "std", ends_with("_sd")) %>%
           mutate(name_std = str_replace(name_std, "_sd","")) %>%
           gather("name_sigma", "sigma", ends_with("_se")) %>%
           mutate(name_sigma = str_replace(name_sigma, "_se","")) %>%
```

```
            {gather(.,"name", "value", one_of(.$name_std))} %>%
            filter(name == name_std, name == name_sigma) %>%
            # select(name,time,value,sigma) %>%
            {.}) %>%
    do.call(dMod::combine,.) %>%
    mutate(D_apap = "D_apap", Ave_apap = "Ave_apap" ) %>%
    {.$D_apap[.$study=="Chan1997"] <- 1400 / 1000
    .$Ave_apap[.$study=="Chan1997"] <- 0
    .$D_apap[.$study=="Chiew2010"] <- 5600 / 1000
    .$Ave_apap[.$study=="Chiew2010"] <- 0
    .$D_apap[.$study=="Critchley2005"] <- 1400 /1000
    .$Ave_apap[.$study=="Critchley2005"] <- 0
    .$D_apap[.$study=="Rawlins1977"] <- .$dose[.$study=="Rawlins1977"] * (.$route[.$study=="Rawlins1977
    .$Ave_apap[.$study=="Rawlins1977"] <- .$dose[.$study=="Rawlins1977"] * (.$route[.$study=="Rawlins19
    .
    } %>%
  mutate(time = time * 3600, value = value/1000, sigma = sigma/1000) %>%
  select(-group, -health_status, - name_std, - name_sigma, -std, -ethnicity, -route, -dose, -substance)
  # filter(!is.na(sigma)) %>%
  # as.datalist() %>%
            {.}
mydatalist <- data %>% filter(!is.na(sigma)) %>% select(-n) %>% as.datalist()

plot(mydatalist)
```



Parameter transformations to define the conditions

```
conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters] <- paste0("exp(log", free_parameters, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p <- NULL
for(i in 1:length(p_list)) { p <<- p + p_list[[i]]}

pouter <- log(pars[free_parameters]) %>% set_names(paste0("log",names(.)))


mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
plotCombined(mypred, mydatalist, name%in% names(observables))
```

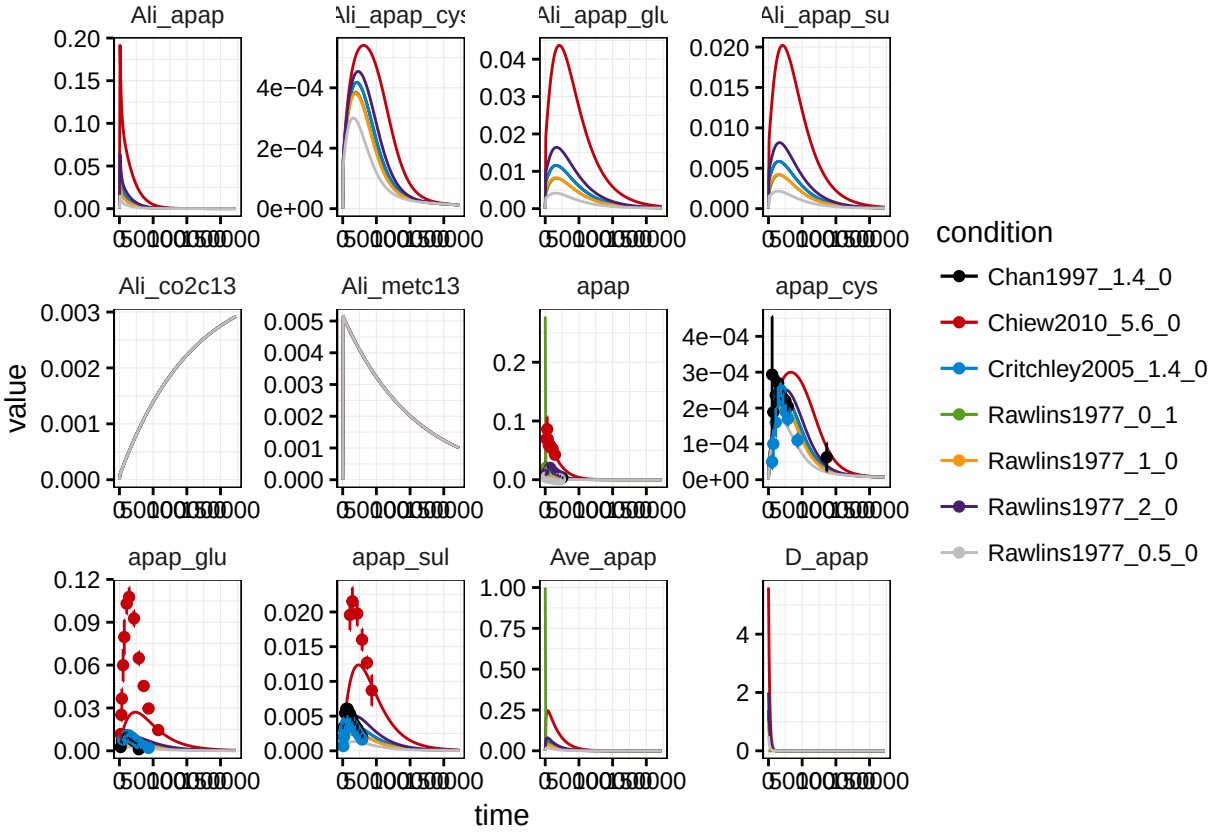


Fitting

```
obj <- normL2(mydatalist, (g*x*p))


# myfit <- mstrust(objfun = obj, center = pouter, studyname = "methacetin", cores = 3)
# save(myfit, file = "fit.rda")
```

```
load("fit.rda")

fitted_pars <- myfit %>% as.parframe() %>% as.parvec()
```

```
mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), fitted_pars)

liver <- names(f)[str_detect(names(f), "li")]
medication <- c(names(f)[str_detect(names(f), "D_apap$")], "Ave_apap")


plotCombined(mypred, mydatalist, name %in% c(names(observables), liver, medication))
```



Look at the pars

```
exp(fitted_pars) %>% sort()
```

```
## logAPAPCYS_HLM_CL:  2.75936204923354e-05
##     logAPAPCYS_Km:  0.00183418625326802
## logAPAPGLU_HLM_CL:  0.00594046463001759
##     logAPAPGLU_Km:  0.118855661904664
## logAPAPSUL_HLM_CL:  0.00220144570190944
```

Profiles

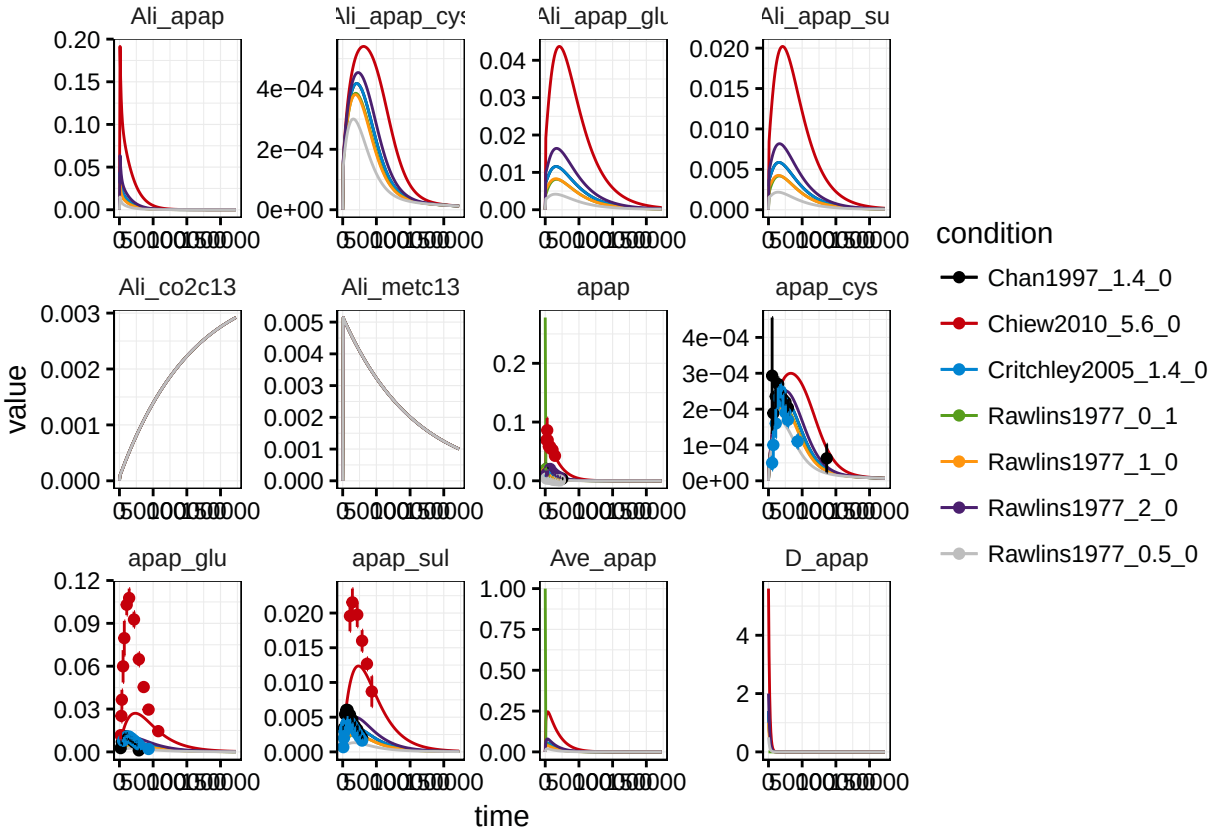
```
# profiles <- profile(obj = obj, pars = fitted_pars, whichPar = names(fitted_pars), cores = 3)
```

```
# plotProfile(profiles)
```

Look at some reactions

```
# reactions
```

```
mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), fitted_pars)

liver <- names(f)[str_detect(names(f), "li")]
medication <- c(names(f)[str_detect(names(f), "D_apap$")], "Ave_apap")


plotCombined(mypred, mydatalist, name %in% c(names(observables), liver, medication))
```



Free some more parameters

Free other parameters 1 - not good

Here I freed some additional parameters, but since I freed "Ka_apap_sul" instead of "Ka_apap", the results don't make much additional sense.

```
load("methacetin.rda")
```

```
x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters1 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap_sul", "F_apap_sul",
                      "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu",
                      "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                      )

fixed_parameters1 <- pars[!(names(pars)%in%c(free_parameters1,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters1] <- paste0("exp(log", free_parameters1, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p1 <- NULL
for(i in 1:length(p_list)) { p1 <<- p1 + p_list[[i]]}

pouter <- log(pars[free_parameters1]) %>% set_names(paste0("log",names(.)))


# mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj1 <- normL2(mydatalist, (g*x*p1))

# job1 <- runbg({myfit <- mstrust(objfun = obj1, center = pouter, studyname = "methacetin", cores = 20,
```

```
# myfit1 <- job1$get()$knecht3
```

```r
# save(myfit1, file = "myfit1.rda")
# job1$purge()
load("myfit1.rda")
myfit1 %>% as.parframe()
```

```
##    index        value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1     71 2.749704e+03     FALSE        100       -3.12142498     0.9276677
## 2     17 2.871109e+03     FALSE        100       -4.82579063    -0.8966849
## 3      4 2.879499e+03      TRUE         82       -4.83651371    -2.0500243
## 4     83 3.006360e+03      TRUE         38       -4.81037490    -1.6071039
## 5     11 3.025134e+03      TRUE         47       -5.06836676    -2.1571283
## 6     60 3.063915e+03     FALSE        100       -4.77817488    -1.9189665
## 7     10 3.137536e+03      TRUE         81       -5.92875885    -3.4815571
## 8     41 3.201166e+03     FALSE        100       -7.45183110    -5.6519410
## 9     75 3.222250e+03     FALSE        100       -0.72703052     2.6237522
## 10    15 3.225951e+03     FALSE        100       -6.23397734    -3.7414419
## 11    59 3.275025e+03      TRUE         90       -5.09916431    -1.6514433
## 12    39 3.307696e+03     FALSE        100       -5.10146665    -3.1014160
## 13    84 3.372714e+03      TRUE         84       -2.90607750     0.4283547
## 14    63 3.379909e+03     FALSE        100       -7.35688109    -4.6177425
## 15    64 3.391689e+03     FALSE        100       -2.51926766     0.7717711
## 16    44 3.436261e+03     FALSE        100       -3.03912632    -0.6151772
## 17     6 3.507761e+03     FALSE        100       -7.11536665    -6.8430974
## 18    87 3.530025e+03     FALSE        100       -0.02282939     2.4929719
## 19   100 3.552855e+03     FALSE        100       -6.68492919    -5.6013539
## 20    37 3.559066e+03      TRUE         84       -5.12593679    -1.0358305
## 21    89 3.573663e+03     FALSE        100       -6.90395214    -4.5513808
## 22    98 3.635002e+03      TRUE         38       -6.04197475    -1.7497664
## 23    40 3.654117e+03     FALSE        100        0.12757339     3.1873736
## 24    29 3.658452e+03     FALSE        100       -4.10752340    -0.6005445
## 25    56 3.701854e+03     FALSE        100       -6.88847478    -6.1220522
## 26    50 3.733214e+03     FALSE        100       -7.88919027    -7.9172196
## 27    65 3.735690e+03      TRUE         78       -5.98453621    -3.0333931
## 28    93 3.815057e+03      TRUE         60       -2.83817406     1.1301364
## 29    34 3.835842e+03      TRUE         79       -4.70100851    -3.1365553
## 30    66 3.846932e+03      TRUE         57       -7.44818223    -5.6625210
## 31    72 3.851422e+03      TRUE         90       -4.70154970    -1.1480937
## 32    62 3.882514e+03     FALSE        100       -4.53788632    -2.7798340
## 33    26 3.895203e+03      TRUE         98       -7.77712192    -7.1476390
## 34    23 3.982315e+03     FALSE        100       -1.69961153     1.8400454
## 35    20 3.993661e+03      TRUE         95       -6.91526554    -4.0178405
## 36    68 4.072758e+03     FALSE        100       -6.78763085    -4.3364186
## 37    49 4.104312e+03     FALSE        100       -2.72365092     2.7575099
## 38    77 4.137384e+03      TRUE         94       -7.98731247    -7.3436584
## 39    92 4.153072e+03     FALSE        100       -5.92947986     0.1429887
## 40    81 4.185162e+03     FALSE        100       -7.22599581    -6.1436471
## 41    16 4.200251e+03     FALSE        100       -7.68463792    -5.0010499
## 42    91 4.251682e+03     FALSE        100       -5.64356584    -1.1669282
## 43    52 4.368082e+03     FALSE        100       -8.18034816    -9.1828822
## 44    18 4.422032e+03     FALSE        100       -4.56378249    -0.7931566
## 45    96 4.428599e+03      TRUE         94       -8.33368644    -7.5933453
## 46    53 4.513783e+03     FALSE        100       -7.16468434    -7.4077410
## 47    38 4.513904e+03     FALSE        100       -0.95829877     3.9956489
## 48    74 4.527715e+03     FALSE        100       -8.05059671    -7.9630560
```

```
## 49    51 4.554153e+03      TRUE         94        4.23634033     8.1886396
## 50    36 4.580651e+03     FALSE        100       -3.37843122    -0.5449133
## 51    42 4.581443e+03     FALSE        100        6.27904113     9.8324316
## 52    54 4.616852e+03     FALSE        100       -8.57924549   -18.3898652
## 53    76 4.667031e+03     FALSE        100       -5.52216562    -3.7898978
## 54    88 4.807979e+03      TRUE         83       -5.56389601    -2.5417910
## 55    55 4.827187e+03     FALSE        100       -0.16379817     3.1639660
## 56     3 4.829264e+03     FALSE        100       -1.90605754     2.2014898
## 57    43 5.061582e+03     FALSE        100       -8.07190561    -7.6168088
## 58    14 5.066829e+03     FALSE        100       -0.49939074     0.2268354
## 59    57 5.105624e+03     FALSE        100       -4.22204234    -2.1881151
## 60    25 5.110459e+03     FALSE        100       -2.91256361    -0.5576255
## 61     1 5.330672e+03      TRUE         75        9.19327678    12.6236739
## 62    31 5.973342e+03     FALSE        100       -9.51046185   -18.1821594
## 63    45 6.044345e+03      TRUE         93        1.64646423     5.1360476
## 64    32 6.171118e+03      TRUE         99       -9.56594740   -22.5939253
## 65    58 6.210266e+03     FALSE        100       -3.93350215    -0.6059348
## 66    61 6.215212e+03     FALSE        100       -0.54848705     3.0272117
## 67    46 6.357598e+03     FALSE        100        9.70541768    13.5178914
## 68    24 6.446816e+03     FALSE        100      -10.00987796   -23.7521988
## 69    73 6.522615e+03      TRUE         50        4.55658070    10.8468122
## 70    67 6.965876e+03     FALSE        100       -6.07839845    -1.3045503
## 71     5 6.988498e+03     FALSE        100       -1.10886491     2.5979700
## 72    19 7.646367e+03     FALSE        100       -1.70074377     3.2044369
## 73    21 7.711495e+03     FALSE        100       -0.88975984     2.9945331
## 74    33 7.868795e+03     FALSE        100        0.35149439     5.5264335
## 75    70 7.871068e+03     FALSE        100       -8.61680105    -3.5395383
## 76     7 7.915360e+03     FALSE        100       -0.37918103     2.7675821
## 77    80 8.768680e+03      TRUE         58      -12.79269544     3.2812308
## 78    95 9.125107e+03      TRUE         28      -13.13209389     3.4595677
## 79    28 9.150715e+03      TRUE         95      -12.04770746     4.1309941
## 80    27 1.068802e+04      TRUE         45       12.64400735    17.5687047
## 81    86 1.523194e+04     FALSE        100        1.24902087     4.4736740
## 82    22 1.794384e+04     FALSE        100       -0.27326264     3.1522361
## 83    82 1.800086e+04      TRUE         93       13.70206982    15.7358314
## 84     9 2.086031e+04     FALSE        100        5.30601792     9.6106460
## 85    85 2.129157e+04     FALSE        100        0.08340816     3.0451403
## 86     8 3.622342e+04      TRUE         64       22.40872351    26.3402924
## 87    47 3.905169e+06      TRUE         33      -18.00009074     8.3989678
## 88    99 1.114027e+08      TRUE         37      -21.23907193    10.9045331
## 89    12 1.132108e+08      TRUE         34      -12.49533128     6.4250560
##    logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap_sul
## 1          -5.966762         -8.877054    -8.0562047      -9.043602
## 2          -7.312292         -9.776533    -6.3177038      -7.411144
## 3          -6.424722         -9.745092    -7.2477581      -7.449345
## 4          -6.432805        -10.767499    -6.4519813      -6.734894
## 5          -6.368207         -9.236633    -7.2985712      -8.975554
## 6          -6.479809        -10.151009    -5.6927767      -5.931667
## 7          -6.109399        -10.006732    -3.9430380      -7.129631
## 8          -7.110727        -10.155874    -6.1645322      -8.084674
## 9          -6.350519        -10.037193    -8.2658497      -6.620710
## 10         -6.261607         -8.595206    -2.8093914      -6.118336
## 11         -5.899626         -9.773133    -4.7259565      -7.748247
## 12         -5.293408        -10.760024    -8.0861927      -7.623910
```

```
## 13        -6.820600       -10.114159    -8.2083820      -8.679922
## 14        -7.419093        -9.517451    -2.3969770      -6.167394
## 15        -6.748113        -9.594424    -5.5275260      -8.509997
## 16        -4.384835       -10.614901    -7.7044536      -6.500339
## 17        -4.860852        -9.104320    -6.9719864      -6.130698
## 18        -4.614758       -11.111664    -8.1882208      -7.724728
## 19        -4.972631        -9.379210    -7.4408016      -7.815844
## 20        -6.260454       -10.613898    -6.3152307      -6.603185
## 21        -6.756416       -10.111994    -3.6886669      -7.508202
## 22        -7.584418       -10.851428    -4.9434381      -8.435150
## 23        -6.193895       -10.527374    -7.5143757      -5.956598
## 24        -5.174935       -11.204949    -7.0189657      -6.900971
## 25        -4.670836        -8.653427    -3.8989060      -6.089580
## 26        -5.714516        -8.484881    -4.6995483      -7.043525
## 27        -5.864815       -10.165474    -9.3911650      -8.126891
## 28        -6.826423        -9.716458    -3.3978000      -9.519148
## 29        -4.442662        -9.095794    -4.1710320      -7.027662
## 30        -6.360314        -8.905906    -3.6296895      -6.340725
## 31        -6.307410       -10.326203    -5.3486849      -6.808919
## 32        -4.601844        -8.204361    -4.0350587      -6.739964
## 33        -6.323308       -10.086662    -3.4848296      -6.726469
## 34        -6.866721        -9.886295    -4.3409185      -7.735414
## 35        -6.091083       -10.898634    -6.7343860      -7.457985
## 36        -5.884565        -8.617484    -4.2077770      -7.065600
## 37        -7.070970        -9.661965    -6.8268260      -7.425963
## 38        -6.271467       -10.814201    -7.2040151      -9.073312
## 39        -7.843027       -10.022699    -1.7770275      -7.776599
## 40        -5.001332        -9.479166    -5.9047288      -8.594568
## 41        -5.917931        -9.393341    -4.7411717      -6.653728
## 42        -6.053875       -10.180964    -4.4181783      -7.269386
## 43        -5.904198        -9.699038    -4.9366875      -6.510543
## 44        -6.821546       -10.294887    -5.7392754      -6.720263
## 45        -6.003579        -9.961431    -4.8403585      -6.518902
## 46        -3.579873        -8.408021    -5.3608159      -7.728047
## 47        -7.667046        -8.995316    -0.1215114      -8.347759
## 48        -4.348054       -10.135608    -9.4335101      -7.175758
## 49        -6.220051       -10.059035    -7.8061144      -9.014269
## 50        -6.014744       -10.732003    -7.3321586      -6.583217
## 51        -5.141772        -8.905856    -1.9244563      -7.055528
## 52        -6.538944        -9.758419    -4.6936046      -8.080629
## 53        -5.423606       -10.728461    -6.6468136      -6.057018
## 54        -5.349930       -10.528612    -8.7292791      -5.050733
## 55        -6.730796        -7.804061    -0.8792097      -8.719816
## 56        -5.778917        -9.670807    -6.7424359     -10.166666
## 57        -4.972652        -8.404867    -4.0819315      -7.094191
## 58        -4.428207        -9.838360    -6.9753653      -4.977068
## 59        -4.449093        -9.188780    -7.0076661      -6.255897
## 60        -5.338503        -9.561469    -3.8236106      -7.272669
## 61        -5.683978        -9.988740    -5.0519732      -7.357343
## 62        -7.499056        -9.849189    -4.0551416      -7.341367
## 63        -5.584166       -10.804406    -8.3871699      -8.896132
## 64        -6.367358       -10.940498   -18.0929924      -6.269076
## 65        -6.632446        -9.486049    -2.3718289      -6.544988
## 66        -6.499809       -10.485290    -5.7376417      -6.965186
```

```
## 67         -6.290610        -10.857065    -5.2771635      -6.717833
## 68         -6.329073        -11.143570   -18.6319181      -7.990090
## 69         -7.591068        -10.055840    -5.6724211      -7.356272
## 70         -6.981299         -9.614989    -1.7354429      -7.334783
## 71         -5.809158         -7.964744    -1.9523790      -7.383379
## 72         -7.133550        -10.864118    -6.2088812      -6.929585
## 73         -6.399408         -8.390860    -1.9236896      -7.073354
## 74         -8.246193        -10.944051    -8.2079756      -7.308718
## 75         -6.060069         -8.017847    -2.5974597      -7.869141
## 76         -6.003383        -10.968676   -10.1013896      -6.682941
## 77         -8.491792        -10.978941   -10.2371580      -8.354460
## 78         -8.873242        -11.137969   -10.0125793      -7.063678
## 79         -9.269151         -9.918074   -10.9183228      -5.406346
## 80         -8.095481        -11.136325    -6.3660530      -7.546267
## 81         -6.643800         -6.299612    -0.4180203      -9.047860
## 82         -7.166326         -5.841417    -0.0483868      -8.365144
## 83         -5.591312          4.756534    11.1554840      -8.759957
## 84         -8.443175        -10.861621    -7.9331117      -8.180766
## 85         -5.887028         -8.817302    -2.3416813      -5.028507
## 86         -8.843526         12.202053    19.2044104      -7.415503
## 87        -27.885567        -19.443792     6.9542896      -6.506505
## 88        -33.805524        -22.667179     9.4755478      -7.819073
## 89        -20.614373        -16.964091     1.9515663      -8.729667
##    logF_apap_sul logKpre_apap logKpki_apap logKpli_apap logKpre_apap_cys
## 1     0.53130523 -0.289529459  -0.98199225   0.32392147       3.47218948
## 2     0.07956807 -0.351007359   0.21601736   0.99467641       0.78606165
## 3    -0.52122381 -0.393263127  -1.06155232  -0.09235355       0.95143688
## 4     0.16252315 -0.378561980   0.13835243   0.27175050      -0.82028265
## 5     1.21332440 -0.210042164  -1.70216056  -0.01216570       1.95650130
## 6    -2.38273975 -0.447413042  -1.62302840   0.04538435       0.48375835
## 7    -1.62626717 -0.141915196  -0.25363967  -0.25433011      -0.47339572
## 8    -0.11483624  0.169080083  -0.22627653   0.77940909      -0.22575829
## 9    -0.76383961 -0.582544183  -0.28073268   0.19985167      -1.10125503
## 10   -2.09845012 -0.184053808  -1.64833535  -0.07188382       0.70807155
## 11   -0.38164956 -0.139261412   0.21490868   0.12160740       0.98372701
## 12    0.93464938 -0.325316483   1.19947063  -1.10836795      -1.32556797
## 13   -0.39654199 -0.711679585   0.36238269   0.28424004      -1.58828559
## 14   -1.65763566  0.206371533  -1.79830029   1.24314406      -1.49319593
## 15   -0.75198842 -0.864334541   0.16324849   0.18282080       1.30127053
## 16   -1.71731049 -0.510513222  -1.15233524  -1.24679254      -0.38095619
## 17   -0.26382059  0.334869325  -1.23320363  -1.90097052       0.18535101
## 18    0.83550850 -0.467020582  -0.30446595  -1.03206919      -2.00286493
## 19   -0.25217031  0.306836159  -1.40520345  -1.59123528       0.66835376
## 20   -0.30860160 -0.495742054   0.73238777   0.63664679      -0.68334531
## 21   -1.30638452 -0.105015151  -2.20756739   0.47838590      -0.26380692
## 22    0.70466027 -0.136307053  -0.87007772   1.67964612      -0.94914150
## 23   -0.11602461 -0.935012962  -1.03015588  -0.09118133      -0.71084963
## 24   -0.03816575 -0.350052770   1.24578464  -0.39772953      -1.98264125
## 25   -0.68669306 -0.435543436   1.60725628  -1.82992469      -0.07639818
## 26   -0.97144504  0.241104626   0.27769967  -0.59989956       1.72232425
## 27    0.12180940  0.235264284   0.95029387  -0.29329765      -1.92122799
## 28   -0.00188430 -0.743635010  -2.81772364   0.85311485       0.72184926
## 29   -0.07417425 -0.312754966  -0.24303643  -1.55370073       0.21684599
## 30   -0.21127540  0.211466314  -2.00665367   0.15845657       1.26442466
```

```
## 31    0.08981890 -0.457868216   2.10163524  -0.05311578       0.16927351
## 32   -0.64207716 -0.811412853  -1.14333853  -1.50383135       0.38821509
## 33   -0.19924126  0.159043590   1.11981364   0.18282484      -0.65359913
## 34   -0.12395792 -0.942259399  -0.06683754   0.44126745       0.71938872
## 35   -0.16756081  0.496786651   1.04506437  -0.27993187      -1.25839386
## 36   -0.16995317  0.007228384  -2.18615837  -0.18623398       1.29138949
## 37   -0.30200084  0.143681104   0.51415431   1.73973543       1.11468385
## 38    1.16959028  0.492310749  -0.39960668  -0.02047813      -1.39484043
## 39   -0.44283685 -0.808601395   0.20523700   3.23262824      -0.59125632
## 40    1.40667891  0.059148225  -0.05079433  -1.20566654      -0.71198431
## 41    0.44902750  0.029655739   0.27621049   0.26571482       1.62573161
## 42    1.99827084 -0.778405110   0.68573822   0.62873809      -0.28441230
## 43    1.08874825  0.678658275  -0.83663212  -0.65928503      -0.02501278
## 44    0.66088330 -0.405074069  -1.72536685   0.80339385      -1.59432742
## 45    1.61224354  0.632236991   1.07109430  -0.45390420      -0.12216334
## 46   -1.15381793  0.280224033   0.55666580  -2.78750641      -0.02003887
## 47    0.57927036 -1.086029787   0.74074110   1.79968380      -0.28145280
## 48    1.50136206  0.715968003  -0.19789618  -2.35123663      -0.43453194
## 49   -3.14094761  0.606073828  -1.40257823   0.18134526      -0.34197434
## 50    0.60180720 -1.004322835   0.68602019  -0.40307325      -0.73077128
## 51    0.88834551  0.237160024   0.51752669  -0.42465561      -1.33256591
## 52   -0.98612078  0.616289462   1.59434865  -0.07959165       0.40278857
## 53    1.89147105 -0.151316077   0.56865636  -1.05630682      -0.83929325
## 54    1.61738781  0.651212612   0.19073423  -0.85103832      -0.36743440
## 55    0.87505891 -0.997080960  -0.26905995   0.21267217       0.41875273
## 56    1.32083677 -1.065047113   1.24377766  -0.04651201       0.89283024
## 57   -0.96103378  0.529073270  -0.02094705  -1.28652833      -0.28941603
## 58    0.47998321 -1.190493036   0.48730375  -2.49193612       0.73677649
## 59   -0.36560117 -0.856277635   0.53943653  -1.57742971       1.92806229
## 60   -1.73154305 -0.716695937   0.77392230  -0.92370669      -0.29838684
## 61   -0.22198080 -1.187042554  -0.51149677  -0.22798977       0.32751201
## 62    1.08184090  0.934916496   0.05363724   0.94399986       0.91936221
## 63   -1.58682217  0.913050408   0.84599461  -0.99700622      -0.84528304
## 64    0.42116208  0.984845516  -0.08479584  -0.36715417      -2.13594817
## 65   -0.31229579 -1.164083832   0.08716832   0.14854470      -0.18614840
## 66    0.58873573 -1.259491553   0.02596311   0.26088902      -0.13025881
## 67   -0.37810524 -1.384010809   0.69851884   0.20516217      -0.64246219
## 68   -0.33608157  1.014511245  -0.43561419  -0.42445466      -2.28663584
## 69   -0.52902650  0.718005792   1.74052826   1.45873176       1.43684548
## 70   -0.05204121 -1.058317623  -0.15338041   1.56788473      -0.07503521
## 71    1.38984984 -1.379608421   0.13777930  -0.11365133       0.32165612
## 72   -0.54853865 -1.012923867  -0.41700454   1.61113015      -2.05545812
## 73    1.58422467 -1.455181732  -1.42049339   0.35483143       0.49339888
## 74    0.03943062  1.068547720  -1.69712113   0.54710800      -0.62412037
## 75    0.34809524  1.052668988  -0.69471350  -0.61413989       0.67590225
## 76    0.15415928  1.063924709  -0.84271062  -1.53931441      -0.73891050
## 77    0.80679122  1.179192940  -0.76019345   0.01396253      -0.96508783
## 78    1.85772960  1.230166086  -0.07048473  -0.06799855      -1.30336817
## 79    0.23694406  1.176858555  -1.72202865   0.03697869       0.50326362
## 80    0.07601846 -2.282699468   0.09102538   1.60662560      -1.20339996
## 81    0.64959782 -2.093963899   0.74186987  -0.38840638      -0.42453379
## 82    0.24935571 -2.293401574  -1.23922367  -0.04874544       1.83161759
## 83   -0.70217075 -2.234503469  -0.51495646  -1.51922599      -0.75760392
## 84   -0.34358549 -2.715531891   0.17344464   0.87786833      -1.14567153
```

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## 85    0.43270192 -2.331204556  -1.02222105  -0.77545380      -1.96886494
## 86    1.12469976 -3.779246189   0.39462883   0.29211576       1.10835768
## 87   -0.18676911  1.357141941  -0.37639609   1.02929503      -0.13573892
## 88   -0.11515123  2.414915019  -1.03743004   0.12008966       0.09203630
## 89    1.51652574  2.414538924   0.28684785  -0.13773191       0.70344144
##    logKpki_apap_cys logKpli_apap_cys logKpre_apap_glu logKpki_apap_glu
## 1      -0.998130592     -0.707898766      -1.17134466     -0.458621727
## 2       1.487664386      0.539193775       0.59384094      0.689422865
## 3       1.305501161      0.441398363       0.79861939      0.381016302
## 4      -0.122292805     -0.278454893      -0.67568756      0.138424894
## 5       1.206910969      0.619861751       0.56616610     -1.133673645
## 6      -0.100020554     -0.149255939       0.68529671     -0.290426884
## 7      -1.275868982      1.300110984       0.29705217     -0.001699886
## 8       0.950559072      0.817978819      -0.97847123      1.798472389
## 9       1.553929341     -0.060958296       0.40662359     -0.226688945
## 10     -1.120932435      1.175348438       0.13302629      0.950183770
## 11     -0.901240406      0.384889946      -0.80022553      0.096923417
## 12     -0.027160597      1.630974831      -0.14789342     -0.833003846
## 13      1.460128731      0.062986125       1.10241741      0.329153219
## 14     -0.182357081      1.939423866      -1.67051730      1.361428459
## 15      0.099312929      0.416032678      -0.16023682     -0.034295488
## 16     -0.087116935     -0.305213517      -0.08874721     -1.297664920
## 17      2.023732811      3.297280430       0.27889168      0.311531574
## 18     -0.396678353      0.712718765      -0.72369990     -0.619872401
## 19      2.008403086     -0.103452725       0.35996783     -0.307507466
## 20      0.199638408      0.807127194      -2.90601063      0.486440404
## 21     -0.907379652     -0.131710279       1.43358303     -0.150466757
## 22     -0.190253050     -1.060445883       0.39425390      1.017995282
## 23      0.395828396      0.409418880      -0.67308561      0.403253178
## 24     -0.608992826      0.224323977      -0.83645741     -1.175800742
## 25     -1.210405035     -0.004376973       1.14576469      0.400677477
## 26      0.660152207      2.811724669      -1.70671068      1.373227187
## 27      1.415210210      0.988929287      -0.67073775     -0.065189909
## 28     -0.942904968     -0.848647693      -1.35934329      1.126972991
## 29     -2.481075878     -0.098638135      -0.57347995     -0.461841731
## 30     -0.932718694     -0.260102170       0.60441076     -0.664836192
## 31     -0.422913131      0.037201903       1.00294552     -1.352290399
## 32      0.362430008      2.176292604       0.33766915     -0.374797515
## 33     -1.378564575      1.150414255      -1.29126081      2.009271636
## 34     -0.560236479     -1.285121322       0.85323959     -0.480631219
## 35     -0.255519924      1.257843427      -1.40730221      0.084958441
## 36      0.982346888      1.161400209       1.18085504      0.561681949
## 37      2.328565033      0.709261002      -0.48980623     -0.069376783
## 38      0.086099429     -1.660099372      -0.64665158      1.060345567
## 39      0.264963404     -0.262365072       0.60242542     -0.335549067
## 40      1.037696247      0.198541759      -1.07981424      2.151096150
## 41     -0.779767734     -0.759710122       0.52698917     -0.353106224
## 42      0.031048736     -0.852638531      -0.20525908     -0.865311608
## 43     -0.149339601      1.102814774      -1.56678169      1.559903069
## 44      0.516028044      0.626563356      -0.01410393     -1.191170071
## 45     -0.467415605     -0.119282491      -0.31254824     -0.248429498
## 46     -0.121078010      0.862178659       1.56728788     -0.018884835
## 47     -2.285746905      0.586444621       0.17928326      1.562965279
## 48      1.273716426     -1.858304361      -0.72915414      0.655362636
```

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## 49      1.327574774     -1.011161606      -0.82377162     -0.830733581
## 50      0.007103653     -0.685610546      -1.88956952      0.879343770
## 51     -2.318492003      0.325574066      -1.70623817     -0.570068658
## 52     -0.073422256     -1.813689748       0.84601315      0.943510170
## 53     -0.553957641      0.172104182      -0.02813746     -1.093069112
## 54      0.542281420      0.651432311      -2.13063464     -0.189632019
## 55     -2.464475767     -0.360627413       0.15995635      2.280070076
## 56      1.700900515      1.067152987      -0.77276603     -0.816819494
## 57      0.387884707     -2.180189036      -0.15515840      1.731935780
## 58     -0.724888590     -0.283820476       0.52733653      0.524987352
## 59      0.215251573     -0.888493111      -0.85232541      2.423033714
## 60     -1.553757144     -0.271756987      -0.43028227     -1.027187688
## 61     -0.247822034      0.971343922      -1.22110507     -0.404052944
## 62     -0.127966749      0.497673307      -0.20140535      0.810071428
## 63      0.102100805      1.701522401       0.11504875     -0.973563430
## 64      0.239152800     -0.687758838      -0.10409634      1.017452713
## 65      1.727173970     -0.195355048       0.17567015     -0.687990204
## 66     -0.179688857     -0.387854110      -0.33389352     -0.510931431
## 67     -0.713966421      0.616695739      -0.71855631      0.062210632
## 68     -0.065730613      0.439517771       0.74003013     -0.430089831
## 69      0.209922409      0.327468658       0.08886099     -0.436029548
## 70     -1.092240850      1.320548913      -0.22343227     -1.072188681
## 71      0.038421267      2.185397279      -0.35306429     -0.847209239
## 72     -0.088795890     -0.536234428      -0.47503850     -1.391681118
## 73     -0.022640899     -2.441588382       0.52714676     -1.418155636
## 74      0.003346571     -0.253038634      -0.34645907     -2.265923936
## 75     -1.021744723     -0.190155402       0.10853519      0.080358585
## 76     -0.029150831      1.058452749      -0.10363841     -1.181892928
## 77      0.357385777     -1.240447527       0.49246106     -0.676240802
## 78      0.144077776     -0.824432826      -0.12554561     -2.207673944
## 79      2.358295220     -0.264215494       1.87519232     -0.178966749
## 80     -0.305609432     -0.086454767       0.99248239      0.302210498
## 81      1.468188230      0.437650484      -2.17709268      0.119652235
## 82     -0.090286997     -0.194173341       1.16347463     -0.857436874
## 83     -1.907018960      0.605470383      -0.59411572      0.543228739
## 84      0.497960139      1.014974672       1.84280190      1.301363345
## 85     -0.366960259      2.026804600      -0.63584496     -0.319512468
## 86     -0.860882909      0.187089347      -0.33618236      2.065833813
## 87      0.712902515      1.145647652      -2.04061469     -0.133938720
## 88     -0.556484610      0.196045220       0.18361163     -0.084888070
## 89      0.989076441      2.156458217      -0.59542379     -0.763530563
##    logKpli_apap_glu logKpre_apap_sul logKpre_co2c13 logKpli_co2c13
## 1       1.282060080      0.861066093   -1.805059873    -1.09587845
## 2      -1.274362216     -2.027940161   -1.633473594     0.29644310
## 3      -0.774665588     -1.523719491    0.313087300     0.36343443
## 4       0.494936595     -0.527170421   -0.846464285    -1.11501702
## 5      -1.423174522     -1.480955643    0.990127114    -0.47693967
## 6       1.705784622     -1.322353947   -1.262116823    -0.91857810
## 7       0.504852621     -0.846161955   -1.344280581    -0.11496525
## 8       0.021033206     -1.928978840   -0.717541050    -0.77004855
## 9      -0.514611893     -0.126918402   -0.242655740    -2.28348329
## 10      0.136658458     -0.433764920   -1.117189926     0.62007143
## 11      0.557741786      0.725235947   -1.155455566     0.06092036
## 12      2.375683893     -0.966625897   -1.455894843     0.58188916
```

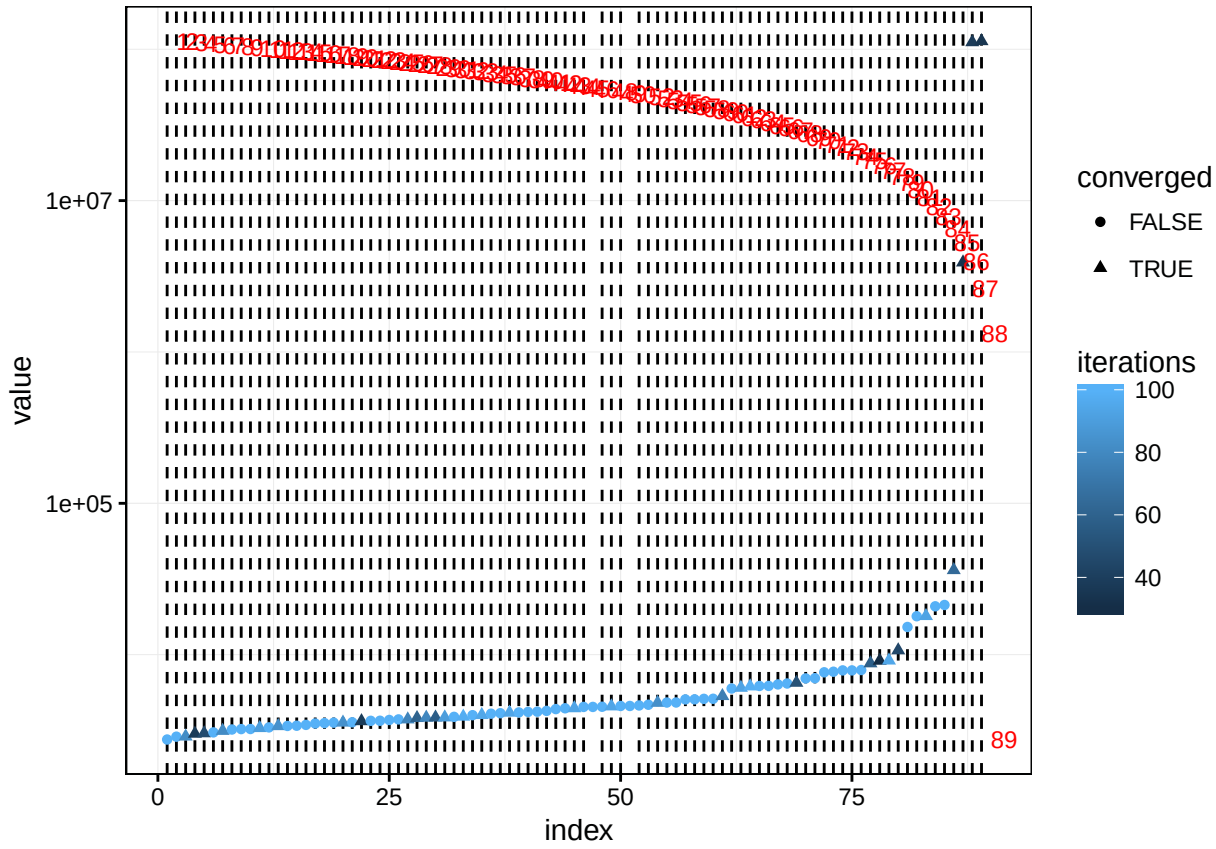
```
## 13      0.627104709    -1.652689837   -1.149438538     1.42082050
## 14      2.100364265    -1.476714526   -0.897713856     0.50973833
## 15     -1.837505752    -2.280463122   -1.284804555    -0.54565216
## 16     -0.456669825     0.946898422   -0.868544031     0.82324626
## 17     -0.267850361    -2.717060444   -0.125051726     0.74117351
## 18     -1.720966976     0.636143336   -1.841797927     0.21444183
## 19     -0.811356843    -1.562103326   -0.568134715     1.55499997
## 20     -0.715986034     1.079280426   -0.948414650    -0.61867588
## 21      1.234789881    -0.739387806   -0.336921465    -2.00724623
## 22      0.005796899    -0.500712336   -0.631383460    -1.00295256
## 23      0.740211566    -0.093874599   -1.117401371    -1.42491943
## 24     -1.576535596     0.608846282   -2.755573533     0.65154688
## 25     -0.271684090    -0.199343527   -0.314995354    -0.55100445
## 26     -0.215786848    -0.132715718    0.277820879    -0.39488656
## 27      1.414868073    -0.092686341   -1.377581088     1.46255190
## 28     -0.880862209     0.212231391   -0.921278562     0.96193336
## 29      1.914062223     0.024398538   -0.052885291     0.80366286
## 30      1.319431591    -0.487599855   -0.115054891    -1.17859665
## 31      0.133715209    -0.166683120   -0.429556102    -1.01714891
## 32     -1.039341261     0.524970203    1.759273520     0.30350751
## 33      1.016830779     0.007173397   -0.820751554    -0.84787077
## 34      1.484676801    -0.882656857   -0.917013444    -0.69553086
## 35      0.027915518    -0.577991537    0.019603618     1.64393390
## 36      0.246020485     0.356052699   -1.714614333     1.22070585
## 37     -1.472195858     1.191569408   -0.007618617     0.86537918
## 38      0.002423825    -0.345813226   -2.199029518    -0.42551599
## 39      1.020864278     0.491031536   -1.270172336    -1.12277405
## 40     -0.230009744     0.331211080   -0.851606108    -0.16858549
## 41     -2.024882318     1.195962034   -1.662128930     0.60092527
## 42     -0.163098929     1.629390676   -2.497824850    -2.49580958
## 43      0.091422277    -1.215400900   -0.482808092    -2.28081287
## 44     -0.195324553    -1.566849076   -1.203963753     1.28185188
## 45     -0.816548569    -1.329712293   -1.811019403     1.07844187
## 46     -0.459481951     0.017570668    0.478980656     0.39376835
## 47     -1.247897987    -0.181523379   -1.812472038     0.20850008
## 48      0.155882265    -1.327976545   -2.642851781    -0.11017246
## 49     -1.073732126    -0.483308291   -2.041132192    -1.08169996
## 50     -1.168941037    -0.139854547   -1.896133936     0.49255276
## 51      0.219665894     2.207274595   -0.582690803    -0.44548323
## 52      1.507004981    -2.191565398   -0.594876614     0.05527398
## 53     -1.799809506    -2.833808328   -1.213462689    -0.31870661
## 54      0.253884837     0.594379839   -0.760152781     0.02368172
## 55     -0.649355362    -0.803241814    0.045447330     2.10947940
## 56      0.316843016     1.452030538   -2.377610995    -0.88266603
## 57      1.000368557     0.384329140    0.331151797    -0.01908245
## 58      0.699647878    -1.277520791   -1.788136938    -0.95063246
## 59      1.712871527     0.934027593    0.535915465    -0.66707264
## 60     -0.504131148    -1.224960440   -1.406235860     0.43292809
## 61      0.035498144     0.484589237    0.076718478    -0.12124554
## 62      1.225297438    -1.726230003   -0.745369744    -1.35379910
## 63      1.017987342    -0.370909641   -2.149723341     1.39976814
## 64     -1.219846657    -1.027433461   -0.560273076    -1.62136269
## 65      0.659116589    -1.237672239   -0.423686786    -3.23048227
## 66      1.101136599    -0.534970951   -0.997657136    -0.35262965
```

```
## 67      0.082786540      0.828870215    0.248706210    -0.69077096
## 68     -1.189445920     -0.909826835    0.827444860    -0.62915512
## 69     -0.266644294      0.468266470   -2.491922139     1.37042538
## 70     -0.558575170      0.092850164   -0.513902657     0.87360748
## 71      0.124797094      0.743647051   -2.897509560    -0.51609860
## 72      0.523391252     -1.042306721    0.134738941     1.02780262
## 73     -0.470411033      0.873550582   -2.074494238     2.11339557
## 74     -0.254146157      1.847222269    0.377478441    -0.88160030
## 75      0.332323590      0.798165947    1.113148543     1.10913087
## 76      1.194482373      1.391678227    0.587557420     0.62516359
## 77     -1.073433449     -0.913785772   -0.146429376    -0.15618799
## 78      0.373923492     -1.214399990   -0.981816316    -0.39010096
## 79      0.226432571      1.571264182   -0.797911996     0.41526264
## 80     -1.759072417     -0.559640805   -2.595637276     2.76996687
## 81     -1.423956388     -1.798801843   -1.425711720    -1.71906999
## 82     -0.093672421     -1.336051187   -0.675397305    -0.17655609
## 83     -0.312214650     -0.447101844    0.572052427    -3.52207856
## 84      1.177981733      0.032481493   -0.253083057    -0.69336411
## 85      0.134258554      0.274525235    0.337561228    -2.65460711
## 86      0.392476610     -0.768417149   -0.342380644     0.49458163
## 87     -0.517792516      0.161331058   -1.165786248     0.07318598
## 88      1.038589643     -1.694070570    0.175189356     0.37015322
## 89      0.022325338     -1.900046417   -1.314242030     1.10473092
##    logKpre_metc13 logKpli_metc13
## 1    -2.424287519    -0.43550589
## 2    -1.307453754    -0.58786078
## 3     0.067282300     1.28347979
## 4    -2.525330958     1.12137663
## 5    -1.058665486     1.36244939
## 6    -1.330211806     1.48173817
## 7    -1.521197619    -0.34876483
## 8    -0.981387461     1.46273112
## 9    -0.622343995     0.47719461
## 10   -2.474499960    -0.70486286
## 11   -0.922558876    -1.38825632
## 12   -1.424743757    -0.61001960
## 13   -0.923007464     0.74188196
## 14   -0.735330032    -0.03801987
## 15   -1.157260416     0.66202417
## 16   -1.380249784    -1.44045841
## 17   -2.774995603     0.41587603
## 18   -2.313817683     0.64459880
## 19   -0.779101135     0.56015034
## 20   -2.467125007    -0.54584228
## 21   -0.824210232     2.08018294
## 22   -1.551012909     0.57390416
## 23   -2.894424475     0.22629647
## 24   -1.431754911     1.05511935
## 25   -1.690676923     1.12984210
## 26   -0.550164455     0.28407366
## 27   -0.612048895     0.31431725
## 28   -1.217970088    -0.96372878
## 29   -2.368677263     0.52960470
## 30   -1.405501699     0.43790225
```

```
## 31   -0.981637440    -0.62241384
## 32   -0.909719940     0.81282824
## 33   -1.823580296     1.09258944
## 34   -2.245862092     0.23396343
## 35    0.781941011    -1.18609337
## 36    0.120932178     1.22639919
## 37   -2.474430636    -2.46835720
## 38   -0.499007803    -0.99303198
## 39   -2.194371096     1.25247762
## 40    1.170846239    -1.20320550
## 41   -2.784618012     0.28118570
## 42   -2.821568272    -0.09352912
## 43   -2.009711336     0.51337937
## 44   -1.157926361     0.14654287
## 45   -1.668614314     0.07687509
## 46   -1.497152815    -1.08292034
## 47   -1.991595032    -0.18968878
## 48    0.752822799     0.34085960
## 49   -0.007025017     1.56421143
## 50   -1.227640490     1.55831881
## 51   -0.156597388    -0.55632642
## 52    0.627885214     0.44394514
## 53   -2.427712730     1.17061325
## 54    0.115149651     0.25782244
## 55   -1.140228803    -1.55376482
## 56   -1.947706737    -0.44396372
## 57   -1.941092665    -1.32342695
## 58   -2.061190220     0.59125813
## 59   -0.954743637     1.50136386
## 60   -1.318645173    -0.83395317
## 61   -2.088013795    -1.66254401
## 62   -0.569491718    -0.78446502
## 63   -1.868925351     2.41499358
## 64   -2.072987018     0.03116380
## 65   -0.135287730     0.38583673
## 66   -1.922052519     1.33373145
## 67   -1.257906017     0.87804723
## 68   -0.109847243     0.26006614
## 69   -0.655293701     0.64823697
## 70    0.358727404    -1.29891611
## 71   -0.961921505    -0.14650365
## 72    0.034648873     0.89193957
## 73    0.267603178    -0.15116114
## 74   -2.299079543    -0.32019558
## 75   -2.006792245     0.87253501
## 76   -0.623131488     1.14547266
## 77   -1.478734531    -1.06352648
## 78   -1.782322863     2.21732648
## 79   -2.918464959    -0.39606640
## 80   -1.654114934    -1.45563817
## 81   -1.435440526     0.93129068
## 82   -1.908779700     0.09853710
## 83   -1.150998435    -0.22058383
## 84   -1.391650855     0.02612314
```

```
## 85   -2.396878946    -1.65384683
## 86   -1.220839026     0.58007643
## 87   -1.643761790     0.03687322
## 88   -1.546729751     1.09810640
## 89   -2.452620490     0.24500850
```

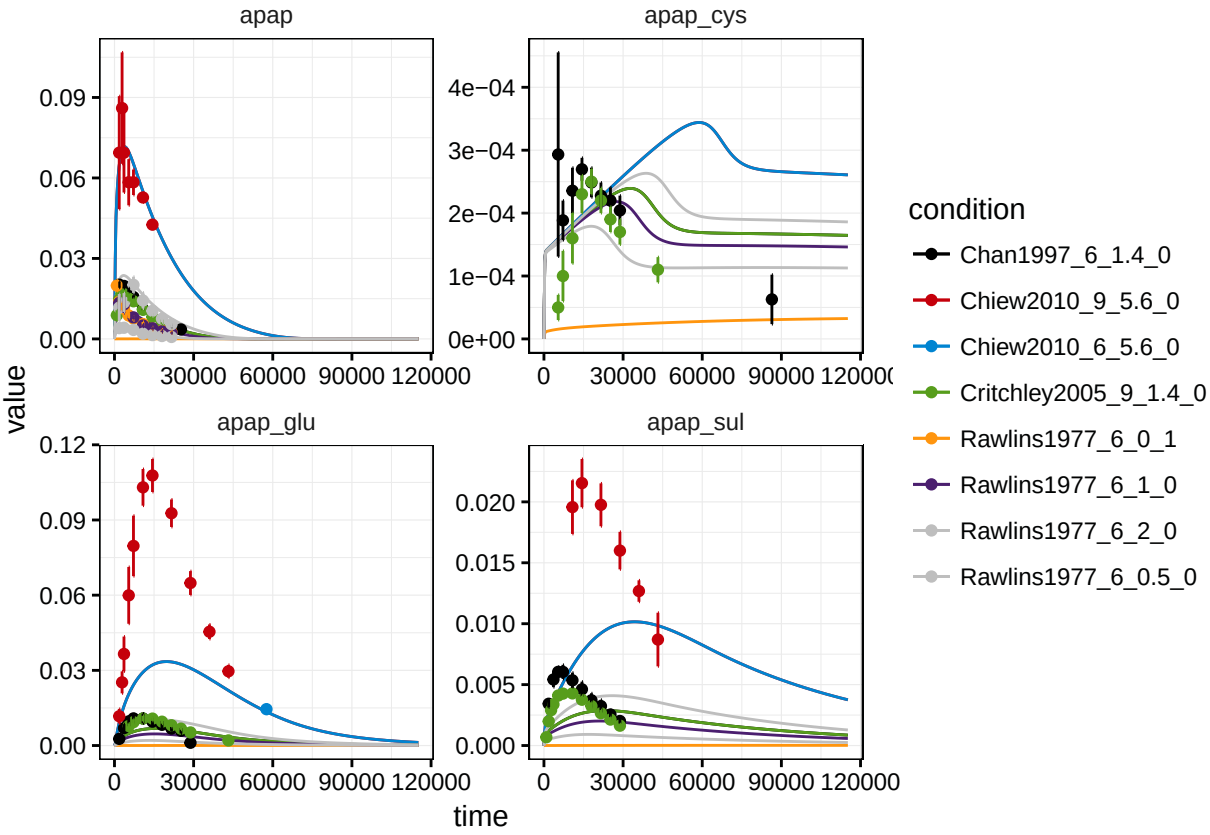
```
plotValues(myfit1 %>% as.parframe())+scale_y_log10()
```




```
mypred1 <- (g*x*p1)(mytimes*4, myfit1 %>% as.parframe() %>% as.parvec)
```

```
## Warning: Parameter vector of an unconverged fit is selected.
```

```
plotCombined(mypred1, mydatalist, name %in% names(observables))
```



Free other parameters 2 - not good

Here I freed some less parameters than in try 1 but it suffers from the same problem

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters2 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap_sul", "F_apap_sul"    #,   # total dumm, Ka und F sind so redundant wie e
                      # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu",
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
```

```
                    )

fixed_parameters2 <- pars[!(names(pars)%in%c(free_parameters2,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters2] <- paste0("exp(log", free_parameters2, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p2 <- NULL
for(i in 1:length(p_list)) { p2 <<- p2 + p_list[[i]]}

pouter <- log(pars[free_parameters2]) %>% set_names(paste0("log",names(.)))


# mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj2 <- normL2(mydatalist, (g*x*p2))

# job2 <- runbg({myfit <- mstrust(objfun = obj2, center = pouter, studyname = "methacetin", cores = 12,
#
```

```
# myfit2 <- job2$get()$knecht4
# save(myfit2, file = "myfit2.rda")
# job2$purge()
load("myfit2.rda")
myfit2 %>% as.parframe()
```

```
##     index    value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1      24 3134.039      TRUE         25         -5.067594     -2.064909
## 2      56 3134.040      TRUE         30         -5.067589     -2.064904
## 3      20 3134.040      TRUE         26         -5.067595     -2.064908
## 4      89 3134.040      TRUE         16         -5.067592     -2.064905
## 5      37 3134.040      TRUE         86         -5.067589     -2.064901
## 6      32 3134.040      TRUE         20         -5.067590     -2.064902
## 7      15 3134.040      TRUE         98         -5.067588     -2.064901
## 8      38 3134.041      TRUE         84         -5.067592     -2.064906
## 9      34 3134.041      TRUE         29         -5.067590     -2.064903
## 10     49 3134.041      TRUE         24         -5.067591     -2.064904
## 11     35 3134.041      TRUE         54         -5.067591     -2.064903
## 12      1 3134.041      TRUE         30         -5.067592     -2.064904
## 13     85 3134.041      TRUE         26         -5.067590     -2.064903
## 14     79 3134.041      TRUE         18         -5.067591     -2.064904
## 15     12 3134.041      TRUE         24         -5.067590     -2.064903
```

```
## 16     76 3134.041      TRUE         73        -5.067592     -2.064904
## 17     67 3134.042      TRUE         86        -5.067590     -2.064902
## 18      6 3134.043      TRUE         40        -5.067589     -2.064901
## 19     57 3134.043      TRUE         72        -5.067590     -2.064903
## 20      3 3134.043      TRUE         97        -5.067590     -2.064902
## 21     48 3134.043     FALSE        100        -5.067589     -2.064902
## 22     13 3134.043      TRUE         43        -5.067589     -2.064901
## 23     28 3134.043      TRUE         69        -5.067589     -2.064902
## 24     72 3134.043     FALSE        100        -5.067589     -2.064901
## 25     93 3134.043      TRUE         83        -5.067589     -2.064901
## 26     78 3134.043      TRUE         88        -5.067592     -2.064906
## 27     88 3134.043      TRUE         88        -5.067589     -2.064901
## 28     87 3134.043      TRUE        100        -5.067589     -2.064901
## 29     66 3134.043      TRUE         32        -5.067589     -2.064901
## 30      4 3134.043      TRUE         75        -5.067589     -2.064902
## 31     30 3134.043      TRUE         69        -5.067589     -2.064901
## 32     68 3134.043      TRUE         43        -5.067589     -2.064902
## 33     95 3134.043      TRUE         69        -5.067589     -2.064901
## 34     91 3134.043      TRUE         58        -5.067589     -2.064901
## 35     96 3134.043     FALSE        100        -5.067592     -2.064905
## 36     99 3134.043      TRUE         49        -5.067589     -2.064901
## 37     41 3134.043      TRUE         64        -5.067589     -2.064901
## 38     47 3134.043      TRUE         70        -5.067589     -2.064901
## 39     17 3134.043      TRUE         27        -5.067589     -2.064901
## 40     33 3134.043      TRUE         77        -5.067590     -2.064902
## 41     39 3134.043      TRUE         93        -5.067589     -2.064901
## 42     55 3134.043      TRUE         95        -5.067589     -2.064902
## 43     65 3134.043      TRUE         68        -5.067597     -2.064909
## 44     42 3134.043      TRUE         60        -5.067589     -2.064901
## 45     75 3134.043      TRUE         73        -5.067589     -2.064901
## 46     18 3134.043      TRUE         96        -5.067589     -2.064901
## 47     70 3134.043      TRUE         53        -5.067589     -2.064901
## 48     63 3134.043      TRUE         47        -5.067589     -2.064901
## 49     25 3134.043      TRUE         40        -5.067589     -2.064901
## 50     23 3134.043      TRUE         47        -5.067591     -2.064903
## 51     82 3134.043      TRUE         81        -5.067590     -2.064902
## 52     83 3134.043      TRUE         38        -5.067589     -2.064901
## 53     10 3134.043      TRUE         35        -5.067588     -2.064901
## 54     92 3134.043      TRUE         85        -5.067588     -2.064901
## 55     11 3134.043      TRUE         38        -5.067589     -2.064901
## 56     44 3134.043      TRUE         68        -5.067588     -2.064900
## 57     69 3134.043      TRUE         91        -5.067738     -2.065067
## 58     29 3134.043      TRUE         36        -5.067589     -2.064901
## 59     46 3134.043      TRUE         66        -5.067589     -2.064901
## 60     53 3134.043      TRUE         68        -5.067589     -2.064901
## 61      5 3134.043      TRUE         86        -5.067597     -2.064911
## 62     36 3134.043      TRUE         62        -5.067590     -2.064903
## 63     43 3134.043      TRUE         36        -5.067589     -2.064902
## 64    100 3134.043      TRUE         80        -5.067592     -2.064904
## 65     77 3134.043      TRUE         32        -5.067589     -2.064902
## 66      7 3134.043     FALSE        100        -5.067593     -2.064905
## 67     14 3134.043      TRUE         58        -5.067589     -2.064902
## 68     86 3134.043      TRUE         70        -5.067594     -2.064907
## 69     64 3134.043      TRUE         42        -5.067587     -2.064899
```

```
## 70     26 3134.043      TRUE         83         -5.067590     -2.064902
## 71     58 3134.043     FALSE        100         -5.067592     -2.064905
## 72     22 3134.043      TRUE         95         -5.067589     -2.064902
## 73      8 3134.043      TRUE         99         -5.067590     -2.064903
## 74      9 3134.043     FALSE        100         -5.067597     -2.064910
## 75     40 3134.043      TRUE         69         -5.067590     -2.064902
## 76     81 3134.043      TRUE         34         -5.067589     -2.064901
## 77     31 3134.043      TRUE         52         -5.067590     -2.064902
## 78     60 3134.043      TRUE         75         -5.067589     -2.064901
## 79     97 3134.043      TRUE         47         -5.067589     -2.064901
## 80     62 3134.043      TRUE         38         -5.067589     -2.064901
## 81     52 3134.043     FALSE        100         -5.067620     -2.064936
## 82     21 3134.043      TRUE         29         -5.067589     -2.064901
## 83     71 3134.043      TRUE         38         -5.067588     -2.064900
## 84     45 3134.043      TRUE         95         -5.067590     -2.064902
## 85     80 3134.043     FALSE        100         -5.067595     -2.064908
## 86     50 3134.043      TRUE         87         -5.067589     -2.064901
## 87     59 3134.043      TRUE         31         -5.067631     -2.064949
## 88     51 3134.043      TRUE         36         -5.067591     -2.064903
## 89     90 3134.043      TRUE         99         -5.067589     -2.064901
## 90     94 3134.236     FALSE        100         -5.072988     -2.070559
## 91     16 3134.847     FALSE        100         -5.085960     -2.084597
## 92     54 3135.270     FALSE        100         -5.100551     -2.100649
## 93     27 3141.378     FALSE        100         -5.132553     -2.135214
## 94     61 3142.242     FALSE        100         -5.144611     -2.148534
## 95     74 3148.674     FALSE        100         -5.189691     -2.198443
## 96     98 3149.057     FALSE        100         -5.201278     -2.211419
## 97     84 3149.328     FALSE        100         -5.222949     -2.235767
## 98     73 3153.326     FALSE        100         -5.117386     -2.117684
## 99      2 3157.072     FALSE        100         -5.360419     -2.391311
## 100    19 3204.874     FALSE        100         -5.169191     -2.174207
##     logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap_sul
## 1           -6.117757        -10.485193     -6.241245      -7.346186
## 2           -6.117757        -10.485205     -6.241296      -7.021465
## 3           -6.117758        -10.485007     -6.240447      -7.216762
## 4           -6.117758        -10.485007     -6.240447      -6.306130
## 5           -6.117757        -10.485014     -6.240481      -7.986534
## 6           -6.117757        -10.485010     -6.240461      -7.899805
## 7           -6.117757        -10.485008     -6.240455      -7.097906
## 8           -6.117757        -10.485009     -6.240457      -6.773478
## 9           -6.117757        -10.484998     -6.240412      -7.826948
## 10          -6.117757        -10.485018     -6.240496      -7.430659
## 11          -6.117757        -10.485009     -6.240457      -8.325042
## 12          -6.117757        -10.485009     -6.240458      -6.858966
## 13          -6.117757        -10.484992     -6.240384      -7.951857
## 14          -6.117757        -10.485010     -6.240460      -7.758526
## 15          -6.117757        -10.485009     -6.240458      -6.824439
## 16          -6.117757        -10.485009     -6.240457      -7.953311
## 17          -6.117757        -10.485010     -6.240462      -7.633372
## 18          -6.117758        -10.485009     -6.240455      -7.301644
## 19          -6.117758        -10.484994     -6.240391      -6.863408
## 20          -6.117758        -10.485000     -6.240419      -8.422053
## 21          -6.117758        -10.485014     -6.240480      -7.900159
## 22          -6.117758        -10.485008     -6.240451      -6.620140
```

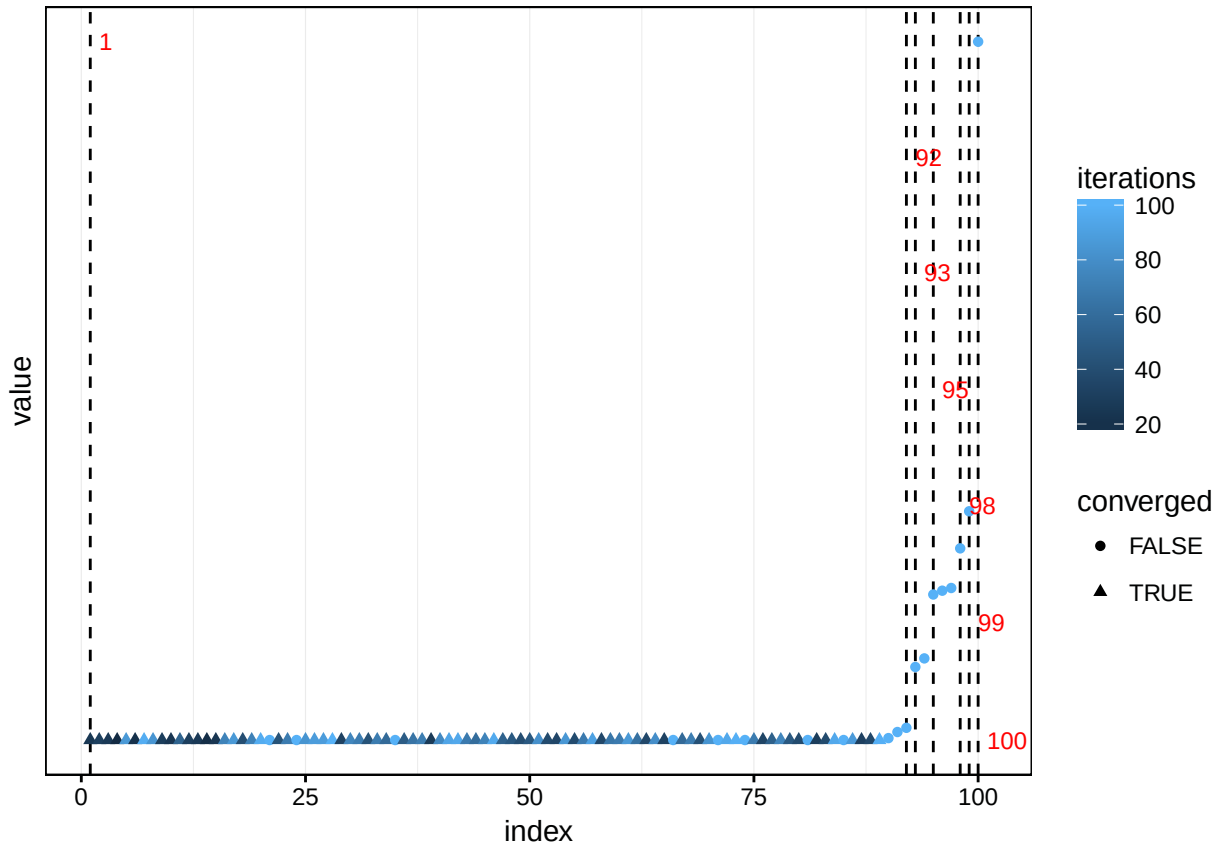
```
## 23        -6.117758       -10.485006     -6.240445      -7.724103
## 24        -6.117758       -10.485022     -6.240514      -7.621225
## 25        -6.117758       -10.485007     -6.240447      -8.076138
## 26        -6.117757       -10.485066     -6.240700      -6.094647
## 27        -6.117758       -10.485007     -6.240450      -7.924491
## 28        -6.117758       -10.485012     -6.240472      -6.729279
## 29        -6.117758       -10.485006     -6.240444      -7.037596
## 30        -6.117758       -10.485009     -6.240457      -8.081180
## 31        -6.117758       -10.485007     -6.240450      -8.083907
## 32        -6.117758       -10.485015     -6.240484      -7.758361
## 33        -6.117758       -10.485006     -6.240443      -7.466215
## 34        -6.117758       -10.485015     -6.240484      -7.832626
## 35        -6.117758       -10.484985     -6.240352      -8.628375
## 36        -6.117758       -10.485016     -6.240486      -8.222905
## 37        -6.117758       -10.485008     -6.240451      -6.723260
## 38        -6.117758       -10.485006     -6.240444      -7.264485
## 39        -6.117758       -10.485016     -6.240485      -8.602704
## 40        -6.117758       -10.484994     -6.240392      -6.459756
## 41        -6.117758       -10.485017     -6.240492      -7.544547
## 42        -6.117758       -10.485017     -6.240489      -5.370935
## 43        -6.117758       -10.484859     -6.239815      -6.889316
## 44        -6.117758       -10.485014     -6.240479      -7.674437
## 45        -6.117758       -10.485023     -6.240515      -6.878867
## 46        -6.117758       -10.485012     -6.240469      -7.870748
## 47        -6.117758       -10.485014     -6.240476      -9.751996
## 48        -6.117758       -10.485017     -6.240489      -7.086394
## 49        -6.117758       -10.485013     -6.240475      -7.548514
## 50        -6.117758       -10.484981     -6.240334      -7.926227
## 51        -6.117758       -10.485009     -6.240459      -5.360426
## 52        -6.117758       -10.485012     -6.240471      -6.374001
## 53        -6.117758       -10.485017     -6.240492      -6.764125
## 54        -6.117758       -10.485012     -6.240468      -6.311120
## 55        -6.117758       -10.485008     -6.240451      -5.003082
## 56        -6.117758       -10.485011     -6.240467      -8.309823
## 57        -6.117760       -10.485048     -6.240622      -5.744147
## 58        -6.117758       -10.485008     -6.240452      -8.630622
## 59        -6.117758       -10.485013     -6.240473      -8.204039
## 60        -6.117758       -10.485012     -6.240471      -8.265124
## 61        -6.117758       -10.485084     -6.240776      -6.561199
## 62        -6.117758       -10.484985     -6.240355      -7.580932
## 63        -6.117758       -10.485017     -6.240491      -7.212485
## 64        -6.117758       -10.484987     -6.240360      -8.467135
## 65        -6.117758       -10.485004     -6.240437      -8.386056
## 66        -6.117758       -10.484973     -6.240303      -8.802637
## 67        -6.117758       -10.485015     -6.240483      -8.065600
## 68        -6.117758       -10.484939     -6.240157      -7.328900
## 69        -6.117757       -10.485015     -6.240482      -7.438690
## 70        -6.117758       -10.485006     -6.240446      -7.743426
## 71        -6.117757       -10.485121     -6.240935      -6.636899
## 72        -6.117758       -10.485017     -6.240492      -8.332596
## 73        -6.117758       -10.485004     -6.240435      -7.372087
## 74        -6.117757       -10.485075     -6.240740      -7.701129
## 75        -6.117758       -10.485005     -6.240440      -5.973226
## 76        -6.117758       -10.485007     -6.240450      -6.943434
```

```
## 77          -6.117758       -10.485003     -6.240432      -6.978083
## 78          -6.117758       -10.485010     -6.240460      -7.772966
## 79          -6.117758       -10.485013     -6.240472      -5.740024
## 80          -6.117758       -10.485015     -6.240482      -6.545088
## 81          -6.117758       -10.485003     -6.240432      -5.032193
## 82          -6.117758       -10.485012     -6.240471      -6.867766
## 83          -6.117758       -10.485011     -6.240467      -8.003600
## 84          -6.117758       -10.485008     -6.240451      -7.419175
## 85          -6.117758       -10.485037     -6.240578      -7.366526
## 86          -6.117758       -10.485014     -6.240477      -7.432317
## 87          -6.117758       -10.485033     -6.240559      -8.234264
## 88          -6.117758       -10.484999     -6.240415      -8.890686
## 89          -6.117758       -10.485013     -6.240473      -7.313897
## 90          -6.117895       -10.452591     -6.105774      -7.724368
## 91          -6.118149       -10.415221     -5.963818      -7.582200
## 92          -6.118396       -10.397979     -5.901902      -7.207008
## 93          -6.119011       -10.251600     -5.444835      -6.382093
## 94          -6.119207       -10.229393     -5.386392      -7.777271
## 95          -6.119909       -10.128703     -5.129865      -7.654788
## 96          -6.120082       -10.124574     -5.119997      -6.553108
## 97          -6.120402       -10.125013     -5.120947      -7.153079
## 98          -6.118807       -10.119940     -5.101261      -6.291966
## 99          -6.122342       -10.056328     -4.962965      -4.997942
## 100         -6.118971        -9.274207     -3.615027      -8.136824
##     logF_apap_sul
## 1   41.1113216771
## 2   43.9336695182
## 3   50.9705455639
## 4   43.7260207762
## 5    7.3976591725
## 6   34.0398396151
## 7    7.2430744380
## 8   25.6954041482
## 9   22.3016832414
## 10   5.6779325637
## 11  20.4219452288
## 12  28.1907876512
## 13  30.7782514167
## 14  23.5520922139
## 15  28.5363470959
## 16   6.2879904781
## 17   7.2134134353
## 18   5.7641203459
## 19   0.1668586759
## 20   1.7450813763
## 21   1.2069431429
## 22  -0.0879249592
## 23   1.0101041897
## 24   0.9114733680
## 25   1.3685427213
## 26  -0.6425088877
## 27   1.1953679056
## 28   0.0004494418
## 29   0.2782588467
```

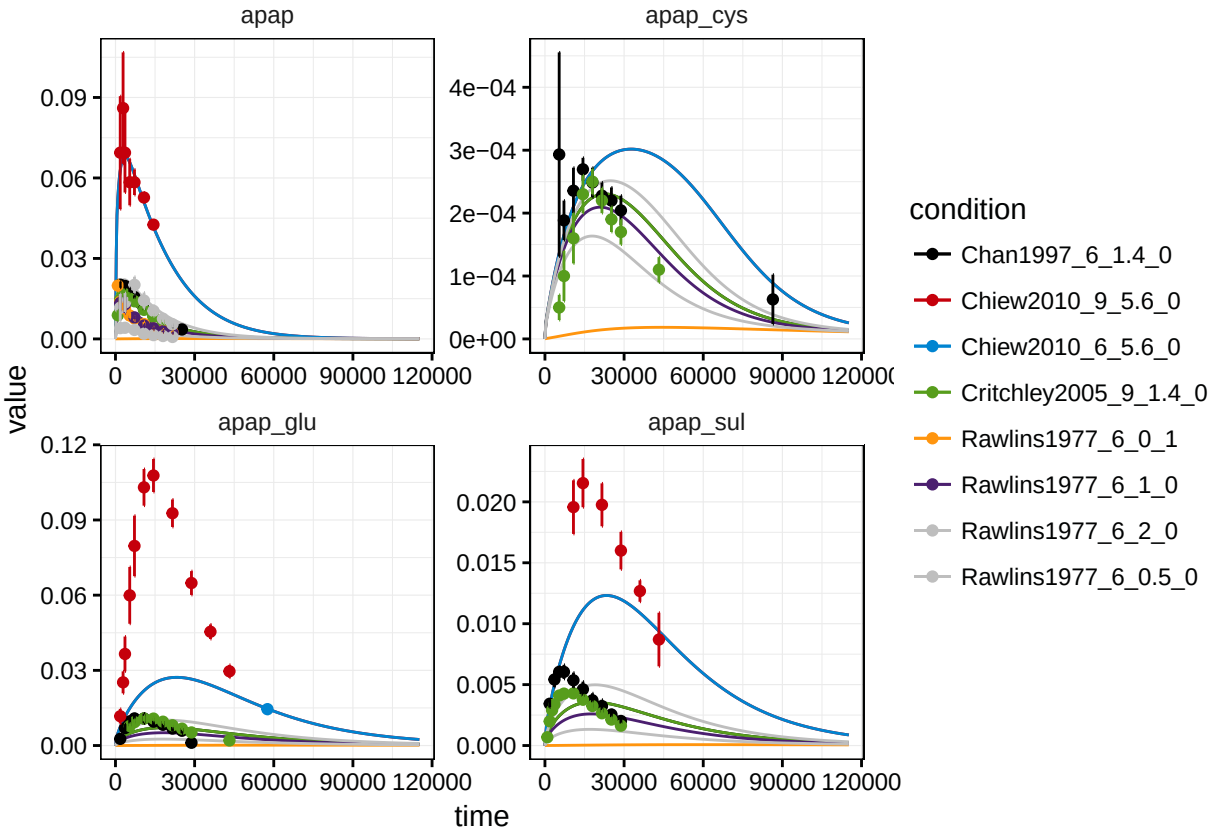
```
## 30   1.3489370776
## 31   1.3281367465
## 32   0.9830577757
## 33   0.7888350019
## 34   1.4222679305
## 35   2.2175856833
## 36   1.8233155919
## 37   0.3347008563
## 38   0.4056127735
## 39   1.7804638821
## 40   0.0838630369
## 41   1.1648721574
## 42  -0.9872398765
## 43   0.2426841700
## 44   1.4038264811
## 45   0.6077142156
## 46   1.6075711593
## 47   3.4359821571
## 48   0.8210552508
## 49   1.2945500680
## 50   1.6722484999
## 51  -0.8849257892
## 52   0.1368722531
## 53   0.5337373655
## 54   0.0876506487
## 55   2.3085982570
## 56   2.1242597081
## 57   0.4085746123
## 58   1.1752422696
## 59  -0.3713663493
## 60  -0.1818235504
## 61  -0.7944113121
## 62  -0.8694000746
## 63  -0.4776920952
## 64   0.3453889328
## 65   2.2500034756
## 66   0.0676877177
## 67  -0.0691158488
## 68  -0.1048376187
## 69  -0.3757110957
## 70   0.2980763261
## 71   0.4715283752
## 72   0.8816581713
## 73   1.8753895962
## 74   1.5608682688
## 75   1.3622339939
## 76   2.2845073027
## 77  -0.2876985719
## 78   3.7653819851
## 79   0.9353789627
## 80   2.6771467165
## 81   0.7611437198
## 82   2.8236429602
## 83   3.3317144126
```

```
## 84   0.1444322388
## 85   2.6849345910
## 86   2.7900242904
## 87  -1.1264351974
## 88  -0.5069345201
## 89  -1.7896812648
## 90  -0.0954215500
## 91  -0.3109162314
## 92  -0.0801547662
## 93  -0.8590323869
## 94   1.3668243457
## 95  -0.8284951992
## 96   0.5418410512
## 97  -0.5114399484
## 98   0.0569545179
## 99  -1.1134500496
## 100  0.2271437947
```

```
plotValues(myfit2 %>% as.parframe())+scale_y_log10()
```




```
mypred2 <- (g*x*p2)(mytimes*4, myfit2 %>% as.parframe() %>% as.parvec)
plotCombined(mypred2, mydatalist, name %in% names(observables))
```



Free other parameters 3 - not good

Same problem as in tries 1 and 2

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters3 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap_sul", "F_apap_sul"    ,
                      "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
```

```
                    )

fixed_parameters3 <- pars[!(names(pars)%in%c(free_parameters3,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters3] <- paste0("exp(log", free_parameters3, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p3 <- NULL
for(i in 1:length(p_list)) { p3 <<- p3 + p_list[[i]]}

pouter <- log(pars[free_parameters3]) %>% set_names(paste0("log",names(.)))


# mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj3 <- normL2(mydatalist, (g*x*p3))

# job3 <- runbg({myfit <- mstrust(objfun = obj3, center = pouter, studyname = "methacetin", cores = 15,
```

```
# myfit3 <- job3$get()$knecht1
# save(myfit3, file = "myfit3.rda")
# job3$purge()
load("myfit3.rda")
myfit3 %>% as.parframe()
```

```
##    index        value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1     59     2562.482      TRUE         84       -5.20109769 -2.097660e+00
## 2     60     2689.397      TRUE         48       -5.38377366 -2.043510e+00
## 3     55     2856.425     FALSE        100       -5.10988348 -1.468816e+00
## 4     48     3019.107     FALSE        100       -6.86587340 -5.295360e+00
## 5      1     3039.058     FALSE        100       -4.63893492 -1.383292e+00
## 6     89     3066.281      TRUE         76       -6.46496560 -4.620926e+00
## 7     21     3111.565      TRUE         45       -4.45561955 -1.805606e+00
## 8     18     3147.849      TRUE         73       -5.01802614 -1.277225e+00
## 9     69     3157.753     FALSE        100       -4.49025487 -8.341202e-01
## 10    23     3204.617      TRUE         52       -5.56946002 -2.568545e+00
## 11    11     3226.803      TRUE         57       -3.89889878  5.453747e-01
## 12    34     3255.622      TRUE         79       -4.68195855 -1.380377e+00
## 13    70     3262.576      TRUE         64       -7.01601244 -4.537364e+00
## 14    22     3308.216      TRUE         72       -5.37771135 -1.745741e+00
## 15    86     3338.269      TRUE         87       -5.45147639 -3.512610e+00
## 16     4     3347.898     FALSE        100       -3.65557123 -1.255457e+00
```

```
## 17    27     3350.615     FALSE        100       -7.46088748 -6.823640e+00
## 18   100     3360.663     FALSE        100       -6.05986291 -4.392540e+00
## 19    26     3452.294      TRUE         75       -6.93402054 -4.407573e+00
## 20    33     3460.486     FALSE        100       -6.14273326 -3.814253e+00
## 21    42     3509.944     FALSE        100       -7.22019863 -7.331438e+00
## 22    72     3544.757     FALSE        100       -5.27912150 -9.555325e-01
## 23    91     3553.507     FALSE        100       -3.21766621  2.651912e-04
## 24    88     3557.382     FALSE        100       -7.43739572 -6.473865e+00
## 25    71     3571.656     FALSE        100       -2.41065303  2.575048e+00
## 26    92     3594.130     FALSE        100       -4.44395491 -3.644598e-01
## 27    96     3638.385     FALSE        100       -2.51158264  4.523668e-01
## 28    84     3643.593     FALSE        100       -7.31723736 -3.582180e+00
## 29    43     3742.237     FALSE        100       -2.75540735  2.016326e+00
## 30    28     3808.129     FALSE        100       -6.06753805 -4.713739e+00
## 31    87     3847.684     FALSE        100       -3.31814603 -1.882905e+00
## 32    17     3864.260      TRUE         63       -6.82838954 -3.444341e+00
## 33    99     3871.949     FALSE        100       -7.02043153 -5.330481e+00
## 34    63     3944.356     FALSE        100       -7.38654393 -5.573825e+00
## 35    76     3955.804     FALSE        100       -3.11456346 -3.102261e-01
## 36    37     3982.506     FALSE        100       -5.88422414 -4.187844e+00
## 37    67     4004.467     FALSE        100       -6.77294431 -5.003848e+00
## 38    95     4016.209     FALSE        100       -4.98385739 -2.571060e+00
## 39    16     4034.449      TRUE         42       -7.09915511 -3.403148e+00
## 40    80     4038.515     FALSE        100        2.12753217  4.965707e+00
## 41    15     4119.568     FALSE        100        3.77144700  6.660440e+00
## 42     7     4120.339     FALSE        100       -4.26622641 -9.194941e-01
## 43    51     4198.846     FALSE        100       -3.74325192 -1.587178e-01
## 44    56     4303.514     FALSE        100       -4.96698124 -3.183245e+00
## 45    74     4309.536     FALSE        100       -6.52375998 -3.489526e+00
## 46    35     4314.103     FALSE        100       -4.41280686 -1.360850e+00
## 47    20     4428.045     FALSE        100       -1.45963377  2.943227e+00
## 48    62     4529.734     FALSE        100       -8.07121115 -8.190182e+00
## 49    29     4722.369     FALSE        100       -7.18872567 -4.818661e+00
## 50    75     4866.026     FALSE        100       -2.63105659 -5.812915e-03
## 51    97     4867.181     FALSE        100        7.43093169  1.045142e+01
## 52    19     4904.625     FALSE        100       -3.35565606 -1.396209e+00
## 53     8     4923.682     FALSE        100       -8.22473049 -7.879620e+00
## 54    90     4962.186     FALSE        100        0.08853582  5.898306e+00
## 55    58     5044.395     FALSE        100       -7.32816752 -6.330193e+00
## 56    54     5109.948     FALSE        100       -1.95822028  7.343261e-01
## 57    94     5112.770     FALSE        100       -8.45771196 -1.212004e+01
## 58    82     5292.190     FALSE        100       -1.88877946  5.972299e-01
## 59    52     5367.124     FALSE        100       -9.16245683 -1.947865e+01
## 60    14     5442.770     FALSE        100       -3.26471663  8.249710e-01
## 61    53     5455.009      TRUE         87       -0.34801873  4.993578e+00
## 62    79     5518.532     FALSE        100       -0.31075469  2.965752e+00
## 63    24     5575.461     FALSE        100       -8.72590511 -6.258230e+00
## 64    40     5591.523     FALSE        100        2.68678718  6.652177e+00
## 65     3     5747.015     FALSE        100       -2.61972034  1.116822e+00
## 66     9     5902.584      TRUE         38        0.94012145  7.103141e+00
## 67    50     6596.176     FALSE        100       12.57387520  1.560504e+01
## 68    83     6768.397     FALSE        100      -10.83862134  1.654739e+00
## 69    73     6925.355      TRUE         54      -12.83534838  3.422471e+00
## 70    66     7080.642      TRUE         65      -10.10834969 -1.129938e+01
```

```
## 71    77     7234.993     FALSE        100        3.42650737  7.210447e+00
## 72    32     7430.059      TRUE         97      -11.47991291  2.854041e+00
## 73    46     7470.441      TRUE         59      -11.42573754  4.401642e+00
## 74     5     7662.475     FALSE        100        8.25259357  1.327114e+01
## 75     6     7771.235      TRUE         21       15.80213345  1.860618e+01
## 76    41     8053.795     FALSE        100       -2.29247858  1.404682e+00
## 77    36     8445.028      TRUE         59       10.00028981  1.293333e+01
## 78    98     8751.072     FALSE        100      -18.50320230 -1.179555e+00
## 79    45     9124.033     FALSE        100        9.26694990  1.347665e+01
## 80    13    11575.452     FALSE        100        1.40984902  4.383559e+00
## 81    44    15520.035      TRUE         82       16.96286849  1.981139e+01
## 82    25    16552.834     FALSE        100        2.53379392  5.797072e+00
## 83    39  6427111.647      TRUE         35      -13.69887623  7.599794e+00
## 84    31  6521701.376      TRUE         36      -22.31059629  1.176859e+01
## 85    47 17914121.286      TRUE         34      -19.24739075  1.090343e+01
## 86    49 20937223.754      TRUE         37      -18.01092577  1.004426e+01
## 87    93 29597098.927      TRUE         35      -17.55724055  8.486914e+00
## 88    81 34229556.482      TRUE         38      -18.96085542  7.631773e+00
## 89    30 87919364.080      TRUE         28      -15.49072697  8.822251e+00
##    logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap_sul
## 1          -6.555927       -10.7096752   -6.33769669      -6.042436
## 2          -6.862922       -10.9106242   -6.20766738      -8.289160
## 3          -6.656348        -9.8725927   -4.75970985      -6.579562
## 4          -6.050377        -9.6189279   -6.86802281      -6.542891
## 5          -6.709802        -7.5218830   -0.09424782      -7.980098
## 6          -5.857182       -10.6829437   -8.86895808      -7.943206
## 7          -6.133259       -10.7626043   -7.58746946      -7.577316
## 8          -6.882947       -11.0870516   -6.07009816      -7.797141
## 9          -6.834923        -9.6842817   -6.98652089      -7.500062
## 10         -6.589175       -10.3806140   -6.45684424      -6.304637
## 11         -7.564251       -11.0062807   -4.93960823      -6.647568
## 12         -6.360407        -9.7584995   -7.28442158      -6.163970
## 13         -6.267519       -10.2919334   -7.47770792      -6.119063
## 14         -6.762882       -10.0110684   -6.23403884      -7.569154
## 15         -4.614922       -10.3861598   -7.43879118      -9.720690
## 16         -4.830222       -10.3322359   -6.11342365      -6.554367
## 17         -5.812449        -8.7147217   -3.16837981      -7.206180
## 18         -4.980522        -8.7755550   -3.27422146      -7.194725
## 19         -6.497902       -10.5866787   -5.61145536      -7.357062
## 20         -5.309191        -9.9945895   -6.44072047      -8.062971
## 21         -4.909993       -10.2353495   -7.78903856      -6.335617
## 22         -6.887220        -9.0406786   -5.66433779      -7.021735
## 23         -6.259488        -8.5829272   -4.83691086      -8.375778
## 24         -5.959940        -8.4262992   -4.09360647      -7.962573
## 25         -7.457443        -9.9528492   -5.49573762      -8.210233
## 26         -6.956463        -9.9395362   -4.39828601      -6.020496
## 27         -5.652937       -10.0669349   -8.60748814      -8.065623
## 28         -7.998259       -10.6979468   -3.68263189      -6.800773
## 29         -6.624682        -9.6299704   -3.93417651      -8.234979
## 30         -4.646940       -10.1893043   -7.63764230      -4.505747
## 31         -4.000415        -9.6154099   -4.74191533      -6.688289
## 32         -6.832525       -10.6056906   -7.01453615      -7.821463
## 33         -5.872034       -10.4024501   -3.14016950      -8.169917
## 34         -6.667442        -9.3113922   -3.83072753      -8.622026
```

```
## 35       -5.788894       -7.8034307   -3.27893761      -7.729490
## 36       -4.029544       -9.8167472   -8.74955879      -8.381770
## 37       -5.778960       -7.9189438   -3.08791014      -7.532662
## 38       -5.990500      -10.0392501   -6.92125143      -6.609862
## 39       -7.193536       -9.7805927   -3.59719635      -6.860206
## 40       -4.850488      -10.4569392   -8.05353016      -6.652138
## 41       -6.104663      -10.0663185   -9.96956281      -6.850396
## 42       -5.324534      -10.0336589   -6.07299714      -7.176072
## 43       -6.453099      -10.2280914   -3.52265308      -6.704616
## 44       -4.811522       -9.8348824   -7.45797923      -6.471283
## 45       -5.739187       -9.1353028   -3.68063950      -7.467659
## 46       -6.202046       -8.9613395   -2.99059293      -6.996466
## 47       -7.565905      -11.0909292   -5.70538717      -8.338211
## 48       -6.362461       -9.9543175   -7.02819574      -7.903626
## 49       -5.429603      -10.0412664   -7.91233566      -6.365706
## 50       -6.013171      -10.1703569   -6.77193220      -9.319208
## 51       -5.670701       -9.8142867   -5.96011855      -5.557915
## 52       -3.854126       -8.5787388   -4.62785454      -5.698677
## 53       -5.678562       -9.4724834   -5.08650509      -6.739284
## 54       -6.718512       -6.4606422    1.65863271      -7.173745
## 55       -4.897351       -9.5755702   -3.17833878      -6.242292
## 56       -5.469997       -9.2876262   -5.91602092      -7.741890
## 57       -5.528132       -9.8873722   -4.32983472      -6.815220
## 58       -5.108900      -10.2622316   -5.08202303      -6.297856
## 59       -7.439574      -10.2040930  -13.30460964      -5.653788
## 60       -6.184839      -10.0475556   -9.55721069      -8.790268
## 61       -7.439378      -10.9097035   -7.88357437      -4.231734
## 62       -6.671882      -10.1637247   -9.18311198      -8.145281
## 63       -7.674352      -10.6981573   -2.95004832      -8.842822
## 64       -6.091017      -10.4210686   -4.59523321      -7.434779
## 65       -5.839658      -10.9399209   -5.61702451      -5.826121
## 66       -7.886567      -10.1413148   -7.94867525      -8.840971
## 67       -5.796956        5.5652546   11.50194638      -9.566947
## 68       -5.946258      -10.5672445   -9.63351745      -8.039381
## 69       -7.299968      -10.1965374  -10.40969459      -6.774638
## 70       -6.762425       -9.2517458   -2.22757482      -6.408773
## 71       -6.442756      -10.1505632   -9.21829521      -7.242640
## 72       -6.734697      -10.4905953  -10.35861786      -8.227723
## 73       -6.984116      -11.6296904   -7.97781435      -6.729905
## 74       -7.700638      -10.3723403   -7.73807281      -7.279762
## 75       -6.554999        7.1791260   13.87252484      -5.990175
## 76       -6.573848       -9.7054627   -3.68982745      -6.052127
## 77       -4.860371      -11.1392135   -8.22127241      -8.905100
## 78       -8.910194      -10.9942046   -7.79641963      -8.324374
## 79       -7.185152        0.5370183    8.75278965      -6.265562
## 80       -6.204700      -10.2713013  -10.58060108      -6.653707
## 81       -6.058980        8.5590794   15.39412682      -7.400714
## 82       -5.730912       -5.3738738    1.66602254      -6.942316
## 83      -23.078496      -16.4398891    4.85551799      -9.009033
## 84      -35.520550      -23.8989238   10.17968266      -6.842467
## 85      -31.940733      -20.6985085    9.45182261      -8.934829
## 86      -29.875173      -19.3035665    8.75125523      -6.461662
## 87      -27.794578      -20.1415069    5.90222815      -7.678508
## 88      -28.092615      -19.3355501    7.25567039      -6.548796
```

```
## 89        -24.987747       -17.0996884    6.28082182      -5.833728
##    logF_apap_sul logKpre_apap logKpki_apap logKpli_apap logKpre_apap_cys
## 1    2.808457812 -0.366923421   0.76138938   0.16726353      -0.60481953
## 2   -1.512335536 -0.133697755  -0.20525859   0.54499201      -1.54253438
## 3    0.009716211 -0.265523279  -1.68981157   0.67682336      -0.27698005
## 4   -0.661252544 -0.133416636   0.22298058  -0.61069419      -0.40459141
## 5    2.748915536 -0.446896625  -0.60035748   0.38377909      -0.31938599
## 6    1.679453017 -0.119262597  -0.55903514  -0.60420758      -2.91913682
## 7    0.263932061 -0.582112499  -1.10164788  -0.28321269      -0.98730367
## 8   -0.539765992 -0.187499772  -2.16735401   0.86340172      -1.57516777
## 9    0.207672498 -0.337382442   0.08490979   0.62218901       0.55819497
## 10   0.707481878 -0.251683835  -0.22070849   0.21726687      -0.09913164
## 11   1.382257196 -0.567018987  -1.18046642   1.55529771      -1.12892561
## 12   1.059999513 -0.293058995   0.13341749   0.21285650       0.63405406
## 13  -0.983085964  0.060619950   0.78574232   0.01712010      -0.45367875
## 14  -2.166016055 -0.224033130  -0.01494465   0.67833450       0.51257876
## 15   2.887471787 -0.445788161  -1.46808250  -1.26329402       0.05950133
## 16   0.283657345 -0.283420098   0.37703176  -1.00324503      -0.02096935
## 17  -0.358491257  0.085327199   0.09728747  -0.56160716      -0.17421302
## 18  -1.417966826 -0.268263658  -0.53215578  -1.15269519      -0.11367229
## 19  -0.507751256  0.170088746  -1.81742688   0.24961370      -0.57093329
## 20   0.566070690 -0.017752080   0.16119645  -0.70256768       0.57941789
## 21  -0.350448803 -0.049672283  -1.60090738  -1.59187360      -0.39016847
## 22  -0.081295133 -0.653609437   1.85529686   0.64587446       2.49779158
## 23  -0.709067045 -0.804807507   0.76402310  -0.15350585       2.30848801
## 24   0.591524385  0.109344111  -1.35980712  -0.44340284      -0.19867226
## 25  -1.413289318 -0.738923246   0.67387620   1.77093655       0.41571307
## 26  -0.669554864 -0.476971730   0.75582091   0.94706941       0.68966686
## 27   0.024032042 -0.493620691  -1.02626897  -0.29488968      -1.45990284
## 28  -1.138942596  0.079503148   0.37387497   2.12247964      -0.51636846
## 29  -0.762692087 -0.268027656  -0.85960232   1.29112234       1.44022154
## 30  -0.215260954 -0.385108159  -0.43127688  -1.52239186      -0.90501572
## 31   2.040504443 -0.231338286   1.36202860  -2.02854122      -0.56823465
## 32   0.245785832  0.460948796  -0.04432228   0.53704246      -1.03363350
## 33   0.291943329 -0.116998059   1.83142611  -0.81055171       1.97721667
## 34  -2.463720255 -0.013295264  -0.53859660   0.46784023       0.30025669
## 35  -0.501417537 -0.808792183   0.46201402  -0.51672299       1.98251791
## 36   0.138577996  0.124936427   0.23177591  -1.80255410       0.96633449
## 37   0.143446679 -0.048342234  -0.07764952  -0.62039967      -2.13182922
## 38  -2.007968188 -0.475699200  -1.22734983  -0.47165957       0.58808315
## 39   1.236015876  0.354286490  -0.61160101   1.15783940       0.48213464
## 40  -0.025653689  0.315041961  -0.41343324  -0.88937482      -0.41701857
## 41   0.167648618 -1.052537321   0.34610149  -0.39783027      -1.04937828
## 42   0.539727455  0.297989284  -0.29164127  -0.37499571       0.42959430
## 43  -0.125860530 -0.319536081  -1.33815931   0.52990687      -0.37944171
## 44  -1.018998642 -0.666325303   1.81738997  -1.72021408       0.71694725
## 45   0.090833043  0.040143506   0.12594798  -0.05684135       0.08118530
## 46   0.388008229 -0.151242028   0.07678178   0.03079648       0.58001810
## 47   0.197997147 -1.064558087  -0.48519991   1.35714981      -1.34127192
## 48  -1.687411177  0.497603508  -0.34542116   0.03689564      -0.13689234
## 49   1.376823292  0.525287465  -0.95709187  -0.72629394       0.19876931
## 50   0.217534443 -1.002523682   0.26807643  -0.57383762       0.13791746
## 51   0.949135946  0.233583848  -0.13250307  -0.33989494       0.17717084
## 52  -0.396851522 -0.335451153   0.15051865  -1.77901201      -0.11336477
```

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## 53   0.532924600  0.452830956 -0.60438567 -0.31713151      -0.03702090
## 54  -0.856801645 -0.464186777  0.87409695  1.78699026       0.30014813
## 55  -0.658688908  0.550664191  0.13464131 -1.59792741      -2.88462340
## 56   1.121902828 -1.117344957 -0.01644767 -0.79006826       1.84883981
## 57   2.111020588  0.545826369 -0.52133709 -0.42051414      -0.23753685
## 58   0.134709732 -0.840526677 -0.73466132 -0.88401900      -0.08396510
## 59   1.506323944  0.876320240  0.39719469  0.90737373      -0.37317392
## 60   0.657907776  0.588770026  1.71813342 -0.15935218      -1.11545582
## 61  -1.001713299  0.850361125 -0.79283678  1.15664395      -1.95955545
## 62  -0.394181779 -1.204006292 -1.27425064  0.09289280      -1.37733822
## 63  -0.604542873  0.801088111 -0.05089428  1.57346470      -1.56972051
## 64  -1.095371392  0.757743968 -0.71760741 -0.08702306      -0.69647249
## 65   0.548001480  0.003797969  0.48822732  0.20645970      -1.29430227
## 66  -0.202364707  0.872416485 -0.90345686  1.68497229       0.54950091
## 67  -0.106078071 -1.384194829  1.54109681 -0.73993442       0.47555578
## 68  -0.950135798  1.048050861  0.48500891 -0.91955014       1.03773450
## 69  -1.339640516  1.059000720  0.19031025  0.40475209      -0.02614353
## 70   0.461812047  1.018290947 -0.43928704  0.15459796      -1.07559684
## 71   1.197730116 -1.337638129  0.03133646  0.28821261      -2.94280385
## 72   0.767741090  1.034359659  1.26847941 -0.44856166      -0.73260064
## 73   1.340225025  1.086458244  0.42930169  0.03924653      -1.40522115
## 74  -0.852300068 -1.625164081  1.13996318  1.57355057      -1.28583780
## 75   0.720481952 -1.469633913  0.57314838 -0.48068933      -0.29135507
## 76  -2.331233102 -1.443158973 -0.39700319  0.29692177      -0.44072637
## 77  -0.234332367 -1.545747362 -0.28031537 -1.08537589      -1.12491256
## 78   1.315792719  1.096447259  0.77196918  1.53393303      -1.33301732
## 79   1.211777450 -1.760667523  0.01046872  0.81276981      -0.83694528
## 80  -0.138993310 -1.731102294 -0.44804216 -0.49674663      -1.74628212
## 81   0.271478786 -2.090493716  0.02853708 -0.75393037      -0.76936130
## 82   0.059796980 -2.080690468  0.10267688 -0.62042581      -0.70057251
## 83  -1.029776019  1.420164294 -1.43345653 -1.19638242      -0.79701640
## 84   0.611364763  1.384259745  0.24236531  1.21231829      -0.72778717
## 85   1.048414451  1.546269425  0.22581733 -1.41546595      -1.15787584
## 86  -0.748059733  1.569540887  0.59126936 -2.67612743       1.79608817
## 87   0.487788475  1.678621137 -1.47749299 -0.71063097       1.25682503
## 88  -0.195887324  1.698736304  0.01961941  1.02746757      -0.47734261
## 89  -0.212417401  2.170622236 -1.49755985  1.35287419      -1.59366128
##    logKpki_apap_cys logKpli_apap_cys logKpre_apap_glu logKpki_apap_glu
## 1      -0.124194779     -0.046143712      -0.86811519     0.3691186669
## 2      -0.251115023      1.520778416      -0.80838173     0.1671252856
## 3       0.722121681     -0.093790877      -1.09416842     0.2663733712
## 4       2.275281809      0.300508942      -1.51937947     1.6428602111
## 5      -2.527295655      1.044563931       0.30866990     0.0422194136
## 6       0.452171874     -0.726133175       0.19944450     0.8565830589
## 7       0.078511922     -0.006937132      -0.11036473     0.9881881444
## 8      -0.400492179      0.043964023      -0.21625571     0.1454875914
## 9       2.058740038     -0.464357616       0.76180965    -0.8055590598
## 10      0.358196738     -0.602071583       0.86606762     0.4002615399
## 11     -0.465698754      0.662695161       0.46618147     0.6321104946
## 12      1.652198145      0.617818933       0.63356414    -0.6925998027
## 13      0.877178212     -0.581853678      -0.55386730     0.4866610501
## 14      0.918793420     -0.076374570       0.13639098     0.7212502925
## 15      0.047545122      0.592408555      -0.48447089     0.4770931123
## 16     -0.583637777     -0.574737740      -1.24130889    -0.3914526717
```

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## 17    -0.514561634     0.213692600    -0.55203135    1.4635754203
## 18    -1.743494221     0.380156291     0.34686368    0.0816742398
## 19    -0.206408349     0.668957750     0.02178535    0.3063569545
## 20     0.140529014     1.574499396    -0.35204847    0.0004019499
## 21     0.537102565    -0.509006536    -0.56782281    2.5418486335
## 22     0.813144965     0.243439391    -0.25446976   -0.0746512205
## 23    -0.589517249    -0.029603737    -0.58351971   -0.4321918819
## 24     2.219929833    -0.498280811    -1.07301058    1.5075657195
## 25     1.287553825    -1.267133827    -0.23704933    0.9234121800
## 26    -0.256490375    -0.129818442     0.18790959   -1.0240120528
## 27     1.367714985    -0.656677589     0.26090292   -1.6728049301
## 28    -0.422603820    -1.194908476     0.76986468    0.9558019057
## 29    -1.018843031     1.651380175     0.37041466   -0.0057804583
## 30     0.712957484    -0.253151143     1.05491945    0.8982868046
## 31    -1.987886203    -0.243864134    -0.43479494   -1.0205638895
## 32     0.410196187     0.246858844    -0.47201623    0.1043746405
## 33    -0.993377722    -1.078847597    -1.65126061    0.8884400755
## 34     0.531926800    -0.602675588     0.55946111    2.7431222755
## 35    -0.819781013     0.845190011     0.82126787   -1.3964247054
## 36     1.077038187     0.774413448    -0.66459526   -0.1479054617
## 37     1.298598299    -1.007080705     1.02753758    0.4363228105
## 38     0.542069273     0.146386145     2.13794136    1.6256469663
## 39    -0.180758769    -0.071066081    -0.34112726    0.1763862455
## 40     0.458158010     0.807168285    -1.02827933   -0.4359977942
## 41     1.656993483    -1.239052294    -0.27858628    0.3930340446
## 42     0.144995540     2.404505363    -1.66810937   -0.2381238362
## 43    -1.313232210     0.324279343    -0.88892146   -0.4129679429
## 44     0.535890976     1.043976702     1.53986249    0.5316208419
## 45     0.070836690     1.397575173     0.94550477   -0.1867640848
## 46    -1.819222950     0.124033452    -0.65623548   -0.5400253863
## 47    -0.403728947     0.337743990    -0.16135503    1.7238692362
## 48     1.550575083     0.565595849     0.44923377    2.4435242083
## 49     1.273449779     0.283875246    -0.45106286    0.3709177021
## 50     0.498801229    -1.697365822     1.82769996   -0.3815012054
## 51     0.413987175     1.855451963    -1.18193715   -0.7542803870
## 52     0.003489957     0.738383009    -0.78830156   -1.4758998033
## 53     0.928421466    -0.162232610     0.79757919    1.5768705652
## 54    -1.005186956    -1.650987418     1.99987219   -0.6258626452
## 55    -2.727476134    -0.049139677     1.92494514    0.1641523399
## 56    -0.568933194     1.009119660     0.61581426   -1.2058065988
## 57    -0.867404912    -0.744567024     0.33720061    0.9746524106
## 58    -1.156368049    -0.310569667    -0.17502127    0.8013822002
## 59     1.669347100    -1.224630751    -1.64661603    0.3687314959
## 60     2.045261981    -0.066663020    -0.49858686   -0.1302362467
## 61     0.220120636    -0.075122378    -1.45227142   -0.0458150323
## 62     1.499425707     0.655395630     1.46430437   -0.7758383130
## 63    -0.948798349     0.333184115     0.24012684   -0.1525211420
## 64    -0.771219142    -0.223859235     0.06636504   -0.5929492816
## 65    -0.666489846    -0.703626704    -1.12036851   -1.1171869696
## 66     1.321477971    -1.017057454    -0.14277794   -0.5665661592
## 67    -1.314061303    -1.196369279    -0.89420118   -0.6499902368
## 68    -0.397121514    -0.648779771     0.73837890    0.6980213504
## 69     1.851641968     1.543214365     0.08842038    0.1966669823
## 70    -1.390769193     1.089936337     0.85580853   -0.5565669236
```

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## 71      1.847010107      0.597927361      -1.41487399     0.7272018832
## 72      1.147185245     -0.087845344      -0.57543369    -0.3265515647
## 73     -0.866656201     -2.252626814      -0.62760899     0.0484199480
## 74      1.111539760      0.415212566       0.77624834     0.2398577939
## 75     -1.266472384      0.377563726       1.36862955     1.8579120184
## 76      0.316018856      0.436406110      -0.66979633     0.6486927944
## 77     -0.439942797     -0.444266071      -1.61989662    -0.2407899067
## 78      0.114905162     -2.308938916       0.94996047     1.0405139946
## 79     -1.228281563      1.219842075      -0.57755135    -0.0649825487
## 80      1.915142123     -0.282068188       1.54336920     1.1001207820
## 81     -1.130322771     -1.000816016      -0.07755558     0.3702419159
## 82     -1.424652250     -0.998804983      -0.41915765    -0.9740160558
## 83     -1.237104049     -0.347744370      -1.07768388    -0.9707714705
## 84      1.573377499      0.179147316       0.88937096     1.2047365268
## 85      0.822326136      0.425950498       0.56115431    -1.1475633069
## 86     -1.456495988     -1.158174903       0.09190679     0.2678767335
## 87     -1.049983991     -1.142615507      -1.59485196    -0.8260705171
## 88     -0.902902258      0.566317283       0.84115560    -0.5888290018
## 89      0.917172025     -0.665925629       0.72749360     0.1267364480
##    logKpli_apap_glu logKpre_apap_sul
## 1      -0.003140001      -1.08948040
## 2      -0.342208285      -2.22432553
## 3      -0.207101279      -0.12233629
## 4      -0.702140533      -2.04167624
## 5       0.408290615      -1.11437092
## 6      -0.820070493      -0.73832855
## 7      -0.276118046      -0.43545430
## 8      -1.580497276      -0.49881915
## 9       0.077572877      -0.68524242
## 10     -1.205479627      -0.88182369
## 11      0.536396481      -0.80267095
## 12     -1.150086683      -0.20077475
## 13      0.379895817      -0.27886880
## 14     -1.810992412      -0.08971054
## 15     -1.481810426       1.15031827
## 16      0.017192612       0.27177368
## 17      0.108461062      -0.41176986
## 18     -0.948566333       0.30381777
## 19     -0.849351262      -0.67116209
## 20      1.006009762       0.35173563
## 21     -1.187759842      -0.62992226
## 22      1.367388143      -0.01025329
## 23      0.638627489      -1.16818509
## 24      0.250552945      -0.58387688
## 25      0.114162312       0.23680384
## 26     -1.059951198      -0.70753737
## 27      0.464840338       0.06978339
## 28      0.705529852      -2.16046760
## 29     -0.711723300       1.18469879
## 30     -2.360349328       0.46393078
## 31     -0.075945275       0.15282236
## 32      0.080332394      -1.32323425
## 33     -0.464293881      -1.62073723
## 34      1.426512758      -0.44344344
```

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## 35     -0.411470125       0.03850684
## 36     -0.836631597       1.21801114
## 37     -2.634749870      -0.46754064
## 38      0.742451584      -0.70830208
## 39      1.414314548      -0.65219114
## 40      0.014341703       0.82483865
## 41     -0.354500880      -0.28823187
## 42      1.139016405       1.19716406
## 43      0.518141376      -0.85098841
## 44      1.510572535      -0.16478858
## 45     -0.940802237       0.97879518
## 46     -1.526562099      -1.90021092
## 47     -1.713375836      -0.84090077
## 48      0.659577290      -0.58752427
## 49      0.473897104       0.49521104
## 50     -0.332255812      -0.47652454
## 51     -0.291202874      -1.23239866
## 52     -1.058646844       0.22131439
## 53     -1.751619103       0.68331439
## 54     -0.514937279       1.92499105
## 55     -0.226742389      -0.61451607
## 56     -0.189919049       0.41128128
## 57      0.060232150       0.93877485
## 58     -0.322360787       2.88606002
## 59      0.383047685      -1.26260278
## 60     -2.655190983       0.55244088
## 61     -0.990640892      -0.34996091
## 62     -1.770199639      -0.57255769
## 63     -0.555237465      -0.48519082
## 64     -0.589239872       0.30753806
## 65     -0.891555645      -0.49739628
## 66      0.664091821      -0.74131142
## 67      0.447876199      -0.73937287
## 68     -1.122700651      -1.95791864
## 69     -1.265020137      -1.56802397
## 70     -0.834788566       0.06917266
## 71     -0.234287717       1.68370503
## 72     -0.031948932      -0.71495972
## 73      0.103644696      -0.54703064
## 74      0.369243020       1.52032321
## 75      1.088105304      -2.28625221
## 76     -0.320440426       1.86507207
## 77     -0.632111528       1.73046901
## 78     -2.157958307       0.83554414
## 79     -0.918819818      -0.46786006
## 80      0.890979616       0.36478386
## 81      0.318991448       0.45451878
## 82      0.608422070       0.31450762
## 83     -0.101459670      -0.49267448
## 84     -1.151313847       1.26671411
## 85      0.839731619       0.40991376
## 86      0.665941904       0.62628380
## 87      0.822108315      -1.29427638
## 88     -0.005235169      -0.58067802
```
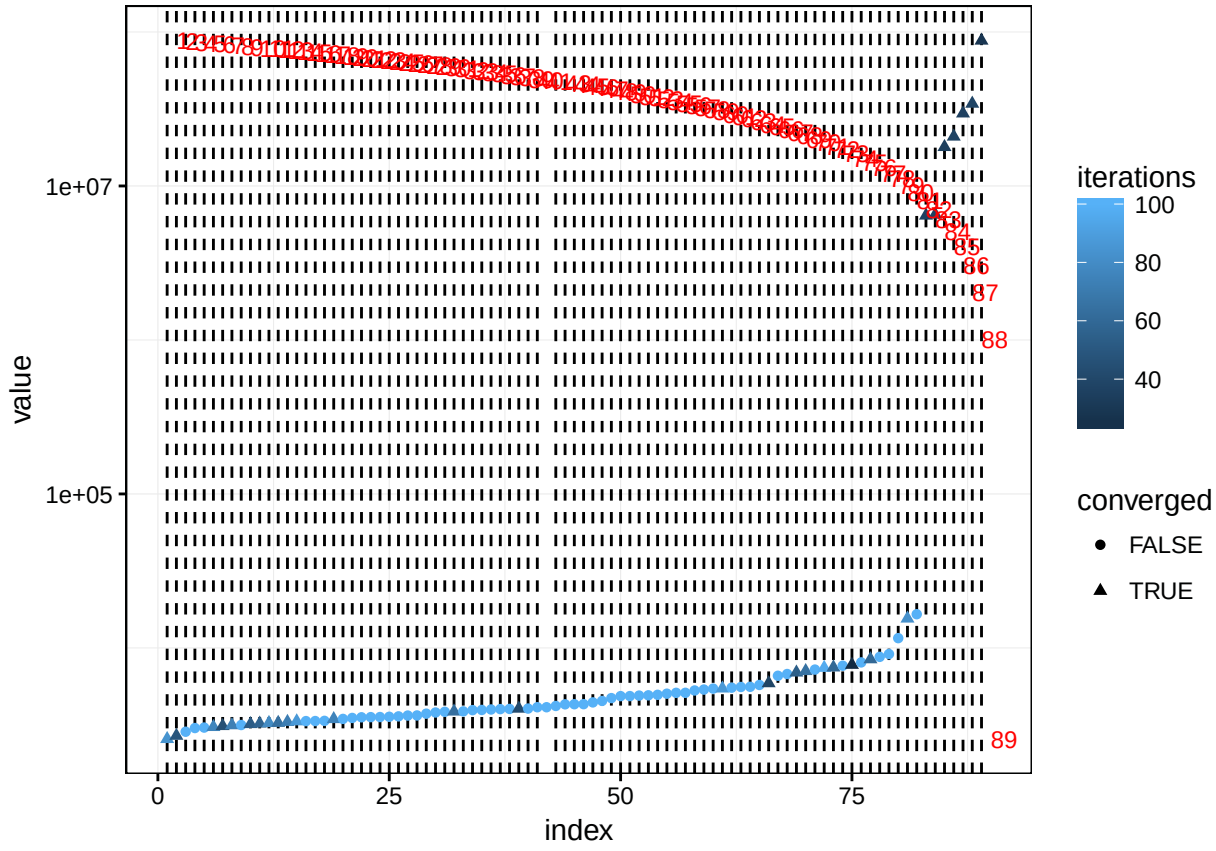
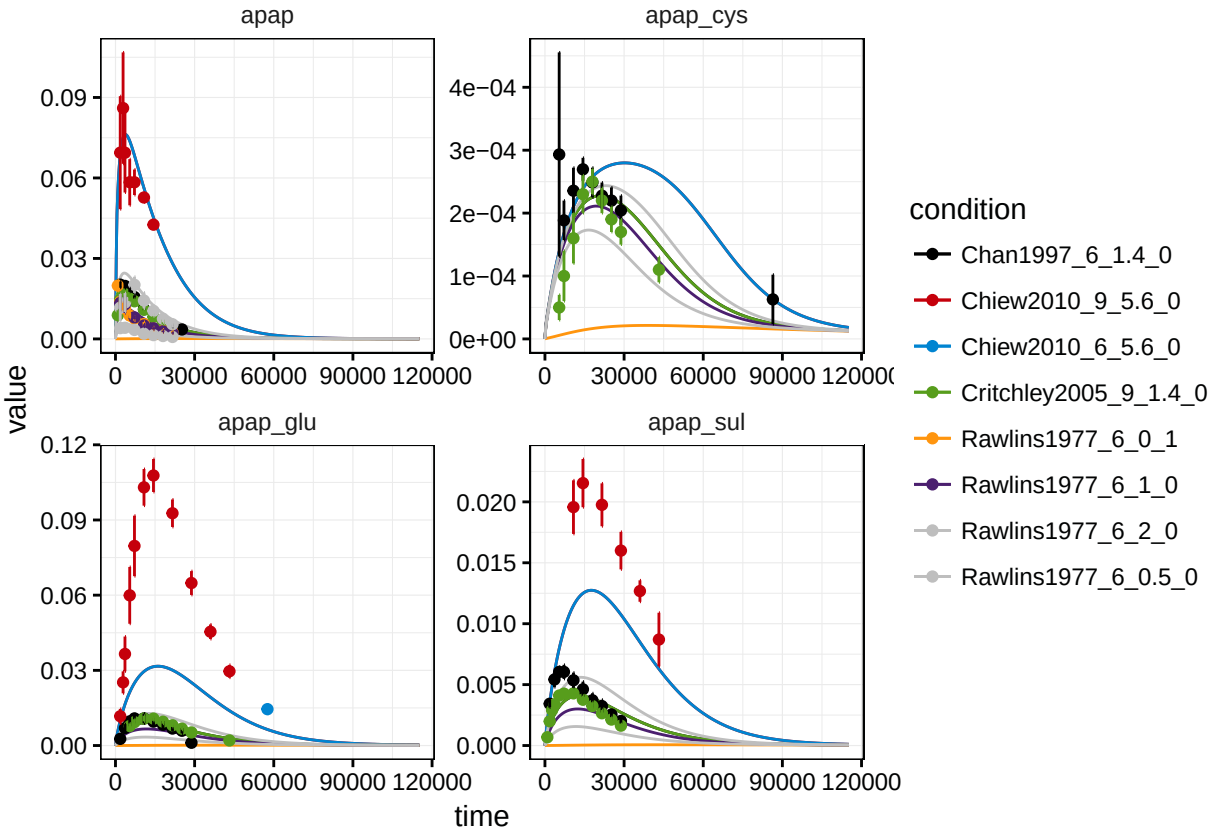

```
## 89       0.033685358        0.02820679
```

```
plotValues(myfit3 %>% as.parframe())+scale_y_log10()
```




```
mypred3 <- (g*x*p3)(mytimes*4, myfit3 %>% as.parframe() %>% as.parvec)
plotCombined(mypred3, mydatalist, name %in% names(observables))
```



Free other parameters 4 - not good

Same problem as in tries 1,2,3. The only difference to try 2 is that I removed the structural non-identifiability of Ka_apap_sul and F_apap_sul.

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters4 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap_sul"#, "F_apap_sul"    ,
                      # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
```

```
                    # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                    )

fixed_parameters4 <- pars[!(names(pars)%in%c(free_parameters4,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters4] <- paste0("exp(log", free_parameters4, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p4 <- NULL
for(i in 1:length(p_list)) { p4 <<- p4 + p_list[[i]]}

pouter <- log(pars[free_parameters4]) %>% set_names(paste0("log",names(.)))


# mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj4 <- normL2(mydatalist, (g*x*p4))

# job4 <- runbg({myfit <- mstrust(objfun = obj4, center = pouter, studyname = "methacetin", cores = 15,

# save(job4, file = "job4.rda")
```

```
# myfit4 <- job4$get()$knecht1
# save(myfit4, file = "myfit4.rda")
# job4$purge()
load("myfit4.rda")
myfit4 %>% as.parframe()
```

```
##     index    value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1      65 3134.039      TRUE         31         -5.067596     -2.064909
## 2      47 3134.040      TRUE         74         -5.067589     -2.064901
## 3      51 3134.040      TRUE         82         -5.067591     -2.064903
## 4      49 3134.040      TRUE         58         -5.067589     -2.064902
## 5      17 3134.040      TRUE         18         -5.067592     -2.064904
## 6      91 3134.040      TRUE         25         -5.067590     -2.064903
## 7      59 3134.040     FALSE        100         -5.067592     -2.064905
## 8      64 3134.040      TRUE         57         -5.067590     -2.064902
## 9      73 3134.041      TRUE         59         -5.067589     -2.064902
## 10      2 3134.041      TRUE         22         -5.067592     -2.064904
## 11     50 3134.041      TRUE         19         -5.067588     -2.064900
## 12     68 3134.041      TRUE         51         -5.067590     -2.064903
## 13     52 3134.041      TRUE         40         -5.067591     -2.064904
```

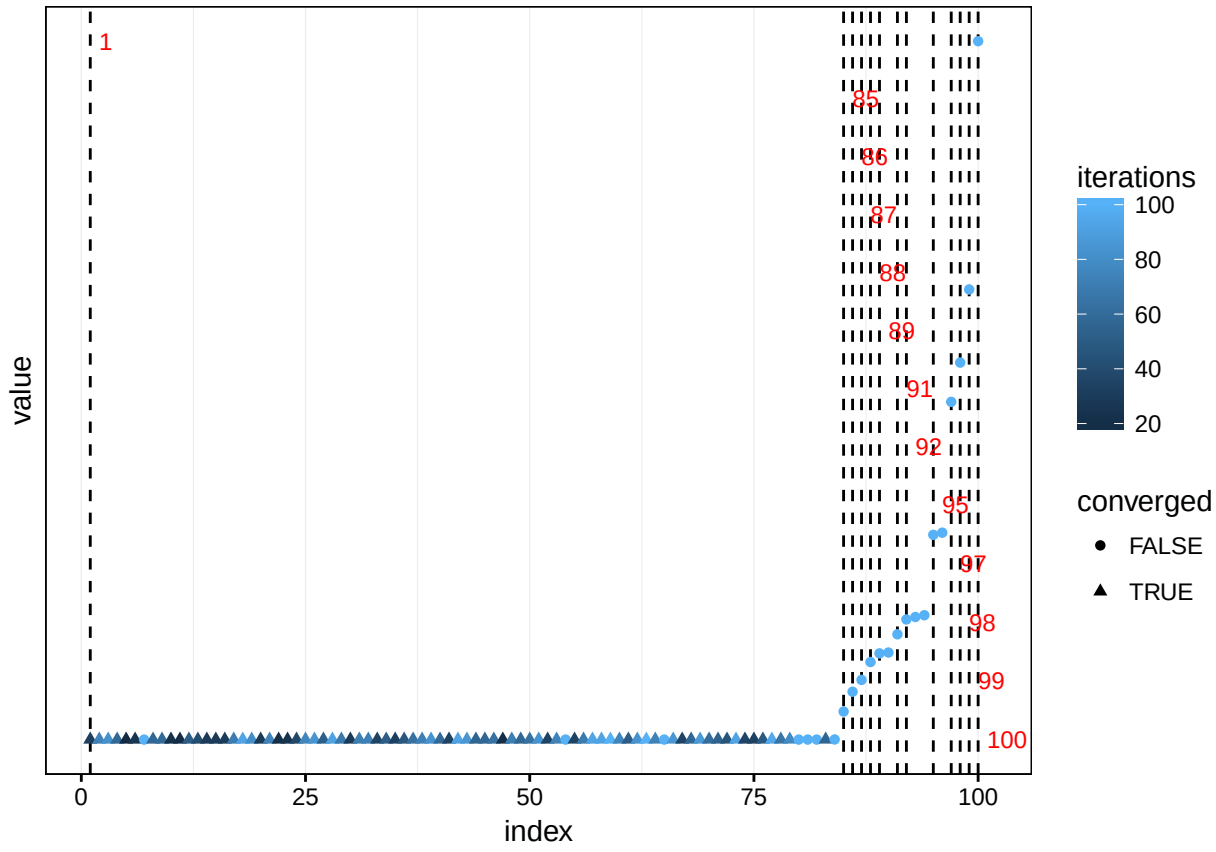
```
## 14     81 3134.041      TRUE         29         -5.067592     -2.064904
## 15     90 3134.041      TRUE         29         -5.067596     -2.064910
## 16     24 3134.041      TRUE         30         -5.067592     -2.064905
## 17     89 3134.041      TRUE         70         -5.067591     -2.064904
## 18     33 3134.041      TRUE         93         -5.067592     -2.064904
## 19      1 3134.041      TRUE         80         -5.067592     -2.064905
## 20     54 3134.041      TRUE         28         -5.067609     -2.064922
## 21     77 3134.041      TRUE         74         -5.067591     -2.064904
## 22     18 3134.042      TRUE         21         -5.067591     -2.064903
## 23      5 3134.042      TRUE         24         -5.067593     -2.064905
## 24     26 3134.042      TRUE         37         -5.067591     -2.064903
## 25      4 3134.043      TRUE         76         -5.067589     -2.064901
## 26      7 3134.043      TRUE         84         -5.067589     -2.064901
## 27     72 3134.043      TRUE         52         -5.067589     -2.064901
## 28     88 3134.043      TRUE         92         -5.067590     -2.064902
## 29     76 3134.043      TRUE         68         -5.067589     -2.064901
## 30    100 3134.043      TRUE         28         -5.067590     -2.064902
## 31     16 3134.043      TRUE         71         -5.067587     -2.064899
## 32     69 3134.043      TRUE         72         -5.067589     -2.064901
## 33     58 3134.043      TRUE         34         -5.067589     -2.064901
## 34     10 3134.043      TRUE         51         -5.067585     -2.064897
## 35     99 3134.043      TRUE         32         -5.067589     -2.064901
## 36     56 3134.043      TRUE         47         -5.067588     -2.064901
## 37     75 3134.043      TRUE         63         -5.067589     -2.064901
## 38     14 3134.043      TRUE         72         -5.067589     -2.064901
## 39     67 3134.043      TRUE         83         -5.067592     -2.064904
## 40     74 3134.043      TRUE         59         -5.067590     -2.064902
## 41     61 3134.043      TRUE         34         -5.067589     -2.064901
## 42     53 3134.043      TRUE         93         -5.067592     -2.064904
## 43     44 3134.043      TRUE         85         -5.067589     -2.064901
## 44     95 3134.043      TRUE         56         -5.067589     -2.064901
## 45     79 3134.043      TRUE         57         -5.067583     -2.064895
## 46     21 3134.043      TRUE         64         -5.067589     -2.064901
## 47     13 3134.043      TRUE         21         -5.067588     -2.064900
## 48     93 3134.043      TRUE         71         -5.067589     -2.064901
## 49     62 3134.043      TRUE         57         -5.067591     -2.064903
## 50     35 3134.043      TRUE         63         -5.067589     -2.064901
## 51     57 3134.043      TRUE         83         -5.067588     -2.064901
## 52     48 3134.043      TRUE         34         -5.067588     -2.064901
## 53     12 3134.043      TRUE         74         -5.067589     -2.064901
## 54     23 3134.043     FALSE        100         -5.067593     -2.064905
## 55     94 3134.043      TRUE         34         -5.067590     -2.064903
## 56     45 3134.043      TRUE         69         -5.067591     -2.064903
## 57     20 3134.043      TRUE         93         -5.067589     -2.064901
## 58     80 3134.043      TRUE         92         -5.067614     -2.064930
## 59     92 3134.043      TRUE        100         -5.067601     -2.064915
## 60     96 3134.043      TRUE         75         -5.067594     -2.064907
## 61     86 3134.043      TRUE         51         -5.067589     -2.064901
## 62     28 3134.043      TRUE         83         -5.067590     -2.064903
## 63      6 3134.043      TRUE        100         -5.067589     -2.064902
## 64     11 3134.043      TRUE         73         -5.067594     -2.064907
## 65     30 3134.043     FALSE        100         -5.067594     -2.064908
## 66     29 3134.043      TRUE         85         -5.067589     -2.064902
## 67     39 3134.043      TRUE         35         -5.067589     -2.064901
```

```
## 68     78 3134.043      TRUE         57         -5.067585     -2.064897
## 69     22 3134.043      TRUE         87         -5.067589     -2.064901
## 70      9 3134.043      TRUE         61         -5.067589     -2.064901
## 71      8 3134.043      TRUE         54         -5.067589     -2.064901
## 72     87 3134.043      TRUE         46         -5.067589     -2.064901
## 73     66 3134.043      TRUE         93         -5.067589     -2.064901
## 74     63 3134.043      TRUE         35         -5.067589     -2.064901
## 75     97 3134.043      TRUE         33         -5.067589     -2.064901
## 76     41 3134.043      TRUE         49         -5.067589     -2.064902
## 77      3 3134.043      TRUE         96         -5.067589     -2.064901
## 78     42 3134.043      TRUE         65         -5.067589     -2.064901
## 79     85 3134.043      TRUE         78         -5.067589     -2.064901
## 80     31 3134.043     FALSE        100         -5.067589     -2.064901
## 81     25 3134.043     FALSE        100         -5.067601     -2.064916
## 82     15 3134.043     FALSE        100         -5.067597     -2.064913
## 83     43 3134.043      TRUE         56         -5.067589     -2.064901
## 84     82 3134.055     FALSE        100         -5.068118     -2.065507
## 85     37 3137.376     FALSE        100         -5.075191     -2.072940
## 86     46 3139.735     FALSE        100         -5.095123     -2.094463
## 87     34 3141.146     FALSE        100         -5.142044     -2.145792
## 88     70 3143.281     FALSE        100         -5.135431     -2.138184
## 89     40 3144.313     FALSE        100         -5.152946     -2.157667
## 90     98 3144.415     FALSE        100         -5.154875     -2.159813
## 91     38 3146.591     FALSE        100         -5.099741     -2.098607
## 92     83 3148.365     FALSE        100         -5.491270     -2.543298
## 93     71 3148.656     FALSE        100         -5.218492     -2.230773
## 94     27 3148.871     FALSE        100         -5.166102     -2.171982
## 95     55 3158.495     FALSE        100         -5.119089     -2.119275
## 96     19 3158.750     FALSE        100         -5.115193     -2.114925
## 97     36 3174.475     FALSE        100         -5.364188     -2.394951
## 98     32 3179.215     FALSE        100         -5.169572     -2.174920
## 99     84 3188.051     FALSE        100         -5.386486     -2.420244
## 100    60 3218.236     FALSE        100         -5.552237     -2.612372
##     logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap_sul
## 1           -6.117758       -10.485007     -6.240449     69.0940136
## 2           -6.117757       -10.485016     -6.240488     -1.9728623
## 3           -6.117757       -10.485007     -6.240450     -1.9723416
## 4           -6.117757       -10.485006     -6.240446     -0.7434353
## 5           -6.117757       -10.485008     -6.240455     21.5604671
## 6           -6.117758       -10.484995     -6.240395     39.2232311
## 7           -6.117757       -10.485009     -6.240458      3.4806716
## 8           -6.117757       -10.485009     -6.240458      0.6840248
## 9           -6.117757       -10.485008     -6.240455      2.4761605
## 10          -6.117757       -10.485008     -6.240454     21.2226699
## 11          -6.117757       -10.485005     -6.240442     30.9021662
## 12          -6.117757       -10.485009     -6.240457      0.1377165
## 13          -6.117757       -10.485009     -6.240456     -1.7477047
## 14          -6.117757       -10.485000     -6.240420      2.2812681
## 15          -6.117757       -10.484995     -6.240399     39.6486645
## 16          -6.117757       -10.484986     -6.240358     -1.8979006
## 17          -6.117757       -10.485008     -6.240454     -1.2828334
## 18          -6.117757       -10.485009     -6.240457     -1.6443319
## 19          -6.117757       -10.485009     -6.240456      6.6306482
## 20          -6.117758       -10.484943     -6.240176     -2.0721184
```

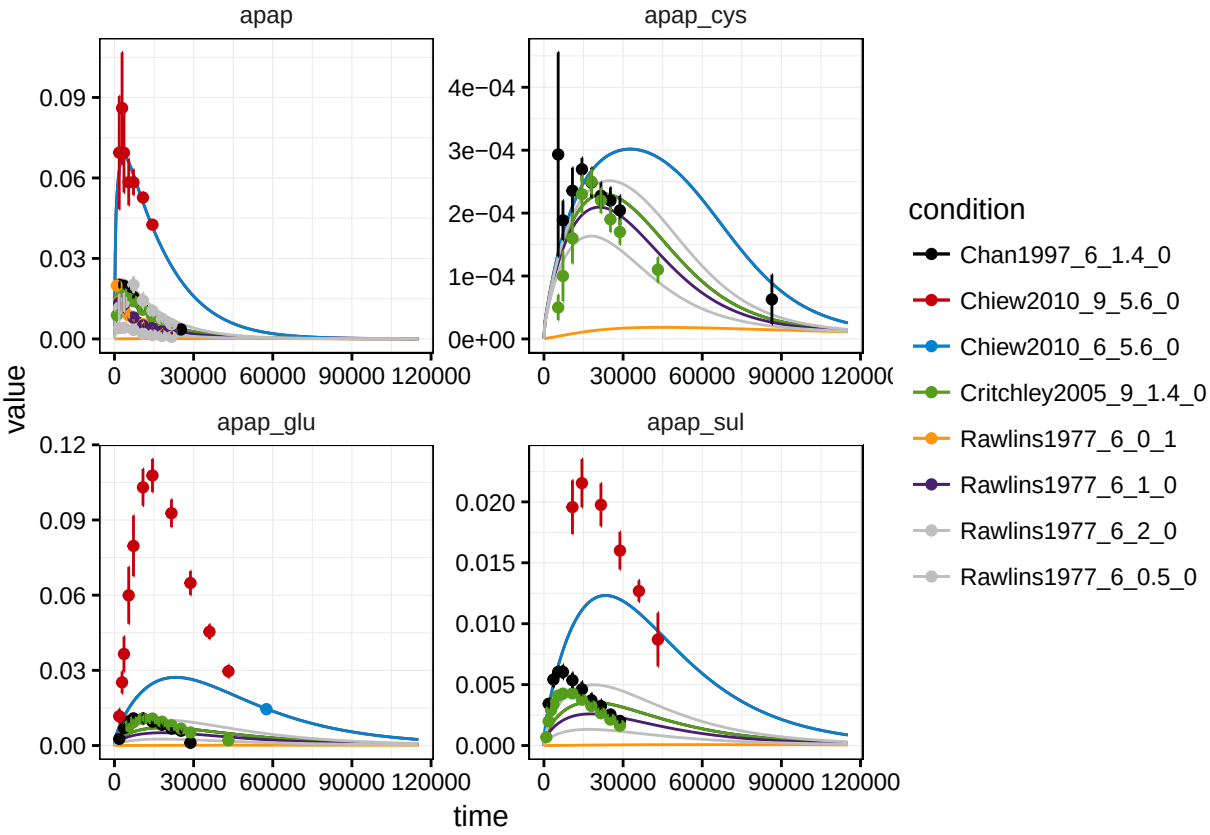
```
## 21          -6.117757       -10.485006     -6.240446     -0.2157220
## 22          -6.117757       -10.485013     -6.240477     15.2548766
## 23          -6.117757       -10.485004     -6.240435     21.7050456
## 24          -6.117757       -10.485009     -6.240457     15.8995731
## 25          -6.117758       -10.485014     -6.240479     -6.6755403
## 26          -6.117758       -10.485007     -6.240450     -6.6759718
## 27          -6.117758       -10.485016     -6.240486     -6.6771799
## 28          -6.117758       -10.485006     -6.240443     -6.6755490
## 29          -6.117758       -10.485008     -6.240452     -6.6674330
## 30          -6.117758       -10.485007     -6.240449     -6.7129872
## 31          -6.117758       -10.485009     -6.240458     -6.6910070
## 32          -6.117758       -10.485009     -6.240456     -6.7294118
## 33          -6.117758       -10.485011     -6.240467     -6.7499658
## 34          -6.117758       -10.484992     -6.240385     -6.7753548
## 35          -6.117758       -10.485006     -6.240444     -6.7982127
## 36          -6.117758       -10.485015     -6.240482     -6.7993152
## 37          -6.117758       -10.485009     -6.240456     -6.7184190
## 38          -6.117758       -10.485010     -6.240461     -6.7181854
## 39          -6.117758       -10.484977     -6.240317     -6.4067626
## 40          -6.117758       -10.484989     -6.240370     -6.3963486
## 41          -6.117758       -10.485011     -6.240467     -6.4487918
## 42          -6.117758       -10.484975     -6.240311     -6.8858124
## 43          -6.117758       -10.485013     -6.240473     -6.8105967
## 44          -6.117758       -10.485014     -6.240480     -6.8801165
## 45          -6.117758       -10.484995     -6.240396     -6.3543138
## 46          -6.117758       -10.485009     -6.240455     -6.2724335
## 47          -6.117758       -10.485016     -6.240488     -6.2713400
## 48          -6.117758       -10.485009     -6.240457     -6.2544553
## 49          -6.117758       -10.484983     -6.240343     -6.2479165
## 50          -6.117758       -10.485014     -6.240480     -6.7652174
## 51          -6.117758       -10.485020     -6.240502     -6.2377692
## 52          -6.117758       -10.485002     -6.240428     -6.2304996
## 53          -6.117758       -10.485008     -6.240453     -6.2218918
## 54          -6.117758       -10.484975     -6.240312     -6.2812702
## 55          -6.117758       -10.485002     -6.240427     -6.1992961
## 56          -6.117758       -10.485003     -6.240433     -7.4500587
## 57          -6.117758       -10.485009     -6.240455     -7.4370724
## 58          -6.117758       -10.485033     -6.240558     -7.5275081
## 59          -6.117758       -10.485020     -6.240503     -7.8137891
## 60          -6.117758       -10.484940     -6.240160     -8.4928510
## 61          -6.117758       -10.485007     -6.240448     -6.1699477
## 62          -6.117758       -10.485011     -6.240467     -7.4507666
## 63          -6.117758       -10.485017     -6.240491     -7.3759811
## 64          -6.117758       -10.485017     -6.240491     -7.4587394
## 65          -6.117757       -10.485122     -6.240939     -6.2337595
## 66          -6.117758       -10.485016     -6.240485     -6.2104326
## 67          -6.117758       -10.485008     -6.240451     -4.6227384
## 68          -6.117757       -10.485011     -6.240465     -4.6823704
## 69          -6.117758       -10.485009     -6.240456     -4.5308114
## 70          -6.117758       -10.485015     -6.240481     -4.5226873
## 71          -6.117758       -10.485011     -6.240467     -4.5802548
## 72          -6.117758       -10.485006     -6.240445     -4.9114159
## 73          -6.117758       -10.485007     -6.240446     -3.6928266
## 74          -6.117758       -10.485006     -6.240445     -4.3641118
```

```
## 75          -6.117758       -10.485008     -6.240450     -3.5890165
## 76          -6.117758       -10.485011     -6.240466     -7.3094377
## 77          -6.117758       -10.485011     -6.240464     -5.0276163
## 78          -6.117758       -10.485008     -6.240454     -4.6387166
## 79          -6.117758       -10.485012     -6.240469     -3.9083782
## 80          -6.117758       -10.485013     -6.240475     -5.0751062
## 81          -6.117757       -10.485093     -6.240818     -7.0676317
## 82          -6.117757       -10.485295     -6.241673     -6.6735734
## 83          -6.117758       -10.485013     -6.240472     -5.9934624
## 84          -6.117761       -10.487212     -6.249134     -5.4604466
## 85          -6.117928       -10.449203     -6.080448     -6.6258821
## 86          -6.118330       -10.381460     -5.832870     -7.9336294
## 87          -6.119157       -10.250605     -5.444169     -6.8631359
## 88          -6.119077       -10.209121     -5.332738     -7.6590339
## 89          -6.119343       -10.198292     -5.302422     -6.6369818
## 90          -6.119373       -10.196730     -5.298386     -5.7178879
## 91          -6.118512       -10.233021     -5.385454     -5.4117831
## 92          -6.124020       -10.255976     -5.457926     -6.4718377
## 93          -6.120340       -10.126747     -5.126990     -6.1306720
## 94          -6.119559       -10.115896     -5.101673     -6.2373374
## 95          -6.118822       -10.037373     -4.914753     -7.3040935
## 96          -6.118761       -10.032765     -4.904798     -8.1316839
## 97          -6.122285        -9.791232     -4.435104     -8.2165663
## 98          -6.119409        -9.727594     -4.317186     -6.6333748
## 99          -6.122431        -9.599693     -4.107126     -8.2058842
## 100         -6.124131        -9.184695     -3.488178     -6.1051159
```

```
plotValues(myfit4 %>% as.parframe())+scale_y_log10()
```




```
mypred4 <- (g*x*p4)(mytimes*4, myfit4 %>% as.parframe() %>% as.parvec, deriv = F)
myplot <- plotCombined(mypred4, mydatalist, name %in% names(observables))
# plotly::ggplotly(myplot)
myplot
```



Further hypotheses

Freeing the parameters in the upper four fits didn't help much. On the other hand, lots of the fits didn't converge. From here, I could do several things.

1. Introduce scaling factors for each condition
2. Fill the empty sigmas with fitted sigmas
3. Run a profile likelihood analysis for the fits 1-4
4. Re-run the fits 2 and 3 without the structural non-identifiability of Ka_apap_sul and F_apap_sul
5. If I re-run the fits, I can take the fitted values of the original free parameters as center for the sampling
6. In data, drop the column n before converting it to a datalist
7. In the upper fits, I freed the parameters Ka_apap_sul, which of course doesn't make sense, since no apap_sul is given. I have to free the parameters Ka_apap

Free other parameters 5 - not good

Here I freed Ka_apap which makes sense conceptually (increase absorption rate). But it doesn't improve the fits much.

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters5 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap"#, "F_apap_sul"    ,
                      # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                      )

fixed_parameters5 <- pars[!(names(pars)%in%c(free_parameters5,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters5] <- paste0("exp(log", free_parameters5, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p5 <- NULL
for(i in 1:length(p_list)) { p5 <<- p5 + p_list[[i]]}

pouter <- log(pars[free_parameters5]) %>% set_names(paste0("log",names(.)))


# mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj5 <- normL2(mydatalist, (g*x*p5))

# job5 <- runbg({myfit <- mstrust(objfun = obj5, center = pouter, studyname = "methacetin", cores = 12,

# save(job5, file = "job5.rda")
```

```
# myfit5 <- job5$get()$knecht1
# save(myfit5, file = "myfit5.rda")
# job5$purge()
load("myfit5.rda")
```

```
myfit5 %>% as.parframe()
```

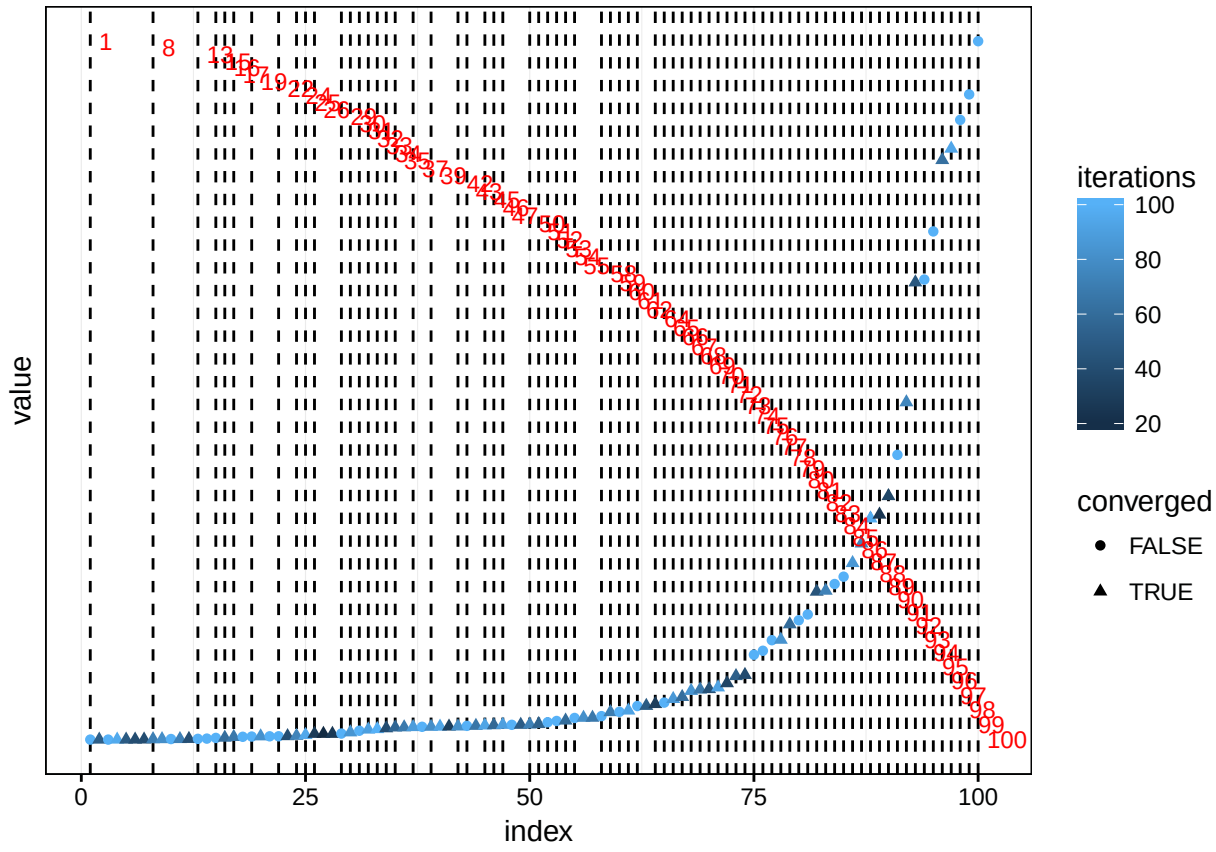
```
##     index    value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1      33 3092.015     FALSE        100         -5.048048     -2.013030
## 2      12 3092.025      TRUE         51         -5.047014     -2.013058
## 3      99 3092.031     FALSE        100         -5.048425     -2.014686
## 4      60 3092.117      TRUE         96         -5.047379     -2.011610
## 5      88 3092.146      TRUE         49         -5.047300     -2.011395
## 6      26 3092.203      TRUE         40         -5.048943     -2.016184
## 7      75 3092.471      TRUE         40         -5.049967     -2.018150
## 8      39 3093.716      TRUE         71         -5.050140     -2.020718
## 9      51 3093.748      TRUE         80         -5.045428     -2.006378
## 10     68 3094.137     FALSE        100         -5.045281     -2.005802
## 11     52 3094.192      TRUE         72         -5.045123     -2.005573
## 12     69 3094.630      TRUE         41         -5.044949     -2.004969
## 13     23 3094.872     FALSE        100         -5.051666     -2.023967
## 14     27 3095.719     FALSE        100         -5.075840     -2.039274
## 15     24 3098.324     FALSE        100         -5.043229     -2.000671
## 16     30 3099.358      TRUE         61         -5.054175     -2.031039
## 17     64 3102.168      TRUE         67         -5.055530     -2.034673
## 18     15 3102.577     FALSE        100         -5.060196     -2.037623
## 19     29 3103.466     FALSE        100         -5.041647     -1.996900
## 20      2 3104.346      TRUE         82         -5.040731     -1.995643
## 21     72 3104.390     FALSE        100         -5.046034     -2.002329
## 22     50 3104.541     FALSE        100         -5.056464     -2.037335
## 23     46 3105.176      TRUE         41         -5.040401     -1.995045
## 24     14 3106.298      TRUE         74         -5.040030     -1.994340
## 25     11 3109.687      TRUE         95         -5.038767     -1.992191
## 26     40 3113.832      TRUE         28         -4.825548     -1.777177
## 27     91 3113.833      TRUE         17         -4.824874     -1.776415
## 28     73 3113.833      TRUE         27         -4.824721     -1.776243
## 29     21 3114.849     FALSE        100         -5.036847     -1.989216
## 30     71 3119.561      TRUE         84         -5.062392     -2.052389
## 31     94 3125.614     FALSE        100         -5.064509     -2.057670
## 32     82 3130.261      TRUE         90         -5.029640     -1.980241
## 33     78 3131.925      TRUE        100         -5.066834     -2.063129
## 34     74 3135.087      TRUE         40         -5.026507     -1.976889
## 35     61 3138.302      TRUE         56         -5.069170     -2.068493
## 36     13 3138.837      TRUE         68         -5.023612     -1.973945
## 37     59 3139.757      TRUE         88         -5.023456     -1.973832
## 38     70 3140.732     FALSE        100         -4.978837     -1.932420
## 39     77 3140.839      TRUE         80         -5.070555     -2.071084
## 40     97 3141.374      TRUE         93         -5.021523     -1.971919
## 41     76 3141.745      TRUE         31         -5.021447     -1.971897
## 42     18 3142.045      TRUE         81         -4.981191     -1.934647
## 43     87 3144.295     FALSE        100         -5.031965     -1.992494
## 44     83 3144.404      TRUE         66         -4.985574     -1.938753
## 45      8 3145.949      TRUE         93         -5.015777     -1.966426
## 46     19 3146.975      TRUE         57         -5.014012     -1.964788
## 47     28 3148.301      TRUE         90         -4.994659     -1.947092
## 48     45 3148.311     FALSE        100         -5.193821     -2.162921
## 49     85 3148.466      TRUE         50         -5.010341     -1.961355
## 50     55 3149.512      TRUE         73         -5.005743     -1.957167
## 51     25 3151.420      TRUE         54         -5.074007     -2.079236
```

```
## 52     44 3158.135     FALSE        100         -5.098649     -2.107816
## 53     92 3163.080     FALSE        100         -5.078409     -2.088624
## 54     36 3164.819      TRUE         60         -5.079690     -2.090699
## 55     53 3174.723     FALSE        100         -5.082924     -2.097938
## 56     48 3175.465      TRUE         81         -5.083216     -2.098530
## 57     38 3175.678      TRUE         67         -5.083344     -2.098754
## 58     58 3181.908     FALSE        100         -5.086805     -2.104824
## 59      3 3197.497      TRUE         70         -5.092141     -2.116165
## 60      6 3198.621     FALSE        100         -5.667636     -2.745662
## 61     56 3203.753      TRUE         92         -5.094827     -2.121265
## 62     79 3221.260     FALSE        100         -5.363321     -2.360381
## 63     81 3222.005      TRUE         49         -5.102893     -2.136245
## 64     42 3229.229      TRUE         30         -5.105307     -2.141263
## 65     54 3234.818     FALSE        100         -5.121329     -2.160179
## 66    100 3249.362      TRUE         86         -5.115699     -2.159164
## 67     65 3257.407      TRUE         61         -5.118766     -2.165044
## 68     22 3281.491      TRUE         84         -5.130019     -2.184829
## 69     35 3286.865      TRUE         67         -5.132671     -2.189371
## 70     31 3288.838      TRUE         43         -5.133347     -2.190710
## 71     90 3295.545      TRUE         92         -5.137110     -2.196859
## 72      4 3312.403      TRUE         35         -5.145391     -2.210955
## 73      7 3341.323      TRUE         52         -5.160390     -2.235817
## 74     93 3345.968      TRUE         39         -5.162856     -2.239855
## 75     49 3429.554     FALSE        100         -5.208755     -2.313268
## 76     43 3446.101     FALSE        100         -5.218333     -2.328163
## 77     47 3490.772     FALSE        100         -6.113453     -3.383613
## 78     98 3492.896      TRUE         83         -5.245221     -2.369769
## 79     86 3559.328      TRUE         59         -5.284311     -2.429141
## 80     17 3576.808     FALSE        100         -5.956349     -3.197008
## 81     95 3602.188     FALSE        100         -5.309764     -2.467286
## 82     62 3704.078      TRUE         45         -5.370256     -2.556695
## 83     16 3708.361      TRUE         73         -5.372827     -2.560450
## 84     37 3738.667     FALSE        100         -5.430106     -2.627314
## 85     89 3772.281     FALSE        100         -5.410468     -2.615316
## 86     32 3835.632      TRUE         85         -5.447291     -2.668516
## 87     10 3928.615      TRUE         73         -5.500455     -2.744546
## 88     66 4050.312      TRUE         97         -5.567756     -2.839627
## 89      9 4069.291      TRUE         25         -5.577862     -2.853824
## 90     20 4162.415      TRUE         36         -5.627617     -2.923004
## 91     41 4377.071     FALSE        100         -5.736622     -3.071627
## 92     63 4667.370      TRUE         75         -5.873234     -3.250624
## 93     84 5402.716      TRUE         47         -6.189660     -3.618262
## 94     57 5421.338     FALSE        100         -6.197813     -3.626719
## 95     34 5749.400     FALSE        100         -6.344636     -3.770575
## 96     96 6273.084      TRUE         62         -6.633897     -4.032914
## 97      5 6360.969      TRUE         94         -6.697614     -4.092807
## 98      1 6588.045     FALSE        100         -7.223027     -4.814143
## 99     67 6796.214     FALSE        100         -7.112142     -4.520640
## 100    80 7252.186     FALSE        100         -7.553036     -4.987803
##     logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap
## 1           -6.142913        -10.483923     -6.226134  -6.853661
## 2           -6.141722        -10.483025     -6.222827  -6.879080
## 3           -6.141694        -10.483600     -6.225265  -6.880146
## 4           -6.143583        -10.483433     -6.224064  -6.838579
```

```
## 5          -6.143710       -10.483324     -6.223574  -6.835689
## 6          -6.140809       -10.483698     -6.225923  -6.898840
## 7          -6.140018       -10.481590     -6.217219  -6.915412
## 8          -6.137818       -10.482448     -6.221512  -6.958648
## 9          -6.146788       -10.482745     -6.220430  -6.762008
## 10         -6.147242       -10.482404     -6.218899  -6.750505
## 11         -6.147301       -10.482619     -6.219797  -6.748926
## 12         -6.147757       -10.482006     -6.217119  -6.737173
## 13         -6.136456       -10.484767     -6.231791  -6.984578
## 14         -6.147504       -10.377083     -5.820361  -6.760132
## 15         -6.150587       -10.481350     -6.213878  -6.658678
## 16         -6.132747       -10.484530     -6.232063  -7.050754
## 17         -6.130966       -10.484826     -6.233982  -7.080629
## 18         -6.132758       -10.464843     -6.137162  -7.052633
## 19         -6.153264       -10.478742     -6.202425  -6.574467
## 20         -6.153634       -10.481131     -6.212586  -6.561319
## 21         -6.152341       -10.464095     -6.129712  -6.607360
## 22         -6.129626       -10.484756     -6.234201  -7.102247
## 23         -6.153980       -10.481024     -6.212107  -6.549190
## 24         -6.154429       -10.480677     -6.210612  -6.533083
## 25         -6.155665       -10.480526     -6.209904  -6.485931
## 26         -6.118762       -10.475580     -6.196832  31.873499
## 27         -6.118752       -10.475531     -6.196624  55.502206
## 28         -6.118750       -10.475518     -6.196574  39.450364
## 29         -6.157285       -10.479962     -6.207502  -6.416566
## 30         -6.122895       -10.484763     -6.237037  -7.203278
## 31         -6.120642       -10.485013     -6.239124  -7.234222
## 32         -6.160829       -10.478451     -6.201464  -6.204004
## 33         -6.118459       -10.484991     -6.240048  -7.263303
## 34         -6.161590       -10.478040     -6.199968  -6.127974
## 35         -6.116384       -10.484976     -6.240980  -7.289907
## 36         -6.162042       -10.477629     -6.198468  -6.061503
## 37         -6.162147       -10.473231     -6.180396  -6.043756
## 38         -6.152868       -10.474911     -6.190212  -5.242344
## 39         -6.115597       -10.483411     -6.234660  -7.299884
## 40         -6.162259       -10.477070     -6.196311  -6.010601
## 41         -6.162286       -10.477402     -6.197725  -6.002505
## 42         -6.153745       -10.474400     -6.188004  -5.279448
## 43         -6.150185       -10.169550     -5.239674  -5.087375
## 44         -6.155368       -10.474578     -6.188497  -5.350840
## 45         -6.162315       -10.476284     -6.193498  -5.894335
## 46         -6.162217       -10.476533     -6.194645  -5.859379
## 47         -6.158464       -10.475558     -6.191961  -5.508233
## 48         -6.162193        -9.922334     -4.689143  -6.308751
## 49         -6.161885       -10.476341     -6.194120  -5.793254
## 50         -6.161180       -10.476133     -6.193588  -5.706645
## 51         -6.112417       -10.484911     -6.242675  -7.338300
## 52         -6.111379       -10.399040     -5.906211  -7.356127
## 53         -6.109146       -10.484801     -6.243895  -7.376172
## 54         -6.108686       -10.484866     -6.244368  -7.381576
## 55         -6.106056       -10.484666     -6.244966  -7.410372
## 56         -6.105865       -10.484657     -6.245030  -7.412447
## 57         -6.105810       -10.485249     -6.247602  -7.413133
## 58         -6.104238       -10.485086     -6.247709  -7.430112
```

```
## 59         -6.100392       -10.484365     -6.246801  -7.469650
## 60         -6.150324        -9.548143     -4.049491  -4.826577
## 61         -6.098905       -10.484233     -6.247039  -7.484501
## 62         -6.167073        -9.120278     -3.405905  -5.985868
## 63         -6.094708       -10.483373     -6.245800  -7.525090
## 64         -6.093081       -10.483855     -6.248832  -7.540169
## 65         -6.092254       -10.437933     -6.059355  -7.550372
## 66         -6.088721       -10.484512     -6.254246  -7.579765
## 67         -6.087010       -10.483173     -6.249519  -7.594696
## 68         -6.082038       -10.482922     -6.251471  -7.636854
## 69         -6.080955       -10.482705     -6.251207  -7.645794
## 70         -6.080549       -10.483382     -6.254191  -7.649038
## 71         -6.079225       -10.482685     -6.252188  -7.659911
## 72         -6.075914       -10.482363     -6.252858  -7.686284
## 73         -6.070402       -10.481818     -6.253965  -7.728690
## 74         -6.069534       -10.481681     -6.253922  -7.735210
## 75         -6.054641       -10.480143     -6.256704  -7.841316
## 76         -6.051855       -10.484385     -6.273623  -7.860077
## 77         -6.067376        -9.811943     -4.504716  -7.812811
## 78         -6.044152       -10.478953     -6.258158  -7.910862
## 79         -6.033800       -10.477787     -6.259505  -7.976511
## 80         -6.055614        -8.643112     -2.860048  -7.884565
## 81         -6.027447       -10.476854     -6.259313  -8.015625
## 82         -6.013307       -10.475080     -6.259833  -8.100969
## 83         -6.012738       -10.474635     -6.258261  -8.104350
## 84         -6.011089       -10.150661     -5.243886  -8.119935
## 85         -6.004539       -10.473357     -6.257229  -8.153006
## 86         -5.996888       -10.471932     -6.255070  -8.198522
## 87         -5.986450       -10.469649     -6.250315  -8.261070
## 88         -5.974136       -10.466276     -6.241200  -8.336843
## 89         -5.972344       -10.465692     -6.239416  -8.348136
## 90         -5.964066       -10.463081     -6.231293  -8.401800
## 91         -5.947932       -10.454315     -6.199176  -8.516291
## 92         -5.932236       -10.439037     -6.139267  -8.657508
## 93         -5.921395       -10.379452     -5.914117  -8.977824
## 94         -5.921663       -10.376172     -5.903049  -8.985584
## 95         -5.930944       -10.344014     -5.791353  -9.121163
## 96         -5.965773       -10.353206     -5.784993  -9.335672
## 97         -5.974380       -10.368935     -5.823149  -9.371582
## 98         -6.001993        -8.543989     -3.021633  -9.460633
## 99         -6.030179       -10.183618     -5.328557  -9.548293
## 100        -6.103996        -7.823505     -2.214118  -9.722764
```

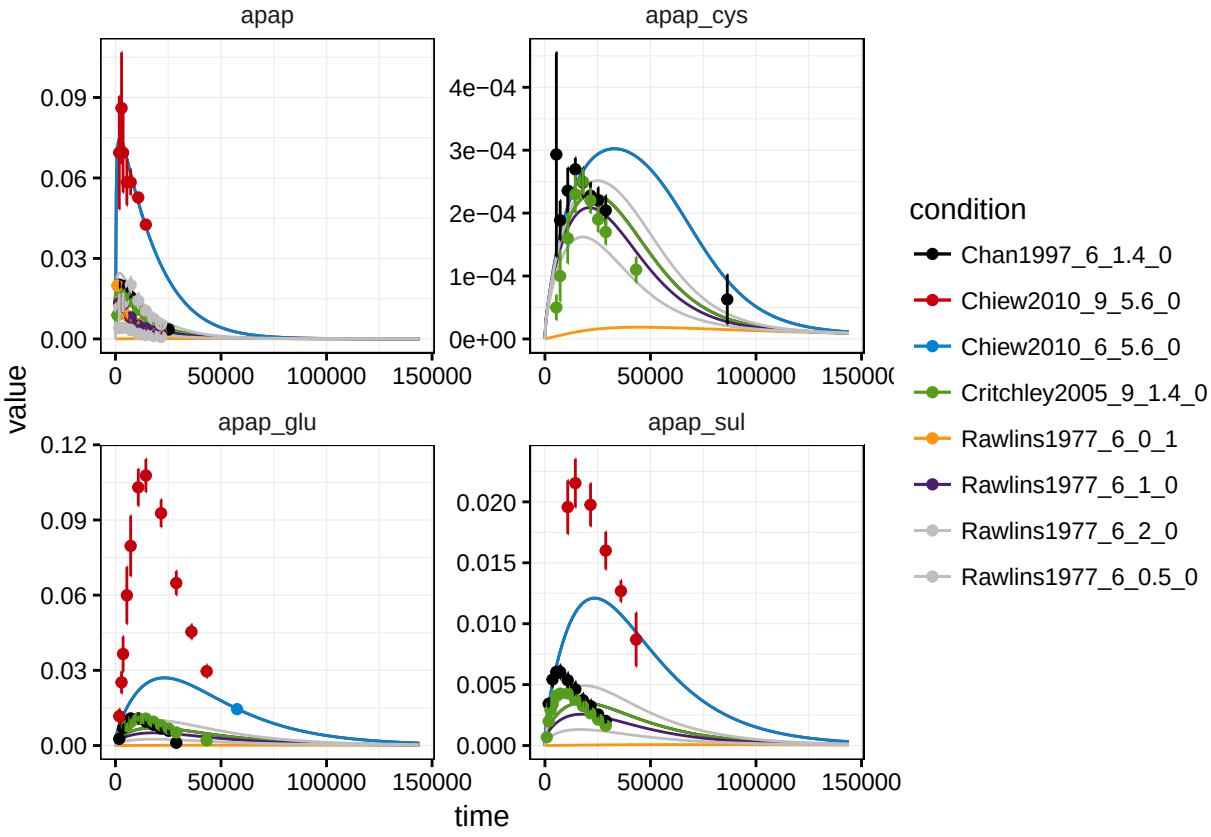
```
plotValues(myfit5 %>% as.parframe())+scale_y_log10()
```




```
mypred5 <- (g*x*p5)(mytimes*5, myfit5 %>% as.parframe() %>% as.parvec, deriv = F)
```

```
## Warning: Parameter vector of an unconverged fit is selected.
```

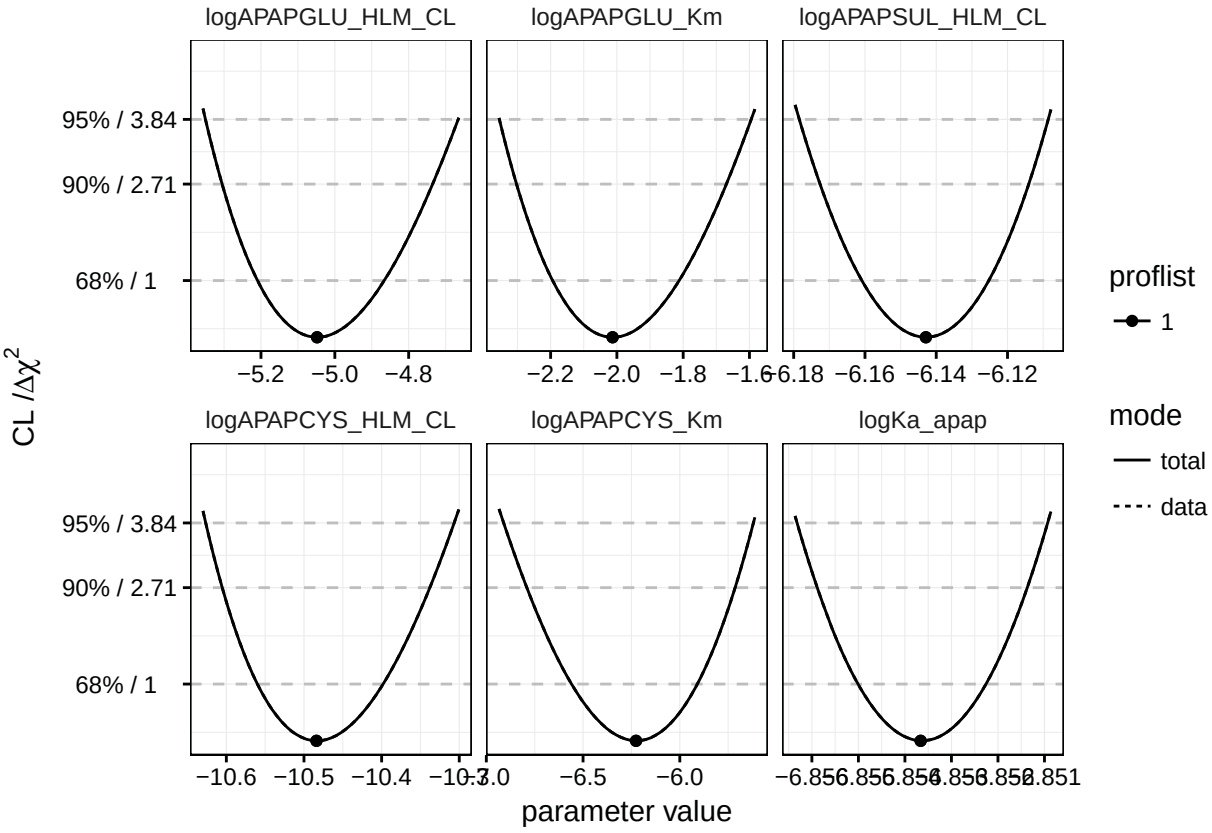
```
myplot <- plotCombined(mypred5, mydatalist, name %in% names(observables))
# plotly::ggplotly(myplot)
myplot
```



Look at profiles of try 5

```
# profile_job5 <- runbg({myprofile <- dMod::profile(obj = obj5,
#                                                   pars = myfit5 %>% as.parframe() %>% as.parvec(),
#                                                   whichPar = names(myfit5 %>% as.parframe() %>% as.pa
#                                                   cores = 12); myprofile},
#                       machine = "knecht5", filename = "methacetin_profile_5")
# save(profile_job5, file = "profile_job5.rda")
```

```
# profiles5 <- profile_job5$get()$knecht5
# save(profiles5, file = "profiles5.rda")
# profile_job5$purge()
load("profiles5.rda")
plotProfile(profiles5)
```



Free other parameters 6 - not enough fits converged

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters6 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap", #"F_apap_sul"    ,
                      "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
```

```
                    )

fixed_parameters6 <- pars[!(names(pars)%in%c(free_parameters6,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters6] <- paste0("exp(log", free_parameters6, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p6 <- NULL
for(i in 1:length(p_list)) { p6 <<- p6 + p_list[[i]]}

pouter <- log(pars[free_parameters6]) %>% set_names(paste0("log",names(.)))
best_fit <- myfit %>% as.parframe() %>% as.parvec()
pouter[names(best_fit)] <- best_fit

# mypred <- (g*x*p)(seq(0, 48*3600, length.out = 200), pouter)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj6 <- normL2(mydatalist, (g*x*p6))

# job6 <- runbg({myfit <- mstrust(objfun = obj6, center = pouter, studyname = "methacetin", cores = 10,

# save(job6, file = "job6.rda")
# job6$check()
```

```
# myfit6 <- job6$get()$knecht3
# save(myfit6, file = "myfit6.rda")
# job6$purge()
load("myfit6.rda")
myfit6 %>% as.parframe()
```

```
##    index        value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1     16     2654.322      TRUE         88       -6.28819055  -4.006405295
## 2     60     3025.841     FALSE        100        5.03628140   8.198860005
## 3     39     3059.748     FALSE        100       -3.42767119   0.208689422
## 4     19     3210.587      TRUE        100       -4.25142567  -1.641754253
## 5     47     3233.777      TRUE         48       -5.80909960  -2.745561196
## 6     48     3302.297     FALSE        100       -4.77085495  -0.860588465
## 7     46     3351.504     FALSE        100       -7.30264386  -5.555581205
## 8     30     3528.728     FALSE        100       -2.84611729   0.871772012
## 9     42     3575.262     FALSE        100       -7.29035435  -5.378360619
## 10    62     3671.498      TRUE         55       -3.35414037   1.351805397
## 11    32     3674.163     FALSE        100       -7.09552238  -5.571430309
## 12     2     3696.864      TRUE         66        6.93088682  11.000639626
```

```
## 13    96     3707.203     FALSE        100       -4.93799139  -3.409831952
## 14    90     3709.900     FALSE        100       -4.91667708  -1.093684684
## 15    89     3727.181      TRUE         73       -7.72903239  -5.002806677
## 16     3     3773.407     FALSE        100       -0.95999313   2.799708371
## 17    95     3800.724     FALSE        100       -7.67546612  -7.475758253
## 18    73     3801.769      TRUE         75        9.16713967  13.894546818
## 19     1     3811.071     FALSE        100       -7.16860415  -5.524541443
## 20     5     3962.946     FALSE        100       -1.30319465   2.413813545
## 21    12     3982.690      TRUE         99       -7.20224999  -4.388141984
## 22    84     4002.798     FALSE        100       -2.79805230   2.254062864
## 23    20     4036.551     FALSE        100       -1.05602233   0.647055917
## 24    71     4084.325     FALSE        100       -0.37947337   1.644677687
## 25    34     4194.968     FALSE        100       -6.37864799  -5.005273275
## 26    85     4206.239     FALSE        100       -1.61646500   3.264392376
## 27    81     4251.968     FALSE        100       -5.19491931  -2.487479200
## 28    13     4253.677     FALSE        100       -6.61617168  -3.996258795
## 29    78     4274.255     FALSE        100       -8.19465759  -7.274086478
## 30    98     4280.238     FALSE        100        0.28767585   4.225302686
## 31    91     4304.887     FALSE        100       -7.56647093  -5.480781584
## 32    40     4309.295     FALSE        100       -4.63232376  -0.817927064
## 33    53     4310.163      TRUE         76        8.71239269  11.517079557
## 34    44     4461.254     FALSE        100       -2.73956482   0.855344663
## 35    80     4544.697     FALSE        100        0.06195615   2.827907427
## 36    57     4562.359      TRUE         65       -5.53570914  -3.694942996
## 37    61     4613.345      TRUE         48        7.80846068  13.489252739
## 38   100     4687.952     FALSE        100       -5.32662456  -3.381779594
## 39    29     4694.181     FALSE        100       -2.41376334   0.302151177
## 40    33     4798.199     FALSE        100       -8.16559834  -5.637462821
## 41    52     4806.863      TRUE         73       -2.94393041  -0.004962181
## 42    67     4832.578      TRUE         27       -5.26522213  -2.805248969
## 43    24     4909.157     FALSE        100       -7.18179976  -5.452332446
## 44    37     5070.099     FALSE        100       -4.18687371  -0.811246811
## 45    93     5114.882     FALSE        100       -7.08410330  -6.357020686
## 46    25     5211.076      TRUE         81        6.64088478  11.515295513
## 47     9     5215.177     FALSE        100       -8.83945182  -7.203601377
## 48    15     5450.106     FALSE        100       -0.56360973   3.931814427
## 49    58     5546.522      TRUE         51       -4.79545014  -0.443840554
## 50    43     5561.124     FALSE        100       -8.33510582  -6.811799846
## 51    18     5731.666      TRUE         47       -2.48755258   2.429196022
## 52    50     5778.216     FALSE        100       -3.76678335  -0.110984966
## 53    68     5823.582     FALSE        100       -8.59703869 -15.679999547
## 54    75     5843.639     FALSE        100       -9.12888512  -7.465251278
## 55    27     5914.688     FALSE        100       -8.42538057  -7.599904569
## 56    45     5956.249     FALSE        100       -9.14107228 -18.463314077
## 57    21     6247.809     FALSE        100       -8.18138039  -5.137368733
## 58    82     6353.826     FALSE        100       -8.62683075 -11.248368951
## 59     8     6620.156      TRUE         89        1.72946974   5.948647258
## 60    92     6656.566      TRUE         70       -0.28305230   5.794653677
## 61    94     6671.815     FALSE        100       -0.24647383   3.412465214
## 62    36     6882.919      TRUE         69      -10.94100122  -9.473022124
## 63    77     6902.612     FALSE        100       -7.82394510  -6.269701572
## 64    14     6910.975     FALSE        100       -7.92399834  -6.221567907
## 65     4     6950.341     FALSE        100       -8.93812229 -11.531089754
## 66    86     7077.814     FALSE        100        2.84114778   6.659544925
```

```
## 67    63     7771.566     FALSE        100       -0.90656228   2.818906219
## 68    59     7847.420      TRUE         92      -10.58468318   3.371774800
## 69    28     8097.233     FALSE        100       -0.37946771   2.587078471
## 70    79     8257.313     FALSE        100       -1.40915139   1.471084234
## 71    56     8479.505      TRUE         80      -11.94573408   4.339411314
## 72    97     8516.742     FALSE        100       -9.08275433 -12.661170009
## 73    54     9004.674      TRUE         61        9.82488392  13.308900643
## 74    65     9219.669      TRUE         70       -2.25528843   0.531844241
## 75    88    18642.628      TRUE         95       14.08217284  17.017356531
## 76    22    21176.498     FALSE        100       -0.66247141   2.678639614
## 77    83    21334.098     FALSE        100        7.65081177   9.402364579
## 78    26    39039.739     FALSE        100       -0.06330348   3.510889791
## 79    38   684703.471      TRUE         27      -22.13243846   9.813246162
## 80    41  1269921.608      TRUE         40      -16.43552020   9.982784441
## 81    76  3458970.665      TRUE         28      -16.06434258   8.689072716
## 82    64 16634928.329      TRUE         32      -15.59699500  10.046728044
## 83    74 16995948.716      TRUE         44      -16.77845013  11.006377601
## 84    51 17644312.397      TRUE         38      -18.84839367   8.503217915
## 85    87 22989692.369      TRUE         31      -17.02819354   6.897140771
## 86    17 32686254.774      TRUE         36      -21.88470664  12.291628143
## 87    35 76489956.632      TRUE         41      -15.32116804   8.712011329
## 88    69 86160933.106      TRUE         39      -15.19369691   9.322028557
## 89     7 95286945.888      TRUE         37      -16.63889902   8.710000736
##    logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap
## 1          -6.242811         -9.413691    -6.9411200  -5.245524
## 2          -5.281948        -10.686351    -6.4089990  -7.197151
## 3          -6.146221         -9.736307    -7.4556767  -6.582344
## 4          -4.910387        -10.540902    -7.4101431  -7.443229
## 5          -6.315936        -10.030452    -1.7010165  -7.739147
## 6          -7.215143         -9.338544    -1.8771337  -7.204190
## 7          -6.538577        -10.656827    -5.2111105  -6.330397
## 8          -6.435082        -10.778276    -7.2171943  -6.611826
## 9          -6.812803        -10.230522    -7.5952564  -6.723813
## 10         -7.231173         -9.700542    -4.6184594  -6.376761
## 11         -5.857160        -10.381901    -7.4489247  -6.490795
## 12         -5.718196        -10.326931    -7.8858593  -7.328448
## 13         -3.979929         -9.903564    -9.1664453  -8.272002
## 14         -5.939546         -9.854170    -5.2260065  -7.645925
## 15         -7.446217        -10.920492    -5.1108897  -7.749523
## 16         -5.868627         -9.820111    -6.4769873  -6.172828
## 17         -5.493021         -9.486167    -5.6509677  -7.718007
## 18         -6.756589        -11.288937    -5.6638616  -7.162550
## 19         -5.540280         -9.776704    -8.7667272  -5.133405
## 20         -6.955072        -11.271019    -6.3368820  -5.604434
## 21         -6.166782        -10.703255    -7.4982036  -7.087708
## 22         -7.636091        -11.796530    -3.7602777  -7.112289
## 23         -4.896579         -9.552671    -9.0870805  -6.586545
## 24         -3.957263         -9.788970    -6.8922202  -7.386709
## 25         -5.301567         -9.266505    -4.2521049  -8.701476
## 26         -7.823657         -9.922362    -4.1510576  -7.622868
## 27         -5.509870         -9.892371    -4.9326106  -8.325541
## 28         -6.143982         -9.849260    -4.7987228  -8.092056
## 29         -6.164843        -11.321398    -7.0153589  -7.576521
## 30         -7.308896         -9.649395    -5.8984909  -7.300376
```

```
## 31        -5.762937       -10.573330    -7.4535200  -5.945974
## 32        -5.814296       -10.823373    -6.8698896  -8.244519
## 33        -4.404380        -9.776936    -9.8030051  -6.094953
## 34        -5.319426       -10.796977    -5.6276613  -8.662528
## 35        -6.216164       -10.830590    -4.6052053  -6.494216
## 36        -5.544580       -10.121290    -5.3904486  -8.916652
## 37        -7.616634        -9.695888    -6.1486669  -5.771661
## 38        -3.913055       -11.499813    -7.8724787  -7.848722
## 39        -5.351213        -9.913499    -6.4002794  -6.612231
## 40        -6.520759       -10.482095    -4.3080710  -7.698891
## 41        -5.973084        -9.874700    -7.3309954  -6.652340
## 42        -5.171923        -9.534405    -4.0320508  -7.357155
## 43        -5.777899        -9.868988    -4.6894059  -8.413483
## 44        -5.115500       -10.232229    -8.7183621  -9.012430
## 45        -4.494657        -9.157764    -5.7655817  -6.715702
## 46        -6.818881       -10.368695    -6.3453991  -5.567331
## 47        -5.498915        -9.966363   -10.7720983  -6.719237
## 48        -5.785726       -10.563575    -8.1047742  -7.664721
## 49        -7.088044        -9.935627    -5.6104748  -6.071775
## 50        -5.321695        -9.902658    -4.8260099  -6.621492
## 51        -6.837367       -10.427509    -5.1375697  -7.611433
## 52        -5.404928       -11.136390    -7.1189325  -5.965857
## 53        -6.808148        -6.466718     1.0441272  -5.661209
## 54        -6.582059       -10.536071    -8.0543551  -7.641212
## 55        -6.538442        -9.631191    -5.3262418  -8.173534
## 56        -7.103399        -9.509075    -2.5127024  -6.583045
## 57        -7.208169       -11.374822    -5.6800690  -8.593986
## 58        -6.457439       -10.160155    -5.9387163  -5.674444
## 59        -6.124735       -11.105750    -8.6756396  -7.739088
## 60        -7.879096       -10.503629    -7.0584833  -7.969766
## 61        -6.532938        -8.420728    -2.2025263  -6.313215
## 62        -7.448683       -10.735865    -8.8117703  -6.948164
## 63        -6.143272       -10.574437    -6.6073748  -9.717999
## 64        -6.572808       -10.325921    -3.8699795  -9.376872
## 65        -6.797305        -9.304196    -3.4038053  -8.517909
## 66        -5.985606       -11.169167    -4.9021653  -7.357989
## 67        -6.965811       -10.370195    -4.0686321  -7.515142
## 68        -6.102086       -10.840246    -9.2944263  -8.255328
## 69        -6.487776        -7.636369    -2.4428449  -7.552099
## 70        -5.440501        -9.224596    -5.0596275  -5.116188
## 71        -7.495641       -10.635786    -8.5525169  -7.927944
## 72        -9.916884        -8.578129    -1.8869180  -7.469868
## 73        -6.338213       -10.553287    -8.7373676  -6.772993
## 74        -5.103405       -10.145519    -6.8620650  -7.634119
## 75        -5.895203         8.986843    14.3821522  -6.752534
## 76        -6.587633        -8.917964    -2.9262989  -5.867164
## 77        -4.905498         2.755618     6.8717592  -5.369580
## 78        -9.046253       -10.796670    -4.1781268  -6.966522
## 79       -32.829204       -25.327919     6.7475070  -5.532551
## 80       -28.195653       -30.199640    -4.4437420  -8.537481
## 81       -26.600904       -23.878748     0.4353026  -7.070923
## 82       -27.425085       -23.077842     2.5650242  -5.688970
## 83       -29.386358       -28.304476    -0.6250137  -7.244744
## 84       -29.105480       -28.562221    -1.2702994  -8.308330
```

```
## 85        -25.553881        -27.638955    -8.2473312  -7.529161
## 86        -35.893274        -24.199535     9.9766550  -7.925094
## 87        -25.778058        -19.741968     4.2906644  -6.937890
## 88        -26.265528        -29.153349   -10.1543071  -8.240934
## 89        -27.004983        -21.264404     4.0837894  -5.784070
##    logKpre_apap logKpki_apap logKpli_apap logKpre_apap_cys
## 1   -0.04690208   0.13589527 -0.375792218       2.19032710
## 2   -0.27191200   1.46390320 -0.553851027      -0.52221741
## 3   -0.42939025   0.33045405  0.222989964       0.05838160
## 4   -0.18759530  -1.72579169 -0.765950278      -0.40658360
## 5   -0.08418012   0.40284111  0.249147945      -3.17511619
## 6   -0.34371554  -1.27341395  1.068367787       0.03096511
## 7    0.03336139   0.82406369  0.058583896      -0.82538887
## 8   -0.61555463  -0.55192198  0.478152019      -1.40344399
## 9    0.26956645  -1.84982773  0.235294222      -1.58560757
## 10  -0.52658787   1.31554119  1.290830811       1.67958014
## 11   0.14682277  -0.02764851 -0.608266197      -0.58985681
## 12  -0.03911657   0.15705661  0.268832010      -0.87251227
## 13  -0.64928516   0.40992349 -1.733432594      -0.07373035
## 14  -0.25313886   1.16414127  0.278657403       1.23878566
## 15   0.42378684   0.62996127  1.246889038      -1.16632804
## 16  -0.27576897   0.34359416  0.147404531       1.22028682
## 17   0.07282258   1.30182070 -0.924438972       1.09850894
## 18  -0.55651560   1.58051181  1.084696189      -1.73515884
## 19   0.06850708   1.43246312 -0.975884249       1.41870641
## 20  -0.80889477  -0.33682144  0.579395088      -1.59647629
## 21   0.48191588  -0.17526354 -0.009403686      -1.13725122
## 22  -1.01079761  -0.88100226  1.998625034      -2.32732370
## 23  -0.78783610   1.69475252 -1.911066726       2.02916973
## 24   0.18674154  -1.28068278 -1.694724248       1.02079353
## 25  -0.32827175   0.24010940 -0.929775946       0.27419371
## 26  -1.34120266   0.22507863  1.787990075       1.09796113
## 27  -0.71287315   0.65389939 -0.312577223       0.64664410
## 28   0.26388981   0.55362312 -0.091366224       0.38850547
## 29   0.72185725  -0.15472441 -0.420342775      -2.25887168
## 30  -1.18565069  -1.94780269  0.804365891       1.39981976
## 31  -0.60088163   2.15209353 -0.827867866      -0.35098516
## 32  -0.04061354   0.50824982  0.402311741      -1.23549160
## 33   0.32821685   0.29201392 -1.357915077      -0.24476548
## 34  -0.50202164  -1.95991509  0.159606958      -0.67470034
## 35  -1.00819664   0.21995567 -0.448086118      -1.20767134
## 36  -0.68818739  -0.91088727 -0.633038790      -0.03911165
## 37   0.41696968  -1.36516433  2.073445717      -0.39476531
## 38   0.09255023  -0.89201123 -1.600755883      -2.50026789
## 39  -1.03921580   0.22673049 -0.844533527       1.06525946
## 40   0.46298200  -1.72224715  0.859082459      -0.36208577
## 41  -0.84579322  -0.30269939 -0.350949378       0.68805221
## 42  -0.34708164   0.12974028 -0.729482675       0.07656203
## 43   0.52383921  -0.96092937 -0.733966324       0.07533225
## 44  -1.54615179  -0.24248966 -0.194620260      -2.25291758
## 45   0.52335285  -1.49161409 -2.006012865       1.23424256
## 46   0.56608572   2.19502301  0.327589532       0.52272338
## 47   0.39687818   2.34770248 -1.077276028      -0.65604804
## 48  -0.82503193   1.60889688  0.218270715      -1.46794422
```

```
## 49  -0.20897343  -2.02576092  1.279181039       0.54555732
## 50   0.64171075   0.72774026 -0.898575506      -0.45021444
## 51   0.16704300  -0.47007921  1.459336483      -0.24960659
## 52  -0.84718450  -0.12886836 -0.247651039      -1.29158501
## 53   0.63354281  -0.40895357  1.028206664       0.24053549
## 54   0.73145583   1.79690177  0.065999056      -0.68421890
## 55   0.53573376   0.02731561  0.621211210       1.73551231
## 56   0.89849562   0.21900927  0.635387902      -0.42137945
## 57   0.39096066   0.57970822  1.680989218      -1.35213763
## 58   0.75454015   0.18814904  0.027803443       0.08664206
## 59   0.81303314   1.15690348 -0.266935413      -2.31140242
## 60   0.90232207   0.60740406  1.470196676       0.40051733
## 61  -1.28800556  -1.59058851  0.252632696       1.30437250
## 62   1.00303359   1.03447703  0.668569788       0.63134011
## 63  -0.28293502   0.26198374 -0.209327380      -0.19014629
## 64  -0.11314747  -0.87710018  0.734667570      -0.52581564
## 65   0.83244383  -0.24792046  0.379575847       0.50378439
## 66  -0.34543595   0.98575174  0.304730040      -1.69705235
## 67  -1.62545596   0.81673790  0.329914142       0.22606538
## 68   0.82232209   2.36331096 -0.593902554      -2.28408825
## 69  -1.63353789  -0.38284691 -0.354447810       1.46349359
## 70  -1.41237387  -0.28003328 -0.872658780       0.78304369
## 71   1.09874005   0.45734772  0.282085785       0.88920153
## 72   1.08658416  -0.21868943 -0.487691159      -1.16687152
## 73  -1.49297394  -0.70167863 -0.017473841      -0.91763613
## 74  -0.41995217  -0.45230169 -0.606309724      -0.59246302
## 75  -2.01501472  -1.17914840 -0.768107736       1.03406142
## 76  -2.22269435   0.79836876 -0.495871811       0.82621063
## 77  -2.12573027  -0.77842833 -2.038863543      -2.85097250
## 78  -3.33042872  -2.08666418  0.083908232      -1.26885096
## 79   1.27943938  -1.28957039  0.775987526       0.36730539
## 80   1.26466410   0.60196741 -0.628801244      -0.49679192
## 81   1.34465620   0.01577446  0.438747062      -0.17018471
## 82   1.52598413   0.44855357 -2.237938695      -0.55474349
## 83   1.54320970  -0.77248853  0.502182996      -0.69086820
## 84   1.54448052   0.13807452 -0.239666310      -1.33146035
## 85   1.59674986  -0.05502054  0.682808984      -0.63221081
## 86   1.70756715  -1.48621770  0.035415338       2.27946453
## 87   2.05236661   0.90309951 -0.886991861      -1.68815577
## 88   2.17332840  -0.18872459 -0.082008957      -0.32471628
## 89   2.24020674  -0.53736438 -0.906048001       0.88940247
##    logKpki_apap_cys logKpli_apap_cys logKpre_apap_glu logKpki_apap_glu
## 1       -0.46598399     -0.298471419      -1.28020384      0.542998388
## 2       -0.39120304      0.276192230      -1.65067275     -0.458727014
## 3        1.82744478      0.279366410      -1.35505078     -0.315090663
## 4        0.12367542      0.009838299      -0.81699019     -0.192394328
## 5       -2.85346958     -0.007563093      -2.00116743      0.042915085
## 6       -1.56964062     -0.671261233       0.57430761     -1.170502598
## 7       -0.58283612      0.591368841       0.80512085      1.083463994
## 8        0.16717457     -0.738220739       0.33829387      0.333230582
## 9        1.21375863      0.603188179       1.20344598      0.460668648
## 10      -0.86198989     -0.958959737      -0.55140445      0.835437650
## 11       0.57712452      0.147582188       1.18553268      0.308460157
## 12       0.97630497     -1.292065239      -1.07495915     -0.351469413
```

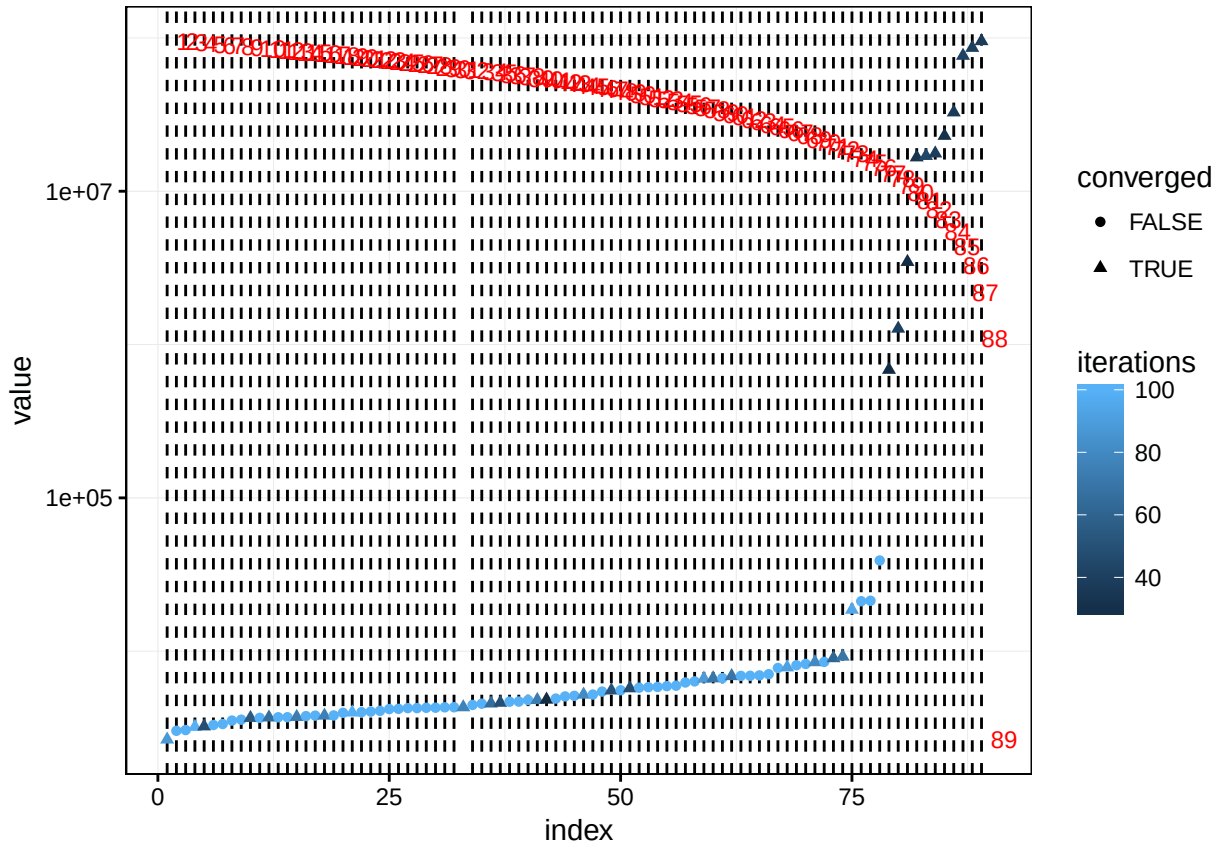
```
## 13      1.53736794     0.296368869      0.39664041    -1.129613260
## 14     -0.67694195    -1.278545890     -1.71724767     0.132625696
## 15     -0.32349955    -1.067846364     -1.19594520     0.725420404
## 16      0.49406573     1.183807407     -0.01313384     0.151480629
## 17     -0.38051686     0.570975890      1.12783834    -0.471274548
## 18     -0.72664646    -1.185019284     -1.23300549    -0.743904437
## 19      0.96864600     0.079841286      0.86869721    -0.077664381
## 20     -0.63663291    -0.256654253      0.48170367     0.918605898
## 21      0.27550692     0.416080822     -1.63558184     0.228008741
## 22     -1.62393805    -0.563047947     -2.01939840    -0.024639656
## 23     -0.13492936    -0.882839785      1.04172212    -1.520164456
## 24     -0.47269666     0.562858255     -0.68879361    -0.547838248
## 25     -1.45498015    -1.100721331     -0.53321003     0.609865237
## 26     -0.21129579    -0.092366820      0.57342020    -0.123810115
## 27     -0.92611576    -1.382679490      0.48912290     1.281797505
## 28     -0.35570047    -0.172335361     -0.46978414     0.098380585
## 29     -0.66328587     0.266809246     -1.30472210     0.631292467
## 30      0.76639685    -0.841361712      0.10566555     0.312176328
## 31      0.13264463    -0.277608653     -1.59920487     1.275567437
## 32      0.04268591    -2.094302797     -0.66241910    -0.043335132
## 33      1.93426586     0.487011932     -1.81267146    -1.224327565
## 34     -0.55023441    -1.577545906     -0.84440573    -0.085085839
## 35     -1.57870879     1.536816510      0.45235698    -0.338497416
## 36     -0.63912631    -0.449733014     -0.25355666    -0.098195482
## 37      2.23365915     0.751034491     -0.73773372    -0.915187685
## 38     -1.02422694     0.585384932     -0.57714839    -0.301911641
## 39     -0.47375312     0.340514498     -1.03007303    -0.077911158
## 40     -0.52620931    -0.209819973     -0.32246611     0.191924393
## 41      1.14292878     0.270950312     -1.76902638     1.652705349
## 42     -1.47919520     1.562776259     -1.62398295     0.214290582
## 43     -1.19391482    -0.471715322     -2.48660347     1.229849861
## 44      1.24743142     0.702759109     -0.56538796     2.016638712
## 45     -2.61651156    -1.780309655      0.09606544     2.506807499
## 46      0.23776777    -0.376721793     -2.11109536    -0.667490860
## 47      2.47584128    -0.447576070     -0.39604033     0.395997778
## 48      0.60247139    -0.490241722     -0.37079131     2.277076471
## 49      1.09176216     0.856416439      0.99705392     0.540883411
## 50     -0.80518896     1.665834605      0.10792662    -0.140797589
## 51      0.34181648    -1.632060218      0.15721562    -0.203360993
## 52     -0.48219250    -1.104274270     -2.75355745     0.656918741
## 53     -1.89108486     0.420134194     -0.43729939     1.288328347
## 54      0.70001334    -1.303024020      0.47412353     0.000872921
## 55     -0.36529086     1.365297327      1.30011183     0.708610944
## 56     -1.02235834    -1.551779131      0.27281831    -0.027922771
## 57     -0.69423508    -0.314313225      0.22072412     0.970811459
## 58      0.55655207    -1.597315184     -2.25217269     1.072966764
## 59     -0.09730938     0.686066724     -0.44274430    -1.729498891
## 60      0.49848105    -1.001399248     -1.21635839    -0.031727006
## 61     -2.09465046    -0.340953030     -0.03589483     0.314163266
## 62     -0.14477190    -0.934246004     -1.93391107     0.682144044
## 63     -0.02659004    -0.075496665     -0.40341804     0.430330378
## 64     -1.18698368     2.326026199     -0.40874620     2.312837119
## 65     -0.37719793     1.159324885     -1.34367810     0.671217116
## 66     -1.26316258     0.794603357     -1.11650080    -1.319958605
```

```
## 67      -1.36139814     -1.139697330       0.36188357      0.851896763
## 68       0.34843545      0.599272850       1.13343208     -1.614407089
## 69       0.49803787      1.042614799      -0.21152578      1.272873518
## 70       0.70683055     -1.523215080      -1.21171517     -0.297471969
## 71      -0.19814400      1.268275504      -0.80203163      0.819214043
## 72      -1.71492173     -0.274213432       1.20458042      0.339149835
## 73       0.71251379     -0.501224537       0.89570662     -1.415943833
## 74       0.27304619      1.172764136      -0.76417101     -2.035675001
## 75      -0.29930778      0.505268840      -1.02106087     -0.613672522
## 76      -0.72945578     -0.331428716       0.73710915     -2.035280504
## 77       2.06945775     -1.419716816      -0.03856364     -1.649644698
## 78      -0.34573626     -0.099602997       0.85123575     -0.511246432
## 79       0.41536410      0.001937790       1.24555687      0.988613439
## 80      -0.13360009      1.192058652       0.11911022      2.339582745
## 81      -0.30223692     -0.716459529      -1.89662417      0.240403013
## 82       0.97130438      0.813669584       1.92529506      1.084193376
## 83      -1.38397881      1.930720973       0.71146856      0.388201762
## 84      -0.13361888      2.060178549      -0.25275433      0.264382078
## 85      -0.97802760      0.044030690      -1.40442793     -0.070969540
## 86       1.07893461      0.255146201       0.60432256      0.483915144
## 87       0.66578544      0.146060170      -2.43582112      0.139946287
## 88       0.73882622      0.007670819       0.34669600     -0.681336107
## 89       1.17753454     -0.649218257      -0.42337222      0.966207855
##    logKpli_apap_glu logKpre_apap_sul
## 1        0.09378855      -1.50864561
## 2       -0.11353331       0.48599584
## 3       -0.10951404      -0.05666556
## 4       -0.32722341       0.78554977
## 5       -0.71993332      -0.54997601
## 6        1.01329858      -1.66492170
## 7       -0.30794116      -1.14085912
## 8        0.56994486       0.43299285
## 9        0.19466346      -2.53611617
## 10       0.47128495       0.09481745
## 11      -0.23684151      -0.57026010
## 12       0.90969431       1.74691475
## 13       0.49050300       0.89427925
## 14       1.02397332       1.53873385
## 15      -0.33960332      -2.10424653
## 16       1.44649463       1.27445121
## 17       1.61118431      -0.64954174
## 18      -0.37946363      -0.27319066
## 19       0.31518191      -0.42963746
## 20       1.86741769      -0.61871096
## 21      -0.45042642      -0.06868110
## 22      -0.60812825      -0.98757675
## 23      -1.66050018      -0.80062175
## 24      -2.25188974       1.05181282
## 25      -0.29687247      -0.47822882
## 26      -1.35402470      -1.17355490
## 27      -0.84151668       0.79824066
## 28      -0.47292153      -0.83447824
## 29      -0.40814012      -1.96335347
## 30      -0.01896119      -1.87938703
```

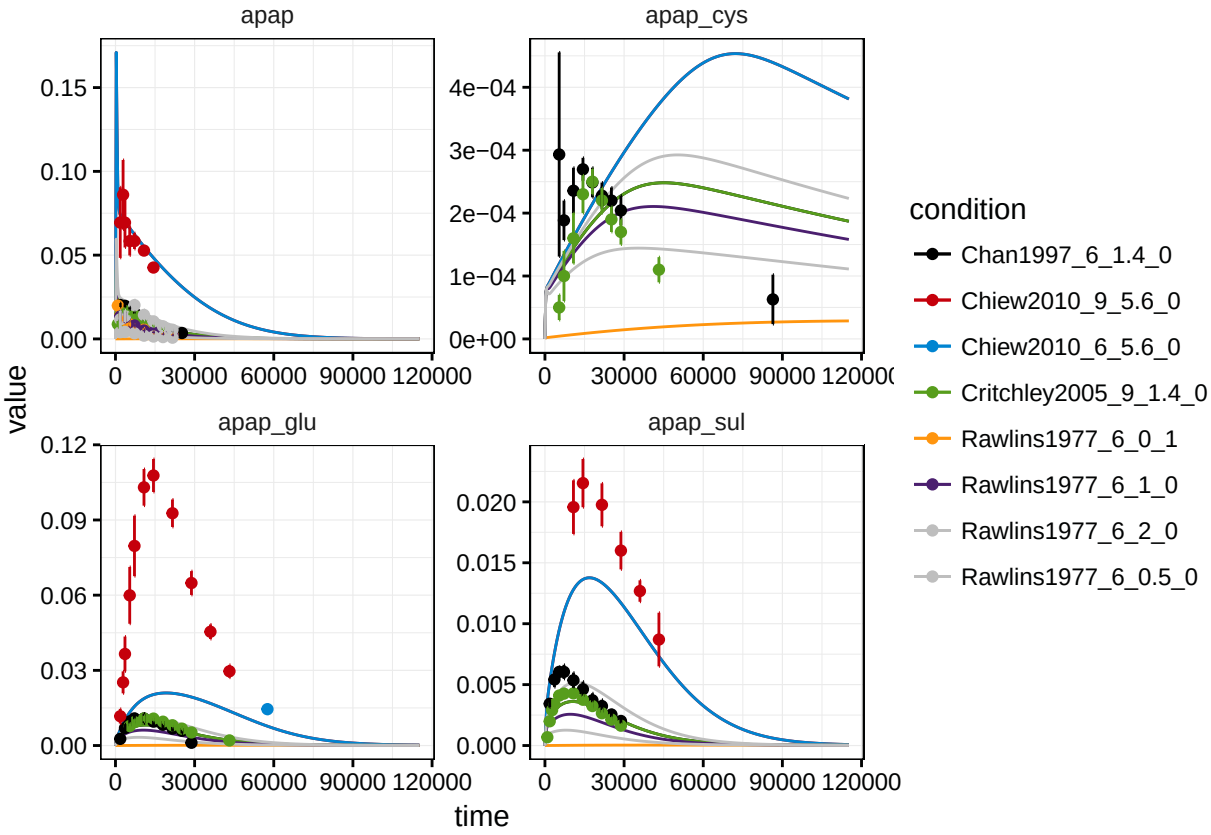
```
## 31      -0.11598643      -0.17173825
## 32       0.13314133       1.23816203
## 33       0.63661032       0.30583940
## 34       1.27228723       1.93054341
## 35       0.15626367      -1.10334746
## 36       0.05718985      -1.62198255
## 37      -0.24818252      -1.00749346
## 38       1.96387810       1.85452262
## 39      -1.05418373       0.39408997
## 40       0.02046116       0.70887482
## 41       0.04415602       0.07737363
## 42       1.52434188       7.49186260
## 43       0.82634848      -1.94101179
## 44      -0.15809122       1.73772111
## 45      -0.25542643      -0.36417278
## 46       0.94926449       0.23699317
## 47       1.43224457       0.33906253
## 48       0.03400620       1.86700557
## 49      -1.04625436       6.26465917
## 50       0.31408270       0.86703659
## 51      -1.08846541      12.11553583
## 52      -0.36833698       2.31944404
## 53       0.99006556       1.25218535
## 54       0.65145986      -0.35199597
## 55      -0.79626923       0.42732319
## 56       0.04624774      -0.48335244
## 57       0.31125443       0.68163953
## 58      -0.07720138       1.50739692
## 59       0.79435727       1.27547476
## 60      -0.26517898      -0.20727540
## 61      -0.56563317       0.42078941
## 62       0.45023728      -1.17016867
## 63       1.97886015      -0.84300867
## 64      -0.92451606       0.26435615
## 65      -1.14953631       0.33436559
## 66       0.14947056      -0.95286649
## 67       0.86211718      -0.21926640
## 68      -0.80832142       0.36262077
## 69      -0.04210192      -0.71860316
## 70      -0.08279439       0.27958686
## 71      -0.96123651       0.06381952
## 72       0.39272455       1.90623038
## 73       0.61562681       0.73251194
## 74       0.31890230      -1.07928541
## 75      -0.47065681      -0.92609068
## 76      -0.29165643       0.76923742
## 77       2.02587201      -0.57647454
## 78       0.11326700      -0.03082680
## 79       1.14482207      -0.46845905
## 80      -0.67632084      -0.55635655
## 81       0.26586854      -0.60925255
## 82       0.73521579       1.81706564
## 83       0.54842344      -0.32021249
## 84       0.56463045       1.64633341
```

```
## 85      -2.13427519      -0.37937662
## 86       0.28556755       1.52508584
## 87       0.10543765      -0.74434030
## 88      -0.44116945      -0.23081586
## 89       0.57928267      -1.31201140
```

```
plotValues(myfit6 %>% as.parframe())+scale_y_log10()
```




```
mypred6 <- (g*x*p6)(mytimes*4, myfit6 %>% as.parframe() %>% as.parvec)
myplot <- plotCombined(mypred6, mydatalist, name %in% names(observables))
# plotly::ggplotly(myplot)
myplot
```



Free other parameters 6_1 - try once again with more iterations In comparison to try 6, I also drop column n before converting the data to a datalist. I use the best fit from try 6 as center for the sampling

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters6 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap", #"F_apap_sul"    ,
                      "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                      )
```

```
fixed_parameters6 <- pars[!(names(pars)%in%c(free_parameters6,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% select(-n) %>% as.datalist()

conditions <- mydatalist %>% attr("condition.grid")

p_list <- lapply(1:nrow(conditions), function(i) {
  trafo <- as.character(pars) %>% set_names(names(pars))
  cond <- unlist(conditions[i,])[2:3]

  trafo[names(cond)] <- cond
  trafo[free_parameters6] <- paste0("exp(log", free_parameters6, ")")

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p6_1 <- NULL
for(i in 1:length(p_list)) { p6_1 <<- p6_1 + p_list[[i]]}

pouter6_1 <- log(pars[free_parameters6]) %>% set_names(paste0("log",names(.)))
best_fit <- myfit6 %>% as.parframe() %>% {.[2,]} %>% as.parvec() # der 2. sieht viel besser aus von der
```

```
## Warning: Parameter vector of an unconverged fit is selected.
```

```
pouter6_1[names(best_fit)] <- best_fit

# mypred <- (g*x*p6_1)(seq(0, 48*3600, length.out = 200), pouter6_1, deriv = F)
# plotCombined(mypred, mydatalist, name%in% names(observables))

obj6_1 <- normL2(mydatalist, (g*x*p6_1))

job6_1 <- runbg({myfit <- mstrust(objfun = obj6_1, center = pouter6_1, studyname = "methacetin", cores =

# save(job6_1, file = "job6_1.rda")
# job6_1$check()
```

```
global_env_without <- function(reg) ls(.GlobalEnv)[!(ls(.GlobalEnv) %>% sapply(. %>% str_detect(reg) %>%
```

Scaling factors

Introduce scaling factors 7 - not enough fits converged, but in principle not bad

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters7 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
```

```
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap"#, #"F_apap_sul"    ,
                      # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                      )

fixed_parameters7 <- pars[!(names(pars)%in%c(free_parameters7,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% select(-n) %>% as.datalist()
conditions <- mydatalist %>% attr("condition.grid")


observables7 <- c(apap = "Ave_apap/(BW*FVve)*scale_apap",
                  apap_glu = "Ave_apap_glu/(BW*FVve)*scale_apap_glu",
                  apap_sul = "Ave_apap_sul/(BW*FVve)*scale_apap_sul",
                  apap_cys = "Ave_apap_cys/(BW*FVve)*scale_apap_cys")
scale_parameters7 <- paste0("scale_apap", c("", "_glu", "_sul", "_cys")) %>% set_names(.,.)

# free_parameters7 <- c(free_parameters7, scale_parameters7)


i <- 2
p_list <- lapply(1:nrow(conditions), function(i) {
  cond <- unlist(conditions[i,])[2:3]

  trafo <- as.character(pars) %>% set_names(names(pars))
  trafo[names(cond)] <- cond
  trafo[free_parameters7] <- paste0("exp(log", free_parameters7, ")")

  scales <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", scale_parameters7, x = scale_parameter
  scales[names(scales) %>% sapply(. %>% str_detect(mydatalist[[i]][["name"]] %>% unique() %>% paste0("$

  trafo <- c(trafo, scales)

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p7 <- NULL
for(i in 1:length(p_list)) { p7 <<- p7 + p_list[[i]]}

g7 <- Y(observables7, x)#, parameters = c(free_parameters7, scale_parameters7))
```

```
## States:
##  [1] "Ali_metc13"   "Ali_apap"     "Ali_co2c13"   "Ali_apap_glu"
##  [5] "Ali_apap_sul" "Ali_apap_cys" "Agu_apap_sul" "D_apap_sul"
##  [9] "Aki_apap_sul" "Ave_apap_sul" "Alu_apap_sul" "Aar_apap_sul"
```

```
## [13] "Are_apap_sul" "Asp_apap_sul" "Agu_apap"     "D_apap"
## [17] "Aki_apap"     "Ave_apap"     "Alu_apap"     "Aar_apap"
## [21] "Are_apap"     "Asp_apap"     "Agu_metc13"   "D_metc13"
## [25] "Aki_metc13"   "Ave_metc13"   "Alu_metc13"   "Aar_metc13"
## [29] "Are_metc13"   "Asp_metc13"   "Agu_apap_cys" "D_apap_cys"
## [33] "Aki_apap_cys" "Ave_apap_cys" "Alu_apap_cys" "Aar_apap_cys"
## [37] "Are_apap_cys" "Asp_apap_cys" "Agu_apap_glu" "D_apap_glu"
## [41] "Aki_apap_glu" "Ave_apap_glu" "Alu_apap_glu" "Aar_apap_glu"
## [45] "Are_apap_glu" "Asp_apap_glu" "Agu_co2c13"   "D_co2c13"
## [49] "Aki_co2c13"   "Ave_co2c13"   "Alu_co2c13"   "Aar_co2c13"
## [53] "Are_co2c13"   "Asp_co2c13"   "time"
## Parameters:
##  [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##  [4] "BW"               "FVli"             "fup_metc13"
##  [7] "MET2APAP_Km"      "CO"               "FQgu"
## [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
## [13] "FQsp"             "FVsp"             "Kpsp_metc13"
## [16] "FQh"              "FVar"             "Kpli_metc13"
## [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
## [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
## [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
## [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
## [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
## [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
## [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
## [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
## [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
## [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
## [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
## [52] "FVki"             "fup_apap_sul"     "FQki"
## [55] "Kpki_apap_sul"    "FQlu"             "FVve"
## [58] "FQre"             "FVre"             "Kpre_apap_sul"
## [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
## [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
## [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
## [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
## [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
## [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
## [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
## [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
## [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
## [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
## [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
## [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
## [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## Estimate:
##   [1] "Ali_metc13"       "Ali_apap"         "Ali_co2c13"
##   [4] "Ali_apap_glu"     "Ali_apap_sul"     "Ali_apap_cys"
##   [7] "Agu_apap_sul"     "D_apap_sul"       "Aki_apap_sul"
##  [10] "Ave_apap_sul"     "Alu_apap_sul"     "Aar_apap_sul"
##  [13] "Are_apap_sul"     "Asp_apap_sul"     "Agu_apap"
##  [16] "D_apap"           "Aki_apap"         "Ave_apap"
##  [19] "Alu_apap"         "Aar_apap"         "Are_apap"
##  [22] "Asp_apap"         "Agu_metc13"       "D_metc13"
```

```
##  [25] "Aki_metc13"       "Ave_metc13"       "Alu_metc13"
##  [28] "Aar_metc13"       "Are_metc13"       "Asp_metc13"
##  [31] "Agu_apap_cys"     "D_apap_cys"       "Aki_apap_cys"
##  [34] "Ave_apap_cys"     "Alu_apap_cys"     "Aar_apap_cys"
##  [37] "Are_apap_cys"     "Asp_apap_cys"     "Agu_apap_glu"
##  [40] "D_apap_glu"       "Aki_apap_glu"     "Ave_apap_glu"
##  [43] "Alu_apap_glu"     "Aar_apap_glu"     "Are_apap_glu"
##  [46] "Asp_apap_glu"     "Agu_co2c13"       "D_co2c13"
##  [49] "Aki_co2c13"       "Ave_co2c13"       "Alu_co2c13"
##  [52] "Aar_co2c13"       "Are_co2c13"       "Asp_co2c13"
##  [55] "time"             "MET2APAP_HLM_CL"  "fumic_metc13"
##  [58] "MPPGL"            "BW"               "FVli"
##  [61] "fup_metc13"       "MET2APAP_Km"      "CO"
##  [64] "FQgu"             "FVgu"             "Kpgu_metc13"
##  [67] "BP_metc13"        "FQsp"             "FVsp"
##  [70] "Kpsp_metc13"      "FQh"              "FVar"
##  [73] "Kpli_metc13"      "APAPGLU_HLM_CL"   "fumic_apap_glu"
##  [76] "fup_apap"         "APAPGLU_Km"       "APAPSUL_HLM_CL"
##  [79] "fumic_apap_sul"   "APAPSUL_Km"       "APAPCYS_HLM_CL"
##  [82] "fumic_apap_cys"   "APAPCYS_Km"       "Kpgu_apap"
##  [85] "BP_apap"          "Kpsp_apap"        "Kpli_apap"
##  [88] "Kpgu_co2c13"      "BP_co2c13"        "Kpsp_co2c13"
##  [91] "Kpli_co2c13"      "Kpgu_apap_glu"    "BP_apap_glu"
##  [94] "Kpsp_apap_glu"    "Kpli_apap_glu"    "Kpgu_apap_sul"
##  [97] "BP_apap_sul"      "Kpsp_apap_sul"    "Kpli_apap_sul"
## [100] "Kpgu_apap_cys"    "BP_apap_cys"      "Kpsp_apap_cys"
## [103] "Kpli_apap_cys"    "Ka_apap_sul"      "F_apap_sul"
## [106] "CLrenal_apap_sul" "FVki"             "fup_apap_sul"
## [109] "FQki"             "Kpki_apap_sul"    "FQlu"
## [112] "FVve"             "FQre"             "FVre"
## [115] "Kpre_apap_sul"    "FVlu"             "Kplu_apap_sul"
## [118] "Ka_apap"          "F_apap"           "CLrenal_apap"
## [121] "Kpki_apap"        "Kpre_apap"        "Kplu_apap"
## [124] "Ka_metc13"        "F_metc13"         "CLrenal_metc13"
## [127] "Kpki_metc13"      "Kpre_metc13"      "Kplu_metc13"
## [130] "Ka_apap_cys"      "F_apap_cys"       "CLrenal_apap_cys"
## [133] "fup_apap_cys"     "Kpki_apap_cys"    "Kpre_apap_cys"
## [136] "Kplu_apap_cys"    "Ka_apap_glu"      "F_apap_glu"
## [139] "CLrenal_apap_glu" "fup_apap_glu"     "Kpki_apap_glu"
## [142] "Kpre_apap_glu"    "Kplu_apap_glu"    "Ka_co2c13"
## [145] "F_co2c13"         "CLrenal_co2c13"   "fup_co2c13"
## [148] "Kpki_co2c13"      "Kpre_co2c13"      "Kplu_co2c13"
## [151] "scale_apap"       "scale_apap_glu"   "scale_apap_sul"
## [154] "scale_apap_cys"
```

```
obj7 <- normL2(mydatalist, (g7*x*p7))

pouter7 <- rep(0, length(getParameters(obj7))) %>% set_names(getParameters(obj7))
pouter7[names(myfit5 %>% as.parframe() %>% {.[2,]} %>% as.parvec())] <- myfit5 %>% as.parframe() %>% {.

# job7 <- runbg({myfit <- mstrust(objfun = obj7, center = pouter7, studyname = "methacetin", cores = 12

# save(job7, file = "job7.rda")
# job7$check()
```

```r
# myfit7 <- job7$get()$knecht5
# save(myfit7, file = "myfit7.rda")
# job7$purge()
load("myfit7.rda")
myfit7 %>% as.parframe()
```

```
##    index        value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1      5 2.490012e+03      TRUE         30       -5.74930296   -3.08097475
## 2     64 2.626769e+03      TRUE         60       -4.45447649   -2.31516013
## 3     67 2.855601e+03      TRUE         87       -5.29300219   -2.39553148
## 4     35 3.037778e+03     FALSE        100       -4.05565558   -2.26447288
## 5     98 3.347208e+03     FALSE        100       -5.76379027   -4.18377196
## 6     14 3.572777e+03     FALSE        100       -2.35327686   -0.00949594
## 7     59 3.689614e+03     FALSE        100       -6.23845930   -3.63347407
## 8     43 3.745606e+03      TRUE         40       -5.58579766   -2.34756820
## 9     93 3.789059e+03      TRUE         67       -4.62882439   -2.45769256
## 10    20 3.836543e+03     FALSE        100        2.02612700    5.52319956
## 11    84 3.854661e+03     FALSE        100       -4.60827636   -1.81904682
## 12    77 3.921896e+03     FALSE        100       -6.15712198   -3.25267015
## 13    31 4.130673e+03      TRUE         85       -6.06525131   -3.21091674
## 14    80 4.137895e+03      TRUE         92       -5.91886519   -4.47908012
## 15    70 4.291561e+03     FALSE        100       -5.92072458   -4.86536620
## 16    90 4.476847e+03     FALSE        100       -1.90987397    2.08806480
## 17    63 4.591705e+03     FALSE        100       -6.74904044   -5.87467530
## 18    60 4.877972e+03      TRUE         71      212.33025383  214.15294446
## 19    88 4.884952e+03      TRUE         47       -3.70575100   -2.68110741
## 20    79 4.954082e+03     FALSE        100       -7.62278784   -9.49673658
## 21    66 4.966072e+03     FALSE        100       11.93575921   13.34233999
## 22    95 5.126587e+03     FALSE        100       -2.25265719    2.68618287
## 23    81 5.244915e+03     FALSE        100       -6.22458407   -4.40288718
## 24    47 5.309418e+03     FALSE        100       -4.44173731   -0.93403949
## 25     1 5.411923e+03      TRUE         47       -4.42772107   -2.17025733
## 26    61 5.549198e+03     FALSE        100        0.58066558    4.73141614
## 27     4 5.655958e+03      TRUE         97       -2.82875375   -0.12870919
## 28    39 5.986789e+03     FALSE        100       -4.78657515   -3.08202285
## 29    27 6.162998e+03     FALSE        100       -6.80278773   -4.13181578
## 30    53 6.233437e+03     FALSE        100        4.57088736    9.59489922
## 31    41 6.244751e+03      TRUE         51       -5.88097549   -4.57117813
## 32    13 6.557834e+03     FALSE        100       -7.04173593   -5.74356494
## 33    56 7.253274e+03      TRUE         66       -4.84859783   -3.71999742
## 34    97 7.290939e+03     FALSE        100       -7.64683534   -8.96538408
## 35   100 7.302828e+03     FALSE        100       -6.68762636   -3.03425424
## 36    37 7.468518e+03     FALSE        100       -4.66740638   -2.43160509
## 37    52 7.728228e+03     FALSE        100       -0.46629292    2.43142661
## 38    73 7.836990e+03     FALSE        100        2.24802024    6.16071994
## 39    78 7.954905e+03     FALSE        100       -5.03500453   -4.23445497
## 40    45 7.967747e+03     FALSE        100       -2.59562898   -0.06874236
## 41    51 8.124259e+03      TRUE         93       11.40957782   13.69736269
## 42    76 8.233267e+03     FALSE        100        3.01640530    5.57919480
## 43    69 8.526130e+03     FALSE        100       -7.95461980  -11.76134622
## 44    26 8.633624e+03     FALSE        100        4.04793367    7.54677961
## 45    68 8.701422e+03     FALSE        100       -0.89595333    1.48244931
## 46    12 8.831965e+03     FALSE        100       -4.68992038   -0.70585956
## 47    74 8.912093e+03     FALSE        100       -8.27021282  -21.98239905
```

```
## 48    62 9.609774e+03     FALSE        100       -0.41011161    3.51832077
## 49    72 1.002845e+04      TRUE         71       15.84668984   20.26630333
## 50    11 1.043380e+04     FALSE        100       -5.72993658   -5.43889348
## 51    21 1.044619e+04     FALSE        100      308.20150938  312.46104008
## 52    44 1.086569e+04     FALSE        100       -7.27216468   -5.04437628
## 53     7 1.184719e+04     FALSE        100       -0.09494665    3.01150489
## 54    82 1.285032e+04     FALSE        100        2.58159718    3.28894572
## 55    32 1.285397e+04     FALSE        100       -5.52085743   -4.31800628
## 56    54 1.289640e+04      TRUE         71       -7.24679610   -3.30871849
## 57     3 1.349315e+04     FALSE        100       -8.52176977   -6.50914417
## 58    18 1.351885e+04     FALSE        100        0.59888385    3.15926587
## 59    99 1.397646e+04      TRUE         72       14.04650495   16.95840296
## 60    15 1.561744e+04     FALSE        100       -6.60260224    7.74955399
## 61    19 1.668324e+04     FALSE        100       -2.64735222    0.28227084
## 62    57 1.818121e+04     FALSE        100       -8.33366086  -23.38867821
## 63    50 1.867700e+04     FALSE        100       -3.97823200    2.12270207
## 64    16 1.921405e+04      TRUE         75       -7.83184899  -22.10740736
## 65    10 2.020967e+04      TRUE         64        6.95566840   10.80336057
## 66    92 2.192394e+04      TRUE         91        4.08462256    9.21156020
## 67     2 2.277895e+04      TRUE         89        3.65747757   10.37930649
## 68    42 2.293112e+04      TRUE         64        9.96167623   12.62266923
## 69    29 2.300625e+04     FALSE        100       -7.88481745  -12.68942798
## 70    24 2.422755e+04     FALSE        100       -7.56882061    2.15863963
## 71    22 2.717503e+04     FALSE        100       -8.11872765  -16.05551094
## 72     9 3.224313e+04      TRUE         63       12.43397244   16.18996016
## 73    71 3.674566e+04     FALSE        100        4.29759467    6.88385730
## 74    58 3.734037e+04      TRUE         75        8.04897325   10.64100141
## 75    23 4.074261e+04     FALSE        100       -8.76939789  -14.80390131
## 76    96 5.158130e+04      TRUE         69       -8.31561839  -20.31440899
## 77    49 5.196053e+04      TRUE         88       12.81917814   15.31336877
## 78    25 5.209246e+04     FALSE        100       -2.45074558   -1.04705903
## 79    86 5.950616e+04      TRUE         34       11.27216346   16.93428242
## 80    55 1.418027e+05      TRUE         27       12.45087097   17.16056716
## 81    36 1.766843e+05      TRUE         58       17.08345885   20.20361459
## 82    40 3.028062e+05     FALSE        100       -9.15974768    2.91103162
## 83    34 3.270362e+05     FALSE        100      -10.61850559    1.91687737
## 84    17 5.276401e+06     FALSE        100       -8.96916880    3.11504487
## 85    28 2.805908e+07     FALSE        100       -9.34230283    3.33704610
## 86     8 4.926280e+07     FALSE        100       -8.91132666    3.24161671
## 87     6 5.660383e+07     FALSE        100       -7.87253591    4.67126818
## 88    75 6.892843e+07     FALSE        100       -9.06956611    2.93457932
## 89    46 7.234477e+07     FALSE        100       -9.52339759    2.47950097
## 90    33 7.355773e+07     FALSE        100       -9.63455470    2.44992075
## 91    94 9.904253e+07     FALSE        100       -9.79945227    2.27406111
## 92    30 1.566314e+08     FALSE        100       -9.36450660    2.75243986
##    logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap
## 1          -5.069446       -10.9582717    -6.6967779  -7.438818
## 2          -5.574571       -12.3105843    -6.9872584  -7.603783
## 3          -5.345860       -11.7376516    -6.3281173  -6.926927
## 4          -5.365076       -11.2499872    -7.0096698  -7.954771
## 5          -5.881820       -10.5170795    -7.1580135  -8.062787
## 6          -5.624627       -10.8243319    -6.8741389  -7.609710
## 7          -5.369795        -9.9788674    -6.0332659  -7.834403
## 8          -6.093333       -10.5129728    -5.0209685  -6.369381
```

```
## 9         -6.143874      -10.1908306    -6.6473611  -8.469903
## 10        -5.035589       -9.6889871    -5.2823437  -3.084044
## 11        -7.476821      -10.1183089    -7.8794440  -6.288192
## 12        -5.734799      -11.6841652    -5.7466277  -7.472356
## 13        -7.629642      -10.7403837    -4.7575726  -1.428842
## 14        -8.888848      -10.4154697    -6.9940167  -8.363564
## 15        -4.910170       -9.7676033    -7.5750095  -8.520535
## 16        -7.131073      -10.7583550    -3.8746249  -6.480656
## 17        -7.522616      -10.6517949   -12.7191475  -8.161827
## 18        -5.724016      -10.8147999    -6.5423774  -8.426904
## 19        -4.288788       -9.5506391    -8.5623802  -8.669280
## 20        -5.809932      -10.8345249    -7.2075496  -8.449354
## 21        -5.456585      -11.0950346    -7.6291968  -8.486779
## 22        -6.573271       -9.2471819    -4.9074235  -6.249523
## 23        -6.641215      -11.6179576    -6.3539107  -8.134785
## 24        -5.336923      -10.8843637    -5.6380507  -6.408296
## 25        -6.645726      -10.4467870    -6.5008456  -7.180041
## 26        -5.812008      -11.6168778    -7.0756293  -4.409436
## 27        -9.795111       -9.9129504    -5.4914658  -6.288658
## 28        -6.199216       -9.3273899    -6.3969186  -8.501373
## 29        -4.854384      -11.4312460    -7.1330646  -8.137634
## 30        -8.071779       -0.1224022     6.9444399  -6.748368
## 31        -5.343066      -10.7542016    -7.7980067  -8.274762
## 32        -6.921756      -10.3870742    -5.3932721  -7.544343
## 33        -3.330012      -11.0701415    -8.5570569  -8.717370
## 34        -5.686251       -9.6297959   -18.4518815  -8.349203
## 35        -4.931873      -10.6101120    -7.5341130  -7.019027
## 36        -7.291628       -9.9631814    -9.4259863  -4.656699
## 37        -4.627201      -11.5846694    -7.7839556  -8.155991
## 38        -5.787409      -10.7770376    -4.4282278  -6.691734
## 39        -5.327043       -9.1946418    -6.8230525  -8.625713
## 40        -6.063647      -11.0999426    -6.2646019  -4.004717
## 41        -6.422734      -11.1383660    -6.1296835   5.935442
## 42        -6.220689      -12.2254201    -6.3341841  -6.443355
## 43        -8.513906      -11.0394558   -11.1210523  -9.020058
## 44        -6.731361        1.7265428     6.3267817  -9.582323
## 45        -5.565983      -11.0180191    -6.5061006  -5.292193
## 46        -6.493141      -10.4401519    -7.1766223  -9.863448
## 47        -7.087088      -10.9854298   -24.2598367  -7.656777
## 48        -7.254931       -9.5605425    -4.2464497  -9.196151
## 49        -6.778386      -11.0651540    -5.6552173  -6.653701
## 50        -4.865947      -10.4596957    -8.4817015  -9.778230
## 51        -5.594969      -10.7443075    -6.8563933  -6.774519
## 52        -6.303466      -11.3993741    -6.3425371  -9.375460
## 53        -6.356004       -9.0178923    -2.8937242  -6.975517
## 54        -3.283783      -10.8935025    -9.2295796  -8.651144
## 55        -6.036271      -10.4746499    -6.1915576  -9.292451
## 56        -4.460263      -10.1165549    -6.7597067  -8.084197
## 57        -6.592283      -10.9375012    -5.0785070 -10.399107
## 58        -4.705141      -12.2257906    -7.3429528  -5.296988
## 59        -5.971661      -11.5960425    -7.6648603  -7.214755
## 60       -13.545662       -8.9380722     0.9818441  -7.834371
## 61        -3.842756       -9.8174901    -5.4472882  -6.930963
## 62        -8.809388      -11.4725633   -16.6403623  -8.959271
```

```
## 63        -9.138303      -11.1829171    -5.2336282 -11.189583
## 64       -10.342253      -11.7094177   -24.3712201   5.571061
## 65        -7.863534       -9.8103690    -7.1636386   5.683877
## 66        -8.064012      -10.5048175   -19.3330482  -9.592735
## 67       -10.328299      -11.4256213   -15.0177928  -9.449626
## 68        -6.088599      -10.3510701    -5.1891474  -7.696183
## 69       -11.249017      -11.3685590    -8.7427174  -8.809700
## 70        -8.246873       -9.8512192    -3.4301307 -10.528259
## 71       -15.394496      -10.8567062   -12.9643808  -8.637398
## 72        -7.934664      -10.8952031   -20.7641559   8.280326
## 73        -4.923056      -10.9113164    -6.8551364  -7.600590
## 74        -5.628690       -9.3617666    -6.0418772  -7.133170
## 75       -15.990494      -13.1485481    -9.9940544  -8.513659
## 76       -22.928742      -13.0979974   -25.5992224  -9.271412
## 77        -8.049445        6.9981595    12.4741285   7.797724
## 78        -5.549971      -10.4586549   -16.2498748  -8.060444
## 79       -25.639308      -11.3728815   -21.0133210   8.572264
## 80        -9.014139      -11.5130005   -21.5087868  11.123984
## 81        -6.909157       11.8525792    17.5956178  14.460263
## 82       -13.645201      -14.9193657    -5.2682291  -7.826819
## 83        -9.259527      -11.5823519   -11.7951509  -8.183759
## 84       -13.664408      -14.9090085    -4.8334258  -7.794977
## 85       -14.171609      -15.6838705    -7.6884962  -7.810633
## 86       -13.723854      -15.1726278    -6.2461094  -7.794319
## 87       -14.040982      -15.4580304    -6.3784675  -7.793240
## 88       -13.582037      -15.0369721    -8.0202133  -7.818263
## 89       -13.585241      -14.4342630    -3.4180526  -7.812915
## 90       -13.666495      -15.0965021    -6.4382523  -7.795058
## 91       -13.657053      -14.9835585    -5.3209141  -7.795491
## 92       -13.695667      -15.0634772    -5.7438114  -7.795095
##    log_scale_apap_Chan1997_1.4_0 log_scale_apap_glu_Chan1997_1.4_0
## 1                    0.735734673                       -0.258980454
## 2                    0.907570358                        0.003338643
## 3                    0.466263677                        0.365011207
## 4                    1.262165735                       -0.338130480
## 5                    1.020343952                       -0.713985018
## 6                    0.762523762                        0.359423877
## 7                    0.424130963                       -0.050383341
## 8                   -0.137697692                        0.330510145
## 9                    0.422558788                       -0.801389292
## 10                   0.533947029                        0.648810858
## 11                  -0.020647201                       -1.133128214
## 12                   0.073549937                       -0.435415828
## 13                  -0.363348628                       -0.692518219
## 14                   0.687132657                       -2.692620241
## 15                   1.657616895                       -0.522229738
## 16                  -0.706014309                        0.055636669
## 17                   0.430717729                       -2.701596000
## 18                   0.917416786                       -0.524026875
## 19                   2.072883900                        0.068333718
## 20                   0.062121555                       -0.559481513
## 21                   1.383407145                        0.319376638
## 22                  -0.745400663                        1.039001657
## 23                   0.338693891                       -0.883589355
```

```
## 24   0.220173064   0.514069081
## 25   0.581420971  -0.305575477
## 26  -0.328415677  -1.127499308
## 27   0.050311637  -0.573187840
## 28   0.898249303   0.451872875
## 29   0.582354336   0.358918991
## 30  -1.044468860  -0.248575763
## 31   1.333754905   0.143173843
## 32   0.007323483  -0.494292650
## 33   2.375661608   1.039525487
## 34   0.239596498  -1.078469373
## 35   0.475272268   1.472909942
## 36   0.543369796  -0.246692562
## 37   0.823710268   0.894865329
## 38  -0.243294732   1.368024995
## 39   1.936486396   0.760723872
## 40   0.568479962  -1.346954736
## 41   0.799344503   0.237472484
## 42   0.465549419   0.403039587
## 43  -0.631789193   0.341785362
## 44  -0.225133501  -1.542436727
## 45   0.964243297  -1.950700177
## 46  -0.235144363   1.325631337
## 47  -0.804037136   1.045282532
## 48  -0.645006881  -0.972615849
## 49  -0.763530199   1.332860249
## 50   2.225765521   0.845872668
## 51  -0.215957072   0.325433103
## 52  -0.108342364   0.316363955
## 53  -0.064757709   1.253464289
## 54   2.709904163   0.737612423
## 55   1.116649380   0.388705433
## 56   0.745750926   2.153718138
## 57   0.249655336  -0.312731069
## 58   1.389570271   0.666048878
## 59   0.177158933   1.219060267
## 60  -1.277616186   3.052950550
## 61   2.276342108  -1.449199546
## 62  -0.841317906  -0.901365198
## 63   0.334614183   1.117464137
## 64  -0.810465143  -1.093375615
## 65  -0.659899155  -0.639341129
## 66  -0.722152456   0.879892592
## 67  -0.932866890   0.588133184
## 68   0.274587711   1.517547039
## 69  -0.726326518  -2.265076241
## 70  -0.210139857   0.248791473
## 71  -0.879539888  -0.191373635
## 72  -0.662980970  -2.464757772
## 73   0.985915732  -0.632709205
## 74   0.714515246  -0.449535611
## 75  -1.092039609   0.925859562
## 76  -0.727562965   1.191229685
## 77   0.396521111   1.236795140
```

```
## 78                   1.695358755                      -1.075897999
## 79                  -1.178443677                      -0.543062980
## 80                  -1.028410707                       0.002972427
## 81                  -0.119171678                       0.083472423
## 82                  -1.300268059                      -0.278608309
## 83                  -1.247581449                      -1.124744085
## 84                  -1.436541894                       1.417523678
## 85                  -1.691474973                       0.409571370
## 86                  -1.874194806                      -0.820013250
## 87                  -1.934440565                      -1.306155455
## 88                  -2.028631109                       0.298004590
## 89                  -2.064206891                       0.755392010
## 90                  -2.074154523                      -0.188861840
## 91                  -2.291380674                      -0.814631824
## 92                  -2.893727296                      -2.092664976
##    log_scale_apap_sul_Chan1997_1.4_0 log_scale_apap_cys_Chan1997_1.4_0
## 1                       -0.039174569                       0.6911869867
## 2                        0.218392692                       0.4441860590
## 3                       -0.261853493                       1.4962657208
## 4                        0.484382433                       0.9564866416
## 5                        0.355016526                       0.2993361023
## 6                       -0.086561871                       0.4475229901
## 7                       -0.923898881                      -0.3199634085
## 8                        0.387475063                      -0.2072048380
## 9                        0.949013289                      -0.0648413304
## 10                      -0.437741274                      -0.0953871588
## 11                       1.751865265                      -0.3074668809
## 12                      -0.794828849                       0.2762706016
## 13                      -1.333785699                       0.8175702295
## 14                      -0.449364181                       0.0786565714
## 15                       0.200189376                      -0.8378162449
## 16                       0.002984498                       1.0711378554
## 17                      -1.235681435                       0.1441234828
## 18                      -2.836823728                       0.5230153898
## 19                      -0.264832178                      -0.6762981477
## 20                      -0.504900208                      -0.8079518253
## 21                      -1.885930429                       0.9084294835
## 22                      -0.059038011                      -1.2681213053
## 23                      -1.946261786                       1.1209056066
## 24                      -1.302109934                      -0.0007858377
## 25                      -0.343543364                       0.1487828885
## 26                      -1.352117280                       0.9622163395
## 27                      -1.718850623                      -1.0962124321
## 28                       0.288751722                      -1.6053836778
## 29                      -1.351780682                      -0.9449968018
## 30                       1.381670092                       0.4018665065
## 31                       0.866988005                      -0.3835575164
## 32                       1.508463394                       0.4564463551
## 33                      -1.443487971                       0.5606471794
## 34                       0.784623442                      -0.6061322698
## 35                       0.162821865                       0.2977378304
## 36                       1.573801006                      -1.4362358043
## 37                      -1.941023036                      -0.8365126480
## 38                      -0.074873689                       1.1007666391
```

```
## 39  -1.387934874  -0.4995891878
## 40   1.238559397   0.6013275394
## 41  -1.577516763   0.6946935340
## 42  -0.209608827  -0.9895216404
## 43   2.285678904  -1.7004976591
## 44  -1.028485452  -1.1363781510
## 45  -1.119440711   0.6341797247
## 46   0.784317967   0.0382270742
## 47   0.745852286   0.1584410122
## 48  -1.084346287  -1.4120825712
## 49   0.168191992   0.8152111879
## 50  -2.241036510  -1.0514805328
## 51   0.052696310  -0.3866418278
## 52  -0.282243647   0.8035237148
## 53  -0.170066727   0.6581464249
## 54  -1.103572376   0.5196774136
## 55   0.417243328   0.7809262481
## 56   0.610624597   0.1885290961
## 57   1.120119729   1.2363160346
## 58   0.390288285   1.0342694367
## 59   1.105215197   1.2341640559
## 60  -1.310611422   0.5109252330
## 61  -0.437473076  -0.4243879540
## 62   0.690858061   0.9115281531
## 63   0.449661301   0.0379784737
## 64  -1.117264633   1.1739317511
## 65  -0.823157330   0.0908403837
## 66   1.196961010   0.0558699929
## 67   0.318555420  -0.5451443769
## 68  -0.140812867   0.0264999171
## 69  -0.777602041  -0.2993846396
## 70  -0.445075997  -0.9080527581
## 71  -1.230348956  -0.1901443018
## 72   1.143595445   0.5026423322
## 73   1.118883595   0.7148917534
## 74   1.058970790  -0.3401928824
## 75   0.993399395   2.5341592175
## 76   1.441021330   0.0834846542
## 77  -0.258378148   0.5022168450
## 78   1.703245661   0.5170634075
## 79  -1.579732118  -1.6804040485
## 80  -1.244078233   0.9674578028
## 81  -0.088304594   0.9233057222
## 82   0.645290299  -0.2027048969
## 83  -1.159957546   2.0219102963
## 84  -1.228659975  -1.2249587679
## 85   0.047458749  -0.1131343494
## 86  -0.062775536   0.2030099327
## 87   1.633478079  -0.5008982543
## 88  -0.741147039  -1.1439119227
## 89  -1.346014003  -0.6452801810
## 90   0.838512684   0.5700087396
## 91   1.640621082   0.0628860241
## 92   1.652663470  -0.2839187220
```

```
##    log_scale_apap_Chiew2010_5.6_0 log_scale_apap_glu_Chiew2010_5.6_0
## 1                       0.28907910                           1.47214497
## 2                       0.32685873                           0.80624507
## 3                       0.04167644                           0.50892105
## 4                       0.28628828                           0.18637389
## 5                      -0.25747805                          -0.53694523
## 6                       0.60731079                          -1.45528979
## 7                      -1.15003563                           1.34560617
## 8                      -0.15258502                          -0.68182442
## 9                       0.35078248                           0.18086210
## 10                      0.76295903                          -1.38286596
## 11                      0.05092963                          -0.72901766
## 12                     -0.47221916                           0.92691492
## 13                     -1.01820399                           0.22872566
## 14                     -0.90340130                          -0.64270979
## 15                     -0.31523866                          -0.43445252
## 16                     -0.18273076                          -0.36262235
## 17                     -0.46541046                          -0.65609238
## 18                      1.40963358                           1.09607716
## 19                     -2.00973035                           0.34691183
## 20                      0.02823272                           0.18940696
## 21                      1.34805896                           1.10839082
## 22                     -1.15806041                           0.69627078
## 23                      0.17428857                          -0.85860933
## 24                     -0.77557137                          -0.26445389
## 25                     -2.19018850                          -0.45014441
## 26                     -0.02505022                           0.96612334
## 27                      0.18125203                          -0.37731929
## 28                      0.24939916                          -0.89389458
## 29                     -0.61521437                          -0.10801819
## 30                      0.09825249                           0.60329487
## 31                     -0.53214167                          -0.25839842
## 32                     -0.46192640                           1.43180247
## 33                      0.20743737                           1.11591508
## 34                     -0.41900184                           0.92546424
## 35                     -0.70759967                           0.14650801
## 36                      0.08172131                           0.96406052
## 37                     -0.30039888                          -0.23735426
## 38                      0.27252560                          -0.11459970
## 39                      0.45694693                          -0.45705572
## 40                     -0.03522854                          -0.32562683
## 41                      1.63517544                           0.21615488
## 42                     -0.90190343                          -0.56754477
## 43                     -0.13784257                          -1.04416585
## 44                      1.13557002                          -1.10530782
## 45                     -0.27853164                           0.54136395
## 46                      0.96402333                          -0.36793722
## 47                     -0.42842413                           0.20273723
## 48                      0.81126535                          -0.66412333
## 49                     -1.58029859                          -1.70362266
## 50                      1.60676806                           0.30650860
## 51                     -0.40678309                           1.55717959
## 52                      0.62856686                          -0.40900179
## 53                     -0.29998870                          -0.77909953
```

```
## 54                      0.38939785                      -0.31701368
## 55                      0.52577305                      -0.98072087
## 56                     -0.06530118                       2.84797057
## 57                      0.67782462                      -0.58188201
## 58                     -0.22870968                       1.13467434
## 59                      0.97387964                      -0.12553563
## 60                      0.42702023                       0.76777568
## 61                     -1.15044765                      -0.95637409
## 62                      0.60578827                       0.11707045
## 63                      2.41350515                      -0.22246422
## 64                      0.13100055                       1.17804284
## 65                     -0.09634465                      -0.88947461
## 66                      1.17225920                       0.49244440
## 67                      1.15073962                       0.45834727
## 68                      0.53208896                      -1.01981673
## 69                     -1.19746921                       0.08754038
## 70                      2.00550879                       0.29536703
## 71                     -0.06443743                       1.51864007
## 72                      1.14928309                       0.69249246
## 73                     -0.17090063                       0.16950793
## 74                     -1.43552153                       0.48520613
## 75                      0.13087525                      -1.38268513
## 76                      1.49223774                       0.04231757
## 77                      2.07602606                       0.89290539
## 78                     -0.16134259                       0.71069092
## 79                      1.19626981                       0.32233169
## 80                      1.16679537                      -0.80989583
## 81                     -0.75552849                       0.58522119
## 82                     -0.56342322                      -0.03741384
## 83                     -0.01354305                       0.56432418
## 84                      0.17680675                       0.05140965
## 85                     -1.65957831                       0.64324645
## 86                     -0.44443541                       0.46556869
## 87                     -1.32004567                      -0.87695024
## 88                     -0.78670210                       0.88250684
## 89                     -0.14043614                      -1.06818626
## 90                      0.04565708                       0.36112422
## 91                      0.21089677                       1.60509186
## 92                     -1.21637108                       0.98493674
##    log_scale_apap_sul_Chiew2010_5.6_0 log_scale_apap_Critchley2005_1.4_0
## 1                          -0.16206314                        -0.31230419
## 2                           0.81756615                         0.17782906
## 3                          -2.18405857                        -0.87368445
## 4                           0.83801413                         0.26512908
## 5                           0.24004123                        -1.64865256
## 6                           0.64591708                         0.13412441
## 7                          -2.11584279                         0.70234541
## 8                          -0.44599046                        -0.46339901
## 9                          -0.48960479                         1.18134189
## 10                         -0.62665199                        -0.03092996
## 11                          0.53744470                        -0.80928484
## 12                          0.02948939                         0.35760336
## 13                         -0.27863700                        -0.38722289
## 14                         -0.77023941                         1.03923645
```

```
## 15 -0.92781834  1.07285520
## 16 -1.03138391 -0.45353279
## 17 -0.67232326  0.46873446
## 18  0.98668747 -0.69202598
## 19 -0.50889516 -0.75643227
## 20 -1.55994450 -0.95287754
## 21  1.56778495  1.48968307
## 22 -1.33676265 -1.05234580
## 23  0.46084281  0.09462622
## 24 -0.02984508 -1.80346528
## 25 -1.45003430 -1.82246968
## 26  0.23287469 -0.49687021
## 27 -0.34299786 -2.45460317
## 28 -0.05586433  1.40463209
## 29 -0.57614234  0.23886147
## 30  0.21984692 -0.11838432
## 31 -0.77964367 -0.20498478
## 32  0.55648651  0.41932968
## 33 -0.78669004  0.81701226
## 34 -0.07129948  0.05479624
## 35 -1.16755304 -0.72160427
## 36 -0.83439201  0.36015604
## 37  0.25452087 -0.02137830
## 38 -0.01762252 -2.78499312
## 39 -0.23760507  1.64310621
## 40  0.74082609 -2.56785050
## 41  1.62048929 -0.62491681
## 42  1.62137655 -1.36631349
## 43  1.05221967 -1.16368427
## 44 -0.29200293  1.10472792
## 45  1.49520331  0.13764095
## 46 -0.60952846  0.88685135
## 47 -1.70899402 -0.11358552
## 48 -0.31360215  0.20724745
## 49  1.31739686  0.17971727
## 50 -0.98638399 -0.39881963
## 51 -0.29215266 -0.19605922
## 52 -0.76533543  1.40998640
## 53  1.12810493 -0.38832225
## 54  1.05013186  0.46296601
## 55  0.32121313  1.80695853
## 56 -0.25760177  0.95720476
## 57 -0.08499270  2.35355863
## 58  1.05938229  0.14631305
## 59 -0.39341421 -0.78187257
## 60 -0.71704855 -0.75387749
## 61 -1.19195760 -1.09574561
## 62  0.98951327  1.16738223
## 63 -0.16447654 -1.04860188
## 64 -0.77891385  0.43653313
## 65  0.15250498  0.01341281
## 66 -0.19849725  0.65176369
## 67  0.62072916 -0.52645695
## 68  0.26418132  0.70607699
```

```
## 69                          0.11211643                        -0.43998583
## 70                          1.96114423                        -1.10883517
## 71                         -0.34282813                         1.22074580
## 72                         -0.38762405                        -0.76924064
## 73                         -1.36237216                         0.36745807
## 74                          0.07749188                         0.41442373
## 75                         -0.56160239                         1.30544738
## 76                          1.37779807                         0.89990666
## 77                         -0.80531251                         0.33843564
## 78                          0.44898597                        -0.25757224
## 79                         -0.83296417                        -0.41955731
## 80                          1.41900686                         1.72271033
## 81                          3.16630752                         1.63643141
## 82                          0.77827837                         0.33447781
## 83                          0.08539423                        -0.36106394
## 84                          0.81088349                        -1.67630538
## 85                          0.31767737                         1.57023522
## 86                         -1.33989240                        -1.46793428
## 87                         -0.55211093                        -0.67308392
## 88                          0.71283128                         0.28783749
## 89                          0.12952707                         0.24361363
## 90                         -0.99539498                        -0.87629424
## 91                         -0.58040653                         0.11248868
## 92                          0.31507928                        -0.58981063
##    log_scale_apap_glu_Critchley2005_1.4_0
## 1                              0.634054031
## 2                             -0.867339444
## 3                             -0.582968056
## 4                              0.172052581
## 5                             -0.635609276
## 6                             -1.155552034
## 7                              0.188586723
## 8                             -0.513627979
## 9                             -0.099252590
## 10                            -1.181445449
## 11                            -0.067676016
## 12                            -0.628631790
## 13                            -0.558159634
## 14                            -0.456977643
## 15                            -0.846777275
## 16                            -0.782924328
## 17                             0.080057687
## 18                            -1.803426179
## 19                            -0.102403548
## 20                            -0.269013699
## 21                            -0.209475190
## 22                            -0.943566936
## 23                            -0.098003606
## 24                             0.228485951
## 25                            -0.185464020
## 26                             0.870734175
## 27                             0.188154282
## 28                            -0.106544462
## 29                             0.562843272
```

```
## 30                          0.514958611
## 31                          0.205092538
## 32                          0.005299672
## 33                          0.497146177
## 34                          0.802582541
## 35                         -1.138451796
## 36                          0.364668783
## 37                         -1.573741065
## 38                         -1.831556305
## 39                         -0.635385861
## 40                          0.762713966
## 41                         -0.989307058
## 42                          0.350736776
## 43                         -0.572710672
## 44                         -0.099789431
## 45                          0.851272715
## 46                          0.071635503
## 47                         -1.837073553
## 48                         -0.081036761
## 49                         -0.933608239
## 50                          0.155531142
## 51                          1.597808772
## 52                         -1.522702289
## 53                         -1.164576523
## 54                          1.065448793
## 55                          0.748538014
## 56                          1.789349148
## 57                          0.538861640
## 58                          1.160600705
## 59                         -0.900207085
## 60                          0.238935239
## 61                          1.468245594
## 62                         -0.786501923
## 63                          0.287299862
## 64                         -0.443373236
## 65                          1.474176213
## 66                         -0.403169892
## 67                         -0.225673334
## 68                         -0.188424733
## 69                         -0.508983762
## 70                         -1.061765732
## 71                         -0.844610706
## 72                         -0.455677559
## 73                          1.773468600
## 74                          1.655109819
## 75                         -0.630507057
## 76                         -0.861046804
## 77                          0.856769573
## 78                          1.592889036
## 79                         -0.361066408
## 80                         -0.769243874
## 81                          2.235573495
## 82                         -0.400939241
## 83                          1.309074315
```

```
## 84                            -1.355387478
## 85                            -0.968873789
## 86                            -0.022169476
## 87                             0.814114575
## 88                            -0.573014567
## 89                             0.346268991
## 90                            -1.826530670
## 91                             0.419858726
## 92                            -0.872545741
##    log_scale_apap_sul_Critchley2005_1.4_0
## 1                             -0.329529503
## 2                             -0.587906534
## 3                             -0.753631197
## 4                             -0.428994092
## 5                              0.365722461
## 6                              0.065926124
## 7                             -0.155201271
## 8                             -0.914096282
## 9                             -1.088079937
## 10                            -0.989133678
## 11                            -0.380404075
## 12                            -2.227008895
## 13                             1.148683448
## 14                             3.237896785
## 15                            -1.750701927
## 16                             0.370528079
## 17                             1.715688398
## 18                             0.470467762
## 19                             0.034033863
## 20                            -0.277440157
## 21                             0.263874014
## 22                            -0.413320656
## 23                             0.800104571
## 24                            -3.008409245
## 25                             0.849389022
## 26                            -0.514737108
## 27                             3.516437618
## 28                             1.087087191
## 29                            -1.016909909
## 30                             0.007590907
## 31                            -1.403812275
## 32                            -1.855962025
## 33                            -0.090031027
## 34                            -0.288250817
## 35                            -1.828100977
## 36                             1.526031277
## 37                            -1.362322885
## 38                             0.026071482
## 39                             1.038332972
## 40                            -0.476847302
## 41                            -0.906688078
## 42                            -1.271884369
## 43                            -1.121150516
## 44                             0.392017903
```

```
## 45                            -0.571312891
## 46                             0.458674417
## 47                            -3.352119421
## 48                             0.479616360
## 49                            -1.846888479
## 50                             1.252756187
## 51                             0.150820014
## 52                             0.261652894
## 53                             0.714526227
## 54                            -0.317229422
## 55                             1.515754130
## 56                            -1.029802727
## 57                            -0.268898320
## 58                            -1.532645979
## 59                            -0.342486997
## 60                             1.886986929
## 61                            -1.151480998
## 62                             0.355638535
## 63                            -1.109858895
## 64                             0.753841575
## 65                             1.843278679
## 66                            -0.684526638
## 67                            -0.396430959
## 68                             1.070058457
## 69                             2.702166817
## 70                             0.968583974
## 71                            -0.186623774
## 72                             0.946389986
## 73                             0.452755040
## 74                             0.982645960
## 75                            -0.247411190
## 76                            -1.199650009
## 77                             2.410044648
## 78                             1.441505208
## 79                             0.171473495
## 80                             1.399924635
## 81                            -2.396520655
## 82                            -1.175113829
## 83                            -1.079485311
## 84                            -0.262813950
## 85                             0.450244498
## 86                            -0.038363347
## 87                             0.181156716
## 88                            -1.261402545
## 89                            -0.678905474
## 90                             1.122233420
## 91                            -0.757520113
## 92                            -1.030437423
##    log_scale_apap_cys_Critchley2005_1.4_0 log_scale_apap_Rawlins1977_0_1
## 1                              0.45207273                    0.123547546
## 2                              1.95086579                    0.196036010
## 3                              1.12787512                    0.010860812
## 4                              0.87942843                    0.341276655
## 5                             -0.47610074                    0.232948430
```

```
## 6                0.34831907                0.156010769
## 7               -0.27049142                0.043993808
## 8                0.48997492               -0.262859967
## 9               -0.61549591                0.128542320
## 10              -1.53229348                0.029858213
## 11              -1.45394829               -0.208636677
## 12               1.44408782               -0.126268415
## 13              -0.92743499               -0.355569027
## 14              -0.23224913                0.142186416
## 15              -0.52840432                0.432861268
## 16              -1.20248280               -0.639361615
## 17              -0.47959225                0.023270050
## 18               0.49514433                0.329610561
## 19              -1.62823941                0.661500546
## 20               0.38468932               -0.054070316
## 21              -0.35736438                0.486720441
## 22              -1.10198649               -0.646678649
## 23               1.27176334                0.030907718
## 24               0.75594850               -0.098518174
## 25              -0.05542541                0.060220929
## 26               0.91852256               -0.378302599
## 27              -0.14002497               -0.189905324
## 28              -0.58041049                0.288332504
## 29               0.98547513                0.137336137
## 30              -0.21401567               -0.908466328
## 31               0.46256759                0.327836753
## 32              -1.72316998               -0.109054822
## 33               0.75410271                0.753383904
## 34              -1.06197467               -0.007849132
## 35              -0.34176410                0.016817451
## 36              -0.34670834                0.042476883
## 37               1.06519029                0.243136720
## 38               0.59472156               -0.326881852
## 39              -0.76333258                0.561765382
## 40               0.93358161                0.026595594
## 41               0.95426206                0.092464143
## 42               1.81226133               -0.007644094
## 43               0.21890341               -0.552209045
## 44              -1.62186485               -0.338334585
## 45               0.87711526                0.153805874
## 46              -0.51418313               -0.314030552
## 47               0.25907111               -0.571173506
## 48              -0.48374476               -0.606551606
## 49              -1.04859493               -0.672755789
## 50               0.28662863                0.600801578
## 51               0.45575876               -0.304133225
## 52               0.88715718               -0.230224974
## 53              -1.85153761               -0.229384161
## 54               0.48579766                0.834312658
## 55               0.19698960                0.354393069
## 56              -0.28795715                0.192833951
## 57              -0.47790730               -0.584003994
## 58               1.99649963                0.278824981
## 59              -0.57549417               -0.100056614
```

```
## 60                              1.29724064                  -1.116390637
## 61                              0.35454917                   0.479621670
## 62                              0.03795345                  -0.739467485
## 63                              0.81228076                  -1.033342375
## 64                              0.18996044                  -0.526088214
## 65                             -1.90236311                  -0.607532448
## 66                             -0.84056665                  -0.900852765
## 67                              0.38763115                  -1.071816814
## 68                              0.75899537                  -0.019984747
## 69                              0.48446531                  -0.558395865
## 70                             -0.05185816                  -1.039154233
## 71                              0.07025119                  -0.669107254
## 72                             -1.48826242                  -0.622017540
## 73                              0.97675073                   0.223985486
## 74                              0.05486480                   0.102531849
## 75                              0.81416071                  -0.907592052
## 76                              2.23184762                  -0.777305556
## 77                             -1.24928589                  -0.060071254
## 78                              0.12657470                   0.475671751
## 79                             -0.31369694                  -1.031766559
## 80                             -0.87072275                  -0.903697559
## 81                              0.59361936                  -0.292280109
## 82                             -0.26159840                  -0.863222246
## 83                             -0.95712287                  -1.085487126
## 84                             -0.65191492                  -1.857346693
## 85                              0.32282676                  -0.109110187
## 86                              0.83269782                  -0.928704023
## 87                              3.18432094                   0.094265090
## 88                              0.12399004                  -0.437361370
## 89                              0.09027106                  -0.677424994
## 90                             -0.64302392                  -0.459450474
## 91                             -0.60968167                   0.113211535
## 92                              1.64115901                  -0.025373155
##    log_scale_apap_Rawlins1977_1_0 log_scale_apap_Rawlins1977_2_0
## 1                       0.27999826                     0.23205478
## 2                       0.40194965                     0.40054980
## 3                       0.07005591                     0.03746354
## 4                       0.69124502                     0.72483500
## 5                       0.55520067                     0.47151149
## 6                       0.28847757                     0.35586546
## 7                       0.06585539                     0.11074041
## 8                      -0.44619644                    -0.35690365
## 9                       0.10373738                     0.31357010
## 10                      0.12542622                     0.06037179
## 11                     -0.33501435                    -0.26475316
## 12                     -0.24819841                    -0.16332876
## 13                     -0.63747915                    -0.55507671
## 14                      0.39647393                     0.29676173
## 15                      1.17034603                     1.10286532
## 16                     -1.03697433                    -0.77631720
## 17                      0.30464429                    -0.16492253
## 18                      0.51210051                     0.73597284
## 19                      1.58170933                     1.68812011
## 20                      0.13791717                    -0.25792873
```

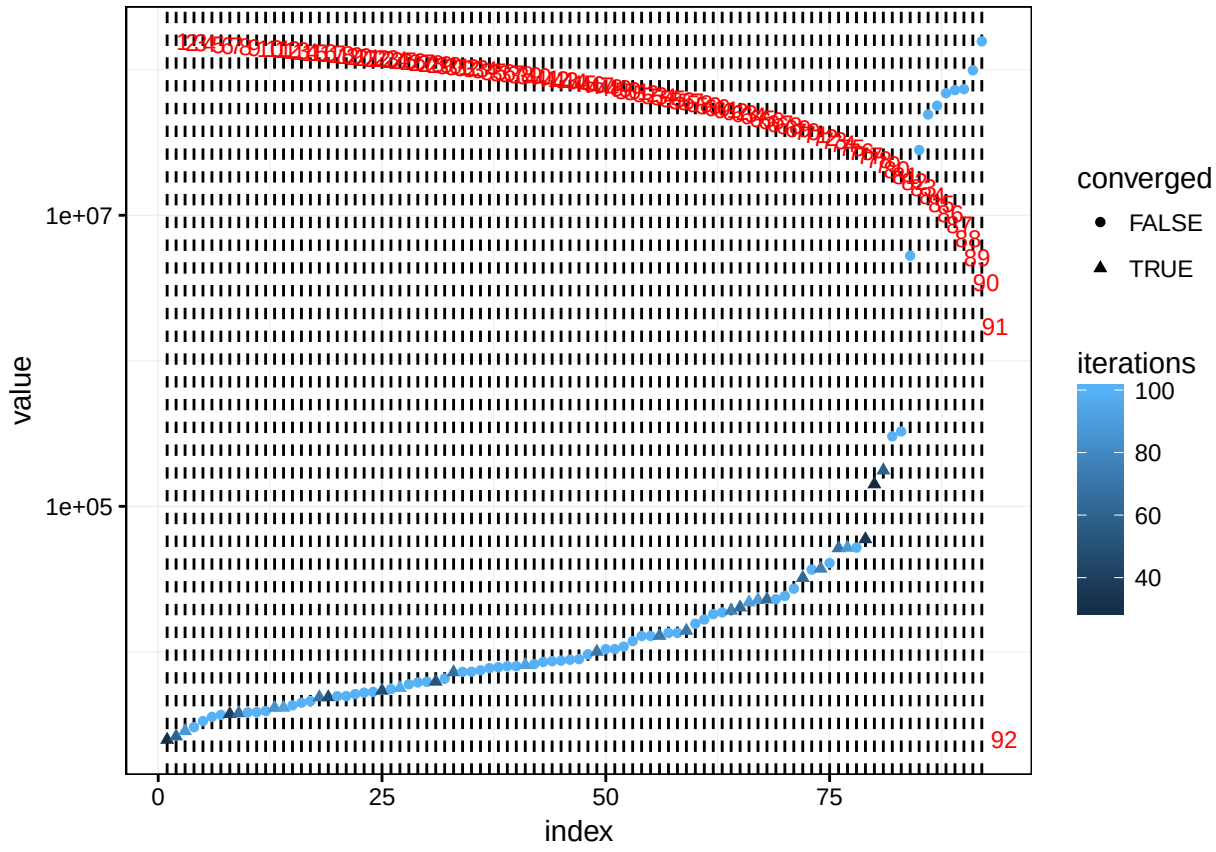
```
## 21          0.92128479          1.11264976
## 22         -1.04928192         -0.83887606
## 23          0.04795638          0.08340891
## 24         -0.13449303         -0.10836141
## 25          0.15691593          0.13797500
## 26         -0.63826244         -0.47469813
## 27         -0.29909572         -0.17345911
## 28          0.53225436          0.64611242
## 29          0.21344312          0.33491887
## 30         -1.40105353         -1.09433737
## 31          0.83811333          0.73741710
## 32         -0.13217386         -0.37094953
## 33          1.87911474          2.00968743
## 34          0.23448123         -0.15443684
## 35          0.08602304          0.03173223
## 36          0.15405340          0.00890617
## 37          0.39045826          0.54964351
## 38         -0.56259969         -0.40279961
## 39          1.43681024          1.36445828
## 40          0.15239924          0.12898020
## 41          0.33262137          0.29341728
## 42          0.05386762          0.08632757
## 43         -0.68191102         -0.85623068
## 44         -0.60583950         -0.28022150
## 45          0.45716499          0.32909547
## 46         -0.62416382         -0.43805795
## 47         -0.96772668         -0.94339893
## 48         -1.02049157         -0.70933352
## 49         -1.08857886         -0.83551245
## 50          1.91964026          1.99164223
## 51         -0.52498631         -0.39169301
## 52         -0.37039331         -0.19685292
## 53         -0.40998899         -0.23861076
## 54          2.15115029          2.26169022
## 55          0.83387715         -0.25531343
## 56          0.32838796          0.43636144
## 57         -0.10012900          0.06029599
## 58          0.75689583          0.45797479
## 59         -0.19057676         -0.05752397
## 60         -1.66412966         -1.32780192
## 61          1.28872272         -0.27543942
## 62         -1.06428376         -1.00678236
## 63         -0.20602616          0.08738221
## 64         -0.87259509         -1.01093770
## 65         -0.97097825         -0.74047008
## 66         -1.15298388         -0.85162155
## 67         -1.38537956         -1.06201637
## 68         -0.10571193          0.07526465
## 69         -0.77680366         -0.87288553
## 70         -0.72602494         -0.38790063
## 71         -1.03328759         -1.04312573
## 72         -0.99098263         -0.73194273
## 73          0.45535281          0.46261194
## 74          0.25494444          0.22253441
```

```
## 75                    -1.39673917                    -1.19609898
## 76                    -0.95783970                    -0.92825460
## 77                    -0.00134220                     0.09128766
## 78                     1.01859272                     1.03188199
## 79                    -1.54678780                    -1.23089599
## 80                    -1.38245887                    -1.07869342
## 81                    -0.46213430                    -0.27421175
## 82                    -1.22315019                    -0.49423896
## 83                    -1.63067820                    -1.30405921
## 84                    -0.81609813                    -0.78146366
## 85                    -0.43563436                     0.48984518
## 86                    -0.58442647                    -1.05772224
## 87                    -0.28951645                     0.50368597
## 88                    -0.24916525                     0.51394487
## 89                    -1.22467424                    -0.15637331
## 90                    -0.35571798                     0.03202553
## 91                    -0.70635423                     0.19140381
## 92                    -0.41648989                    -0.16357200
##    log_scale_apap_Rawlins1977_0.5_0
## 1                        -0.32097913
## 2                        -0.03674230
## 3                        -0.03173343
## 4                        -0.78815698
## 5                         0.17669530
## 6                         0.45105346
## 7                        -0.55370671
## 8                        -1.01502654
## 9                        -0.22098524
## 10                       -0.44218446
## 11                       -0.68428241
## 12                        0.29350495
## 13                       -1.42800362
## 14                        0.27713410
## 15                        0.56211905
## 16                       -1.18259477
## 17                        1.00477939
## 18                       -0.51984682
## 19                        1.35035772
## 20                        1.43055656
## 21                        0.56131052
## 22                       -1.38811195
## 23                        1.06501201
## 24                       -1.14730574
## 25                       -0.72951709
## 26                        0.37777600
## 27                       -2.10977049
## 28                       -0.63227501
## 29                        1.21733731
## 30                       -1.31973738
## 31                       -0.53048449
## 32                       -0.25020255
## 33                       -0.40719159
## 34                        1.56477949
## 35                        0.52261372
```

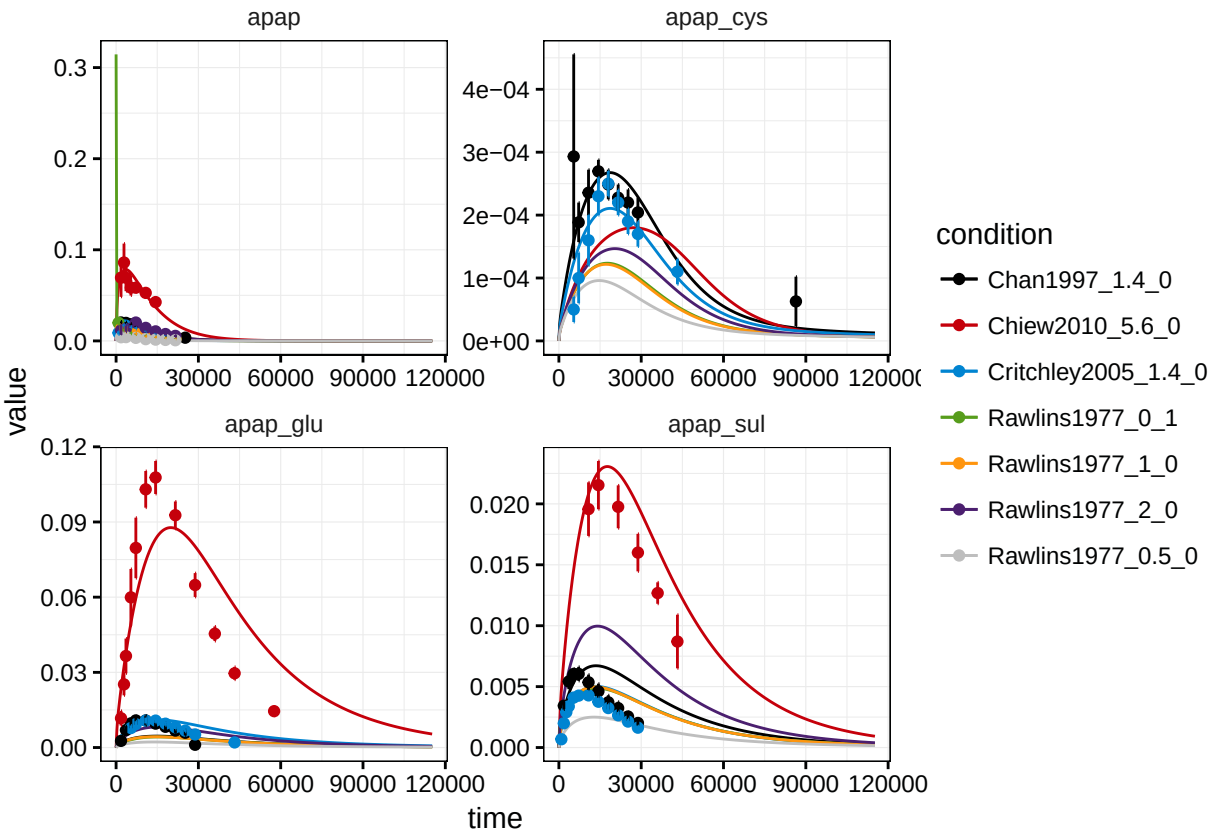
```
## 36                    1.10039090
## 37                    1.24241609
## 38                   -0.99228880
## 39                   -0.03932763
## 40                    0.02757981
## 41                   -0.32651936
## 42                   -0.01086108
## 43                    1.06307625
## 44                   -0.85668578
## 45                   -1.87298124
## 46                   -0.32783644
## 47                    0.43131513
## 48                   -0.69738105
## 49                   -0.43611301
## 50                    0.43167775
## 51                    0.45410950
## 52                    0.79299334
## 53                   -0.94973696
## 54                    1.65040989
## 55                    0.63623822
## 56                    0.61489659
## 57                    0.54151751
## 58                   -1.12536545
## 59                    0.38838058
## 60                   -2.26320734
## 61                   -0.96300755
## 62                    0.55244331
## 63                   -0.27963690
## 64                    1.31213875
## 65                   -0.18530053
## 66                    0.24389626
## 67                   -0.56524574
## 68                    0.06320703
## 69                    2.42718681
## 70                   -0.04046188
## 71                    1.65059372
## 72                    0.60581673
## 73                   -0.82949359
## 74                   -1.17482910
## 75                    0.56822548
## 76                    1.39111663
## 77                   -1.06645663
## 78                   -0.44764932
## 79                   -0.14729148
## 80                    0.42702548
## 81                   -0.52155584
## 82                    1.16429727
## 83                    1.51852786
## 84                   -0.49965608
## 85                   -0.90853805
## 86                    0.36502092
## 87                    0.74953256
## 88                    1.96917455
## 89                   -0.44548662
```

```
## 90                        -0.07684904
## 91                         0.15063258
## 92                        -0.35459671
```

```
plotValues(myfit7 %>% as.parframe())+scale_y_log10()
```




```
mypred7 <- (g7*x*p7)(mytimes*4, myfit7 %>% as.parframe() %>% as.parvec %>% {names(.) <- names(.) %>% st
myplot <- plotCombined(mypred7, mydatalist, name %in% names(observables))
# plotly::ggplotly(myplot)
myplot
```



Error model

8 Introduce error model and scaling factors in the dynamic model - very weird results. Negative objfun value??

Mistake: Don't remove the rows with sigma=NA! Stupid...

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters8 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap"#, #"F_apap_sul"    ,
                      # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
```

```
                      # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                      )

fixed_parameters8 <- pars[!(names(pars)%in%c(free_parameters8,names(f)[1]))] %>% names

mydatalist <- data  %>% filter(!is.na(sigma)) %>% select(-n) %>% as.datalist()
conditions <- mydatalist %>% attr("condition.grid")


observables8 <- c(apap = "Ave_apap/(BW*FVve)*scale_apap",
                  apap_glu = "Ave_apap_glu/(BW*FVve)*scale_apap_glu",
                  apap_sul = "Ave_apap_sul/(BW*FVve)*scale_apap_sul",
                  apap_cys = "Ave_apap_cys/(BW*FVve)*scale_apap_cys")
scale_parameters8 <- paste0("scale_apap", c("", "_glu", "_sul", "_cys")) %>% set_names(.,.)

# free_parameters8 <- c(free_parameters8, scale_parameters8)

error_model8 <- c(apap = "srel_apap*apap^2 +s0_apap",
                  apap_glu = "srel_apap_glu*apap_glu^2 +s0_apap_glu",
                  apap_sul = "srel_apap_sul*apap_sul^2 +s0_apap_sul",
                  apap_cys = "srel_apap_cys*apap_cys^2 +s0_apap_cys")
error_parameters8 <- setdiff(getSymbols(error_model8), names(error_model8)) %>% set_names(.,.)

i <- 1
p_list <- lapply(1:nrow(conditions), function(i) {
  cond <- unlist(conditions[i,])[2:3]

  trafo <- as.character(pars) %>% set_names(names(pars))
  trafo[names(cond)] <- cond
  trafo[free_parameters8] <- paste0("exp(log", free_parameters8, ")")

  scales <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", scale_parameters8, x = scale_parameter
  scales <- scales[names(scales) %>% sapply(. %>% str_detect(mydatalist[[i]][["name"]] %>% unique() %>%

  errors <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", error_parameters8, x = error_parameter
  errors <- errors[names(errors) %>% sapply(. %>% str_detect(mydatalist[[i]][["name"]] %>% unique() %>%

  trafo <- c(trafo, scales, errors)

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p8 <- NULL
for(i in 1:length(p_list)) { p8 <<- p8 + p_list[[i]]}

g8 <- Y(observables8, x)#, parameters = c(free_parameters8, scale_parameters8))
```

```
## States:
##  [1] "Ali_metc13"   "Ali_apap"     "Ali_co2c13"   "Ali_apap_glu"
##  [5] "Ali_apap_sul" "Ali_apap_cys" "Agu_apap_sul" "D_apap_sul"
##  [9] "Aki_apap_sul" "Ave_apap_sul" "Alu_apap_sul" "Aar_apap_sul"
## [13] "Are_apap_sul" "Asp_apap_sul" "Agu_apap"     "D_apap"
```

```
## [17] "Aki_apap"     "Ave_apap"     "Alu_apap"     "Aar_apap"
## [21] "Are_apap"     "Asp_apap"     "Agu_metc13"   "D_metc13"
## [25] "Aki_metc13"   "Ave_metc13"   "Alu_metc13"   "Aar_metc13"
## [29] "Are_metc13"   "Asp_metc13"   "Agu_apap_cys" "D_apap_cys"
## [33] "Aki_apap_cys" "Ave_apap_cys" "Alu_apap_cys" "Aar_apap_cys"
## [37] "Are_apap_cys" "Asp_apap_cys" "Agu_apap_glu" "D_apap_glu"
## [41] "Aki_apap_glu" "Ave_apap_glu" "Alu_apap_glu" "Aar_apap_glu"
## [45] "Are_apap_glu" "Asp_apap_glu" "Agu_co2c13"   "D_co2c13"
## [49] "Aki_co2c13"   "Ave_co2c13"   "Alu_co2c13"   "Aar_co2c13"
## [53] "Are_co2c13"   "Asp_co2c13"   "time"
## Parameters:
##  [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##  [4] "BW"               "FVli"             "fup_metc13"
##  [7] "MET2APAP_Km"      "CO"               "FQgu"
## [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
## [13] "FQsp"             "FVsp"             "Kpsp_metc13"
## [16] "FQh"              "FVar"             "Kpli_metc13"
## [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
## [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
## [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
## [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
## [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
## [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
## [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
## [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
## [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
## [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
## [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
## [52] "FVki"             "fup_apap_sul"     "FQki"
## [55] "Kpki_apap_sul"    "FQlu"             "FVve"
## [58] "FQre"             "FVre"             "Kpre_apap_sul"
## [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
## [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
## [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
## [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
## [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
## [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
## [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
## [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
## [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
## [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
## [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
## [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
## [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## Estimate:
##   [1] "Ali_metc13"       "Ali_apap"         "Ali_co2c13"
##   [4] "Ali_apap_glu"     "Ali_apap_sul"     "Ali_apap_cys"
##   [7] "Agu_apap_sul"     "D_apap_sul"       "Aki_apap_sul"
##  [10] "Ave_apap_sul"     "Alu_apap_sul"     "Aar_apap_sul"
##  [13] "Are_apap_sul"     "Asp_apap_sul"     "Agu_apap"
##  [16] "D_apap"           "Aki_apap"         "Ave_apap"
##  [19] "Alu_apap"         "Aar_apap"         "Are_apap"
##  [22] "Asp_apap"         "Agu_metc13"       "D_metc13"
##  [25] "Aki_metc13"       "Ave_metc13"       "Alu_metc13"
```

```
##  [28] "Aar_metc13"       "Are_metc13"       "Asp_metc13"
##  [31] "Agu_apap_cys"     "D_apap_cys"       "Aki_apap_cys"
##  [34] "Ave_apap_cys"     "Alu_apap_cys"     "Aar_apap_cys"
##  [37] "Are_apap_cys"     "Asp_apap_cys"     "Agu_apap_glu"
##  [40] "D_apap_glu"       "Aki_apap_glu"     "Ave_apap_glu"
##  [43] "Alu_apap_glu"     "Aar_apap_glu"     "Are_apap_glu"
##  [46] "Asp_apap_glu"     "Agu_co2c13"       "D_co2c13"
##  [49] "Aki_co2c13"       "Ave_co2c13"       "Alu_co2c13"
##  [52] "Aar_co2c13"       "Are_co2c13"       "Asp_co2c13"
##  [55] "time"             "MET2APAP_HLM_CL"  "fumic_metc13"
##  [58] "MPPGL"            "BW"               "FVli"
##  [61] "fup_metc13"       "MET2APAP_Km"      "CO"
##  [64] "FQgu"             "FVgu"             "Kpgu_metc13"
##  [67] "BP_metc13"        "FQsp"             "FVsp"
##  [70] "Kpsp_metc13"      "FQh"              "FVar"
##  [73] "Kpli_metc13"      "APAPGLU_HLM_CL"   "fumic_apap_glu"
##  [76] "fup_apap"         "APAPGLU_Km"       "APAPSUL_HLM_CL"
##  [79] "fumic_apap_sul"   "APAPSUL_Km"       "APAPCYS_HLM_CL"
##  [82] "fumic_apap_cys"   "APAPCYS_Km"       "Kpgu_apap"
##  [85] "BP_apap"          "Kpsp_apap"        "Kpli_apap"
##  [88] "Kpgu_co2c13"      "BP_co2c13"        "Kpsp_co2c13"
##  [91] "Kpli_co2c13"      "Kpgu_apap_glu"    "BP_apap_glu"
##  [94] "Kpsp_apap_glu"    "Kpli_apap_glu"    "Kpgu_apap_sul"
##  [97] "BP_apap_sul"      "Kpsp_apap_sul"    "Kpli_apap_sul"
## [100] "Kpgu_apap_cys"    "BP_apap_cys"      "Kpsp_apap_cys"
## [103] "Kpli_apap_cys"    "Ka_apap_sul"      "F_apap_sul"
## [106] "CLrenal_apap_sul" "FVki"             "fup_apap_sul"
## [109] "FQki"             "Kpki_apap_sul"    "FQlu"
## [112] "FVve"             "FQre"             "FVre"
## [115] "Kpre_apap_sul"    "FVlu"             "Kplu_apap_sul"
## [118] "Ka_apap"          "F_apap"           "CLrenal_apap"
## [121] "Kpki_apap"        "Kpre_apap"        "Kplu_apap"
## [124] "Ka_metc13"        "F_metc13"         "CLrenal_metc13"
## [127] "Kpki_metc13"      "Kpre_metc13"      "Kplu_metc13"
## [130] "Ka_apap_cys"      "F_apap_cys"       "CLrenal_apap_cys"
## [133] "fup_apap_cys"     "Kpki_apap_cys"    "Kpre_apap_cys"
## [136] "Kplu_apap_cys"    "Ka_apap_glu"      "F_apap_glu"
## [139] "CLrenal_apap_glu" "fup_apap_glu"     "Kpki_apap_glu"
## [142] "Kpre_apap_glu"    "Kplu_apap_glu"    "Ka_co2c13"
## [145] "F_co2c13"         "CLrenal_co2c13"   "fup_co2c13"
## [148] "Kpki_co2c13"      "Kpre_co2c13"      "Kplu_co2c13"
## [151] "scale_apap"       "scale_apap_glu"   "scale_apap_sul"
## [154] "scale_apap_cys"
```

```
err8 <- Y(error_model8, g8)
```

```
## States:
## [1] "apap"     "apap_glu" "apap_sul" "apap_cys" "time"
## Parameters:
##   [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##   [4] "BW"               "FVli"             "fup_metc13"
##   [7] "MET2APAP_Km"      "CO"               "FQgu"
##  [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
##  [13] "FQsp"             "FVsp"             "Kpsp_metc13"
##  [16] "FQh"              "FVar"             "Kpli_metc13"
```

```
##  [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
##  [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
##  [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
##  [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
##  [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
##  [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
##  [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
##  [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
##  [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
##  [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
##  [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
##  [52] "FVki"             "fup_apap_sul"     "FQki"
##  [55] "Kpki_apap_sul"    "FQlu"             "FVve"
##  [58] "FQre"             "FVre"             "Kpre_apap_sul"
##  [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
##  [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
##  [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
##  [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
##  [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
##  [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
##  [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
##  [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
##  [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
##  [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
##  [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
##  [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
##  [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## [100] "srel_apap"        "s0_apap"          "srel_apap_glu"
## [103] "s0_apap_glu"      "srel_apap_sul"    "s0_apap_sul"
## [106] "srel_apap_cys"    "s0_apap_cys"
## Estimate:
##   [1] "apap"             "apap_glu"         "apap_sul"
##   [4] "apap_cys"         "time"             "MET2APAP_HLM_CL"
##   [7] "fumic_metc13"     "MPPGL"            "BW"
##  [10] "FVli"             "fup_metc13"       "MET2APAP_Km"
##  [13] "CO"               "FQgu"             "FVgu"
##  [16] "Kpgu_metc13"      "BP_metc13"        "FQsp"
##  [19] "FVsp"             "Kpsp_metc13"      "FQh"
##  [22] "FVar"             "Kpli_metc13"      "APAPGLU_HLM_CL"
##  [25] "fumic_apap_glu"   "fup_apap"         "APAPGLU_Km"
##  [28] "APAPSUL_HLM_CL"   "fumic_apap_sul"   "APAPSUL_Km"
##  [31] "APAPCYS_HLM_CL"   "fumic_apap_cys"   "APAPCYS_Km"
##  [34] "Kpgu_apap"        "BP_apap"          "Kpsp_apap"
##  [37] "Kpli_apap"        "Kpgu_co2c13"      "BP_co2c13"
##  [40] "Kpsp_co2c13"      "Kpli_co2c13"      "Kpgu_apap_glu"
##  [43] "BP_apap_glu"      "Kpsp_apap_glu"    "Kpli_apap_glu"
##  [46] "Kpgu_apap_sul"    "BP_apap_sul"      "Kpsp_apap_sul"
##  [49] "Kpli_apap_sul"    "Kpgu_apap_cys"    "BP_apap_cys"
##  [52] "Kpsp_apap_cys"    "Kpli_apap_cys"    "Ka_apap_sul"
##  [55] "F_apap_sul"       "CLrenal_apap_sul" "FVki"
##  [58] "fup_apap_sul"     "FQki"             "Kpki_apap_sul"
##  [61] "FQlu"             "FVve"             "FQre"
##  [64] "FVre"             "Kpre_apap_sul"    "FVlu"
##  [67] "Kplu_apap_sul"    "Ka_apap"          "F_apap"
```

```
##  [70] "CLrenal_apap"     "Kpki_apap"        "Kpre_apap"
##  [73] "Kplu_apap"        "Ka_metc13"        "F_metc13"
##  [76] "CLrenal_metc13"   "Kpki_metc13"      "Kpre_metc13"
##  [79] "Kplu_metc13"      "Ka_apap_cys"      "F_apap_cys"
##  [82] "CLrenal_apap_cys" "fup_apap_cys"     "Kpki_apap_cys"
##  [85] "Kpre_apap_cys"    "Kplu_apap_cys"    "Ka_apap_glu"
##  [88] "F_apap_glu"       "CLrenal_apap_glu" "fup_apap_glu"
##  [91] "Kpki_apap_glu"    "Kpre_apap_glu"    "Kplu_apap_glu"
##  [94] "Ka_co2c13"        "F_co2c13"         "CLrenal_co2c13"
##  [97] "fup_co2c13"       "Kpki_co2c13"      "Kpre_co2c13"
## [100] "Kplu_co2c13"      "scale_apap"       "scale_apap_glu"
## [103] "scale_apap_sul"   "scale_apap_cys"   "srel_apap"
## [106] "s0_apap"          "srel_apap_glu"    "s0_apap_glu"
## [109] "srel_apap_sul"    "s0_apap_sul"      "srel_apap_cys"
## [112] "s0_apap_cys"
```

```
obj8 <- normL2(mydatalist, (g8*x*p8), errmodel = err8)

pouter8 <- rep(0, length(getParameters(obj8))) %>% set_names(getParameters(obj8))
pouter8[names(myfit5 %>% as.parframe() %>% {.[2,]} %>% as.parvec())] <- myfit5 %>% as.parframe() %>% {.

# obj8(pouter8)

job8 <- runbg({myfit <- mstrust(objfun = obj8, center = pouter8, studyname = "methacetin", cores = 12, r

# save(job8, file = "job8.rda")

job8$check()
```

```
## Not ready!
```

```
## [1] FALSE
```

```
# myfit8 <- job8$get()$knecht5
# save(myfit8, file = "myfit8.rda")
# job8$purge()
load("myfit8.rda")
myfit8 %>% as.parframe()
```

```
##    index     value converged iterations logAPAPGLU_HLM_CL logAPAPGLU_Km
## 1     46 -486.5434      TRUE         68        0.84480403    3.06901379
## 2     95 -477.9974      TRUE         86        2.32210056    4.54478235
## 3      3 -458.5112      TRUE         85       -2.87880000   -0.50523641
## 4     91 -451.1060      TRUE         84        2.03596411    4.25790746
## 5     50 -437.6416     FALSE        100        2.18766166    4.40511124
## 6     44 -426.7063      TRUE         82       -0.90891783    1.31087026
## 7     48 -417.6661     FALSE        100       -4.00735703   -1.41198381
## 8     54 -414.2863      TRUE         67       -3.07730884   -0.40378855
## 9     62 -407.2330     FALSE        100       -2.68193926    1.20711720
## 10    37 -399.1658     FALSE        100        1.25958334    3.58360695
## 11    66 -398.7581      TRUE         97        2.98739270    5.20445288
## 12    59 -397.5421     FALSE        100        1.20979463    3.58276839
## 13    99 -393.1357     FALSE        100        1.77768368    4.00039597
## 14    45 -387.2042      TRUE         81        1.59743091    3.81942901
## 15    22 -386.6790      TRUE         69        4.94091971    7.15678121
## 16    30 -381.2340      TRUE         74        1.37336592    3.59735592
```

```
## 17     6 -379.3275     FALSE        100        0.98002319    3.21859253
## 18    90 -377.8988      TRUE         76       -2.46784885    0.07333258
## 19    23 -371.3712      TRUE         76        2.66918487    4.88595210
## 20     8 -371.2987     FALSE        100       -0.01359518    2.21955623
## 21    56 -370.8515      TRUE         86        6.02260056    8.23687223
## 22    64 -368.0023     FALSE        100       -0.86456341    1.36678512
## 23    94 -361.1413     FALSE        100        0.21446005    2.44028013
## 24    53 -360.1036     FALSE        100        0.63956889    2.86378801
## 25    69 -358.9269     FALSE        100       -2.89725157    0.88015633
## 26    33 -358.4769     FALSE        100        2.64493127    4.86723614
## 27    28 -356.6549     FALSE        100       -0.62434093    1.60854402
## 28     7 -352.6024     FALSE        100        0.35982356    2.72319249
## 29    86 -352.4075      TRUE         84        2.22123040    4.44349400
## 30    35 -351.2236     FALSE        100       -3.71385815   -0.43226224
## 31    68 -348.3400     FALSE        100        5.64063150    7.85515191
## 32    82 -347.9156     FALSE        100       -4.79504500   -1.32244479
## 33    74 -346.2455     FALSE        100        0.53207762    2.75661247
## 34    47 -343.7205      TRUE         74        3.17071557    5.38824830
## 35    18 -341.9355      TRUE         85        3.35842052    5.57502346
## 36    17 -340.9707     FALSE        100        0.30912760    2.53657204
## 37    49 -340.7551      TRUE         83       -2.02319068    0.79739254
## 38    20 -339.1826      TRUE         73        4.56077582    6.77517436
## 39    21 -336.8350     FALSE        100       -1.02236457    2.27743412
## 40    71 -336.8309     FALSE        100        1.74342575    3.96566746
## 41     5 -334.2124      TRUE        100        1.71150780    3.93462524
## 42    80 -331.2920      TRUE         69        1.02482735    3.46657450
## 43    87 -329.8186     FALSE        100        2.56247145    4.78478994
## 44    83 -328.1110     FALSE        100        1.26880638    3.49226376
## 45    43 -327.9086      TRUE        100        5.66671318    7.88277805
## 46    96 -325.8168     FALSE        100        1.97057017    4.19363241
## 47   100 -325.2455      TRUE         70        1.92398793    4.14626652
## 48    27 -324.6955     FALSE        100        0.30492890    2.53107835
## 49    72 -323.7286      TRUE         93        4.77856515    6.99513986
## 50    88 -322.2826      TRUE         92        1.32313671    3.54620558
## 51    34 -319.9767      TRUE         83        4.70671662    6.92293600
## 52    25 -319.6439     FALSE        100        0.31228649    2.98986379
## 53    40 -318.8957      TRUE         71        1.27482500    3.49317682
## 54    70 -317.7407      TRUE         94        1.77760861    4.00040059
## 55    61 -310.6908     FALSE        100        1.98547507    4.20918372
## 56     2 -310.0881     FALSE        100        1.66145374    3.88381538
## 57    73 -305.3344      TRUE         81        3.63417619    5.85069185
## 58    31 -304.0247      TRUE         80        1.68378934    3.90702149
## 59    89 -302.1540      TRUE         82        3.18582583    5.40787707
## 60    85 -296.8041      TRUE         75        1.70311274    3.92609752
## 61    52 -296.4889     FALSE        100        4.17297577    6.38922282
## 62    65 -296.3408     FALSE        100       -0.22959958    1.99765874
## 63    41 -295.2617     FALSE        100        0.37855580    2.97904125
## 64    38 -294.4642      TRUE         93        1.07753272    3.30137936
## 65    97 -294.2711      TRUE         94        2.44463309    4.66670244
## 66    79 -294.0032     FALSE        100       -2.89400440   -0.50668978
## 67    15 -290.6373     FALSE        100        1.29083158    3.50709686
## 68    98 -287.8832      TRUE         77        0.47907363    2.69859376
## 69    77 -287.1968      TRUE         70        5.13097366    7.34413648
## 70    78 -286.3194      TRUE         81        0.75428466    2.97852630
```

```
## 71    32 -286.1508     FALSE        100        2.44708399    4.66970351
## 72    39 -283.5832      TRUE         84       -2.42336507    0.23492424
## 73    13 -283.4147     FALSE        100        1.83537038    4.05882207
## 74    60 -275.4950     FALSE        100        0.41314498    2.64165513
## 75    19 -275.3549     FALSE        100        0.73826750    2.96351587
## 76    24 -273.8481     FALSE        100        3.78318207    6.00675512
## 77    76 -269.2638     FALSE        100       -1.08756111    1.14921001
## 78    67 -266.5582     FALSE        100        2.73391858    4.95603255
## 79    36 -266.4101      TRUE         82        2.17866816    4.40092780
## 80    92 -265.4608     FALSE        100        1.86395080    4.08651827
## 81    81 -262.6077     FALSE        100        0.96397389    3.18778882
## 82    75 -257.2708     FALSE        100        2.07975180    4.30268931
## 83    63 -256.3812      TRUE         83        5.68005442    7.89592158
## 84    42 -254.3839      TRUE         62        2.67299317    4.88950283
## 85    57 -245.3618      TRUE         81        1.32825737    3.55196183
## 86    16 -245.0925      TRUE        100        2.19595968    4.41875224
## 87     9 -244.5274      TRUE         86        6.17349912    8.38858491
## 88     1 -244.5244     FALSE        100        1.18329094    3.40696933
## 89    55 -243.9418     FALSE        100       -5.98972306   -0.96196957
## 90    14 -219.2012     FALSE        100       -1.63283162    0.62851698
## 91    93 -213.0993      TRUE         97        1.77516756    3.99765259
## 92    29 -212.8790      TRUE         77        2.00169788    4.22524376
## 93    58 -201.8819     FALSE        100       -1.53732779    1.17592108
## 94    12 -195.4929      TRUE         76        5.77845342    7.98761866
## 95    10 -186.1711     FALSE        100        2.63383770    4.85602636
## 96    51 -169.9097      TRUE         77       -2.60702137    0.91258887
## 97    84 -169.4156      TRUE         87        6.36145307    8.57619527
##    logAPAPSUL_HLM_CL logAPAPCYS_HLM_CL logAPAPCYS_Km logKa_apap
## 1         -10.788256        -13.569167    -3.1263001 -6.2951792
## 2         -12.281700        -11.212139    -1.1280998 -6.2802913
## 3          -6.651499        -14.825401    -3.5520274 -6.3251548
## 4         -12.473814        -13.549989    -2.4200639 -6.2890211
## 5         -11.711911        -13.734286    -2.5954428 -2.2785415
## 6         -10.442107        -14.438483    -3.4068445 -2.3071665
## 7          -5.839142        -12.423766    -4.1951061 -6.4366095
## 8          -5.710942        -10.707604    -2.3001680 -3.4663821
## 9          -4.948465         -7.685311    -1.7792015 -6.3274719
## 10         -7.049597        -13.699473    -2.8780701 -6.3066199
## 11        -12.337276        -15.874618    -3.1055667 -1.1227874
## 12         -6.674724        -13.533125    -2.8465002 -6.2857780
## 13        -11.762646        -13.680356    -2.7201559 -6.2774564
## 14        -11.340782        -15.961777    -4.6836312 -6.2787950
## 15        -14.351912        -14.297054    -1.6824017  0.3315816
## 16        -10.623440        -12.279878    -2.4334914 -6.2206575
## 17         -8.799966        -14.887024    -3.9750991 -6.2828068
## 18         -6.005399        -13.705857    -2.6807212 -6.3295658
## 19        -12.580282        -11.388195    -1.0862451 -1.8197456
## 20         -9.367139        -10.734975    -2.0653524 -6.3184823
## 21        -15.586309        -16.346803    -2.1706178  2.4416502
## 22         -9.228510        -11.104516    -2.5745156 -6.3993063
## 23        -10.188104        -11.157425    -2.1787809 -6.2477424
## 24        -10.686281        -13.326259    -3.1939546 -6.2640623
## 25         -4.946432        -14.270845    -3.7245025 -6.3142997
## 26        -12.632234        -13.105857    -1.9596859 -6.2744398
```

```
## 27        -9.291192       -10.928279    -2.4410534 -6.2351887
## 28        -6.741355       -13.724704    -3.0870464 -6.3143156
## 29       -12.349901       -13.505757    -2.3746282 -6.2802849
## 30        -5.132608       -13.594778    -3.9531345 -6.3075646
## 31       -14.586463       -15.774724    -2.4857443  0.9779739
## 32        -5.042795       -10.847223    -2.8781856 -6.3126438
## 33       -10.386830       -12.875776    -3.0873777 -6.2467533
## 34       -12.919689       -12.931817    -1.7238379 -5.3336846
## 35       -12.421351       -13.846596    -2.3350877 -1.1808175
## 36        -9.934556       -11.740840    -2.4493609 -6.3070118
## 37        -5.507601       -13.695181    -3.4631852 -6.3258109
## 38       -13.232375       -13.822983    -2.0087188 -0.1172616
## 39        -5.126721       -12.804719    -2.3275547 -6.3234662
## 40       -11.915646       -13.516567    -2.6826333 -6.2794018
## 41       -11.532795       -12.823640    -2.2785615 -6.2899645
## 42        -6.339401       -12.379424    -2.1580450 -6.3250089
## 43       -12.604654       -12.116403    -1.4620093 -6.2683623
## 44       -11.293782       -11.111209    -1.6085585 -6.3241255
## 45       -15.430693       -15.831795    -1.8713859  1.2020812
## 46       -11.670387       -11.864452    -1.7684727 -6.2658757
## 47       -11.926754       -12.978657    -2.2832356 -6.2939564
## 48       -10.223788       -12.474896    -2.8333635 -6.2829846
## 49       -15.015089       -13.831442    -1.1142662  0.5307671
## 50       -11.383615       -13.397736    -2.8216248 -6.2781084
## 51       -14.507552       -12.701756    -0.7759368  0.1654594
## 52        -5.716775       -16.445096    -4.6824684 -6.3143120
## 53       -10.832160       -12.848221    -2.6599185 -3.2625327
## 54       -11.832212       -11.945786    -1.7744992 -6.2758376
## 55       -11.215102       -12.785364    -2.1995771 -6.2974639
## 56       -11.608751       -13.109513    -2.5141927 -6.3044905
## 57       -13.573823       -12.503006    -1.1972476 -0.5916350
## 58       -11.301114       -13.290199    -2.5922657 -6.2747661
## 59       -13.249161       -13.639787    -1.9229411 -6.2795939
## 60       -11.689140       -11.856932    -1.7600109 -6.2788534
## 61       -13.928356       -10.246992     0.2086676 -0.3366902
## 62        -9.735239       -14.056715    -4.2852723 -6.3041486
## 63        -5.868070       -12.628332    -2.3290428 -6.3203704
## 64       -10.984913       -12.926521    -2.6766135 -6.2853591
## 65       -12.349777       -13.786779    -2.4608477 -6.2823461
## 66        -6.552076       -14.092200    -5.9078933 -6.2994064
## 67       -11.242163       -12.806505    -2.5630332 -3.9940514
## 68       -10.432264       -13.385435    -3.3718674 -4.2248078
## 69       -13.743887       -14.158707    -1.9932770  0.4418557
## 70       -10.767013       -12.592642    -2.6466977 -6.2910859
## 71       -11.811585       -13.107001    -2.0436444 -6.2699167
## 72        -5.739215       -12.638763    -2.8694013 -3.1666789
## 73       -11.397392       -13.203239    -2.4279942 -6.2986379
## 74        -9.780569       -12.905384    -2.9488958 -6.3098352
## 75       -10.366626       -16.438164    -5.7161228 -6.2972685
## 76       -10.889854       -11.859069    -1.6687918 -6.2097547
## 77        -8.663455       -13.052990    -3.7376756 -6.2910248
## 78       -12.761943       -11.792172    -1.2257321 -6.3143441
## 79       -12.164419       -16.724580    -4.6135286 -6.2687067
## 80       -11.847130       -13.737169    -2.7193267 -6.2894453
```

```
## 81        -10.973451        -12.739385    -2.6565297 -6.2729127
## 82        -11.877358        -10.098105    -0.9224136 -6.2155891
## 83        -15.210676        -15.483482    -1.8053108  1.7766520
## 84        -12.552267        -14.722132    -2.9268740 -1.8531834
## 85        -11.050765        -13.564881    -2.9419763 -6.2822401
## 86        -11.268131        -14.220355    -2.9533239 -6.3159711
## 87        -15.222345        -15.333397    -1.7879272  1.5360875
## 88        -11.156243        -11.551653    -1.8843545 -6.2798007
## 89         -4.771876        -13.988946    -3.7470377 -6.2940167
## 90         -7.936191        -14.327247    -4.8072519 -6.2835758
## 91        -11.803128        -12.417593    -2.0376374 -6.2648565
## 92        -11.758254        -10.800309    -1.3376986 -6.2903452
## 93         -5.656814        -13.487551    -3.8415852 -6.3114664
## 94        -14.163634        -16.052626    -3.0739190  1.0746235
## 95        -12.638202        -14.689776    -2.8380840 -6.2697210
## 96         -5.029344        -12.766616    -2.3767629 -6.3055171
## 97        -15.323512        -12.937696    -0.2917607  1.7188572
##    log_scale_apap_Chan1997_1.4_0 log_scale_apap_glu_Chan1997_1.4_0
## 1                     -0.34147420                         0.35245400
## 2                      0.87395974                        -0.22021929
## 3                      0.28419894                        -1.21171280
## 4                     -0.23704451                        -0.51414641
## 5                     -0.00256986                         0.76405060
## 6                     -1.39510256                        -0.83120816
## 7                      1.49212817                         0.21325002
## 8                     -0.64679590                        -1.81550616
## 9                     -1.37919483                         1.20808381
## 10                    -0.59836745                         1.41124861
## 11                     0.48091720                         0.88349014
## 12                    -1.27460038                         0.37045216
## 13                    -1.20983293                        -0.15490480
## 14                    -0.72306404                         0.78073943
## 15                     0.06079003                         0.38982148
## 16                    -0.88713397                         0.84018641
## 17                     0.27566983                         0.47634252
## 18                    -1.14055521                         0.40845810
## 19                     0.97838682                        -0.24291038
## 20                     0.06193614                         0.38703124
## 21                     2.03134357                        -1.42816499
## 22                     0.64628912                        -0.16274491
## 23                    -0.85755658                        -0.45634460
## 24                     0.61218761                        -0.16342724
## 25                    -0.60611217                         0.96876628
## 26                     1.01415891                         1.06076949
## 27                     0.06729703                        -0.57503771
## 28                    -0.16675918                        -0.26325588
## 29                    -1.18885928                         0.48164925
## 30                    -1.36489273                         1.23232485
## 31                    -1.50181877                         2.13584107
## 32                     0.51380936                         0.53631028
## 33                     0.96031368                         0.11214691
## 34                    -0.63970485                        -0.49659705
## 35                     1.16867383                         1.36987899
## 36                     0.82969335                        -1.08461241
```

```
## 37          -0.56157372           0.02949614
## 38          -1.81033508           0.24502039
## 39           0.07660979          -2.37779052
## 40          -0.17615881          -1.88108047
## 41          -0.47637565          -0.86002494
## 42          -0.18313261           0.11474182
## 43           0.93617231          -0.39798298
## 44           0.40724157          -0.04130685
## 45          -1.79075393           0.85903547
## 46           0.01689524           0.86782835
## 47           1.04681090          -1.75190770
## 48          -1.98979397           0.10722399
## 49           0.37253088           0.08804560
## 50          -0.21811045          -1.88347197
## 51          -1.47397997          -2.00995101
## 52           1.19796148           0.34747989
## 53          -1.94230218          -1.40358147
## 54           0.71546459          -0.56828175
## 55          -0.39968230           0.85050796
## 56          -0.29001416           0.43469763
## 57           0.17569982          -0.32811008
## 58           0.48809313          -2.03098733
## 59          -2.09881263          -0.37002396
## 60          -0.64106295          -0.00559598
## 61           1.50381650          -0.04525530
## 62           0.02817034          -0.17538347
## 63          -1.06095552          -1.32069575
## 64           0.28155136           1.81785711
## 65          -0.92450949          -0.27039246
## 66           0.83684524           1.41829114
## 67           2.55922320          -0.15738101
## 68          -0.80478882          -0.56518858
## 69          -0.51003507           0.13850543
## 70          -0.86323349           1.00050055
## 71           1.38922112          -1.52252836
## 72           0.22695866           1.05604214
## 73          -0.69572259           0.87185173
## 74          -0.58170094          -1.99131754
## 75          -0.38156224          -1.12139413
## 76           2.85730029           1.32383283
## 77           1.27042747          -1.20577400
## 78          -0.65663660          -0.91187769
## 79          -0.38114088          -0.14251554
## 80          -1.36220319          -0.16287352
## 81           0.57781708          -1.06757356
## 82          -0.75489914           0.41386003
## 83           0.55674299          -0.03157002
## 84           0.82329030          -1.59670667
## 85           0.80743165           1.11848229
## 86          -1.55926522          -0.71196130
## 87          -0.21807537           1.24454189
## 88           0.85916891           0.13783641
## 89          -1.02265814           0.83167424
## 90          -0.10888649           0.55290540
```

```
## 91                    1.64432449                         0.63829812
## 92                   -0.16873237                        -0.31956965
## 93                   -0.97045452                         1.23625601
## 94                   -0.99160910                        -0.08014797
## 95                   -1.33881700                         0.14579431
## 96                    0.33842752                        -1.51267798
## 97                    1.17988812                         1.16327975
##    log_scale_apap_sul_Chan1997_1.4_0 log_scale_apap_cys_Chan1997_1.4_0
## 1                       -0.090542245                         0.49096737
## 2                       -2.051767556                         0.17135479
## 3                        1.591522064                         0.95674825
## 4                       -0.642960930                         0.68227993
## 5                       -0.283813843                         1.20336342
## 6                       -0.424470866                        -0.93838017
## 7                        0.263668748                        -1.46986870
## 8                        0.693915507                        -0.74119185
## 9                       -0.633188155                         0.77315070
## 10                      -1.812985850                         1.31120819
## 11                      -1.443942773                         2.01755447
## 12                       0.818576358                         0.34800676
## 13                       0.601917914                         0.92708146
## 14                      -1.999970893                        -1.75990306
## 15                       0.316283068                         0.91444685
## 16                      -0.193228691                         0.77249742
## 17                      -0.062382620                         1.32152800
## 18                       0.775080156                        -0.44178915
## 19                       0.921870939                        -0.47389364
## 20                      -0.093152759                         0.10351836
## 21                       0.730921953                         0.57399941
## 22                      -0.192355657                        -0.14377236
## 23                      -0.715625044                        -0.83261613
## 24                      -1.637538696                         0.03418539
## 25                       0.182573348                         0.62784830
## 26                       1.342412004                        -2.42081763
## 27                      -0.666795825                        -0.97533838
## 28                       1.333238968                        -0.16469390
## 29                       0.469114068                        -0.17860433
## 30                      -0.975773940                        -1.31025756
## 31                       0.035023983                        -0.23564591
## 32                       0.207450304                         0.52334030
## 33                       0.567601493                        -0.03115967
## 34                       0.223455540                        -0.12586652
## 35                       1.356111492                        -0.25045148
## 36                       0.131574080                        -1.07339471
## 37                       1.280014930                        -1.06136824
## 38                       1.072908943                         1.52547338
## 39                      -0.299920503                        -1.73045740
## 40                       1.382108956                         0.56507547
## 41                       1.790703209                        -1.43603572
## 42                      -0.238389243                         0.92713643
## 43                      -0.346905631                        -0.53775279
## 44                       0.539257400                        -1.23217138
## 45                       1.562115955                        -1.01376289
## 46                       0.763009198                         0.80367614
```

```
## 47                       0.310920993                       1.36473251
## 48                      -2.032737608                      -1.16849499
## 49                       1.324363817                      -0.31540655
## 50                      -1.612680474                       0.40441168
## 51                       1.636560845                      -0.61164249
## 52                       1.137478127                      -1.25548830
## 53                       2.014778484                      -1.07948852
## 54                       0.162892690                      -0.38629064
## 55                      -0.515426775                      -0.01383143
## 56                       0.004407352                      -1.53810591
## 57                       0.120381700                      -0.68548961
## 58                       0.438361445                       0.24899368
## 59                       0.550824472                       0.18451579
## 60                      -0.837097196                      -0.57483993
## 61                      -1.116702808                      -1.96966995
## 62                      -0.286264799                       1.07043391
## 63                       0.281895510                      -2.64814725
## 64                      -1.135519165                      -1.02758235
## 65                      -1.527179170                       0.79677520
## 66                       0.574042440                      -0.36694847
## 67                       0.185917783                      -1.80651698
## 68                       1.165747027                      -0.13625569
## 69                      -1.185028661                       1.04411853
## 70                      -1.031452814                      -1.02724733
## 71                       0.003076280                       0.51839347
## 72                       1.038371178                       0.64405233
## 73                       1.413987602                      -1.14879404
## 74                       3.295576015                      -0.42820622
## 75                      -1.535951869                       1.02647242
## 76                      -1.064005380                      -1.79183349
## 77                      -1.529735544                       1.14808161
## 78                      -2.293169000                      -0.46094220
## 79                       0.084754419                       2.44518611
## 80                       0.038136034                      -1.03385817
## 81                       0.888664278                      -0.83042853
## 82                      -0.062367245                      -0.03891437
## 83                       0.852313844                      -0.17725353
## 84                      -1.173851658                      -0.72006132
## 85                      -1.447742215                       2.41530326
## 86                      -0.189895668                      -0.99383524
## 87                       1.539888638                       0.21153199
## 88                       0.270744221                      -1.85422221
## 89                      -0.138933643                      -0.10745175
## 90                       0.163957469                       2.41844108
## 91                       1.305112007                      -0.68873309
## 92                      -1.292034902                      -0.23062046
## 93                       0.685692691                       0.69362553
## 94                      -0.260597456                      -0.22725340
## 95                      -0.177328706                       1.26542763
## 96                       0.517467229                      -0.78217900
## 97                      -0.153525056                       2.03886285
##    log_srel_apap_Chan1997_1.4_0 log_s0_apap_Chan1997_1.4_0
## 1                    0.25695886               -1.90147941
## 2                   -0.61949638                1.42240621
```

```
## 3                0.48842574               0.46206268
## 4                0.44316862               0.34374404
## 5               -1.07748693              -0.71116877
## 6               -0.10592875              -0.42873233
## 7                1.27938545              -2.26027271
## 8                0.07050413              -0.10954292
## 9               -0.34065652              -0.14768381
## 10              -0.94892077               0.46553322
## 11               0.25166669              -1.63840452
## 12              -0.85111439              -1.39642520
## 13              -0.99628120              -1.69167316
## 14              -0.71268708               0.92471068
## 15              -0.05201992              -1.15051516
## 16               1.48118331               0.70177697
## 17               1.21315161              -0.10009754
## 18               0.65603705              -1.11444792
## 19               1.23624705               1.06308373
## 20              -0.29317946              -0.64441216
## 21              -0.51221961              -0.78962811
## 22               0.70527358              -0.45867593
## 23              -1.20894728               0.48039108
## 24              -0.27750972              -0.29534816
## 25              -0.21522494              -0.56611252
## 26              -0.01542063              -0.06626009
## 27              -0.13085229              -0.26572679
## 28              -1.39485069               0.14973341
## 29               0.10596251              -0.79145836
## 30              -0.83901113               0.99835182
## 31              -0.53078970               0.94901963
## 32              -0.12760883              -0.92839169
## 33               0.76839501              -1.36401687
## 34               0.22916120              -1.61798109
## 35               0.12792537              -0.26794367
## 36              -0.15666712               0.56590400
## 37               1.37411614              -0.80612231
## 38               0.57783265               0.41544373
## 39               0.84247630               1.03834259
## 40              -0.33893197               0.54339802
## 41              -1.21331771              -0.01582473
## 42              -2.03872036              -0.81530157
## 43              -1.43063079              -0.57968894
## 44               0.45147855              -1.25327499
## 45               1.00310181              -1.09964329
## 46               0.88825056               0.62229148
## 47              -1.41115736               1.94893497
## 48              -1.73872318               0.04136263
## 49              -0.62674057               0.92754542
## 50              -0.58505779              -0.67576313
## 51               1.51090521              -0.90112364
## 52               0.37239206               0.03855192
## 53              -1.12300851              -0.14660740
## 54              -0.33412218              -1.99816872
## 55               1.01842570               1.04969105
## 56               0.19091611               1.57840824
```

```
## 57                   0.41955362                -0.90478851
## 58                  -1.08505855                 0.99371774
## 59                   0.56243967                -1.16009232
## 60                  -0.20053687                 0.12178462
## 61                   0.50406869                 0.18229568
## 62                  -2.17655377                 0.58959790
## 63                  -0.33206014                -0.27568183
## 64                   0.80234950                 0.04207052
## 65                   0.33425995                -0.11181331
## 66                   0.11629321                 0.42294629
## 67                  -0.99745976                -1.15676230
## 68                   0.31883141                -0.45909065
## 69                  -0.40648967                 0.69465833
## 70                   0.46843394                 0.06019813
## 71                   1.36440173                -0.39698363
## 72                  -0.21168364                 0.91610351
## 73                  -1.17152068                -0.38154420
## 74                  -0.87925522                 0.01753237
## 75                   0.79035020                 0.79275967
## 76                   0.15945664                 0.03761220
## 77                  -1.01437009                -0.56835180
## 78                  -0.37096475                 1.11625274
## 79                   0.87674728                 0.67250611
## 80                  -0.40439645                 2.51381344
## 81                  -0.66866478                -0.35093336
## 82                  -0.34529050                 0.19550254
## 83                   0.05928407                -0.07326718
## 84                   1.18234332                 0.18016555
## 85                  -0.90783371                -0.57100179
## 86                  -0.47437529                 1.93088323
## 87                  -2.99818584                 1.11698625
## 88                  -0.78042190                 0.46853702
## 89                   1.40175376                 0.20502316
## 90                   2.04525033                 1.51264983
## 91                   0.40770601                -1.18992600
## 92                  -0.70136126                -1.76552305
## 93                  -1.15678814                 0.97309613
## 94                  -0.76245359                 0.89253227
## 95                   0.69062573                 0.93514709
## 96                  -0.25289528                 0.46495307
## 97                   1.11504811                 0.23611527
##    log_srel_apap_glu_Chan1997_1.4_0 log_s0_apap_glu_Chan1997_1.4_0
## 1                      -0.956927431                    -0.15475447
## 2                       0.683094562                    -0.93583214
## 3                       0.125211295                     1.40794576
## 4                      -1.050525237                    -1.19699375
## 5                       1.300733116                    -1.56564547
## 6                       2.108121311                    -1.77620226
## 7                      -0.131179890                    -2.25824667
## 8                      -1.369015174                    -0.44327987
## 9                       0.264605899                    -1.65233460
## 10                     -0.272155387                     0.03095698
## 11                      1.339300061                    -1.29646334
## 12                     -0.635461257                    -1.17465146
```

```
## 13          2.079057661          0.74084544
## 14         -1.576151074         -1.28890621
## 15         -0.277171400         -1.50951419
## 16          1.465085581         -1.20118567
## 17         -0.200033972          0.46450099
## 18          1.019548463         -0.74109980
## 19          0.547475278         -0.05865516
## 20          1.212493851         -0.13080735
## 21          0.171093665         -0.44855839
## 22         -0.198821197          0.08872731
## 23         -0.722208694         -2.62015371
## 24         -0.836537266         -1.01972699
## 25          0.664595610          1.40538534
## 26          0.390251043         -0.29216265
## 27         -1.102712188         -1.51441140
## 28          1.287378520          1.23172875
## 29          0.792123876         -0.67706597
## 30         -0.824353135         -0.75970565
## 31         -1.538033749         -0.15994964
## 32         -1.702658317         -0.95413104
## 33          1.522824063         -1.00787053
## 34         -1.059102926         -1.40353405
## 35          0.798909790          0.80788000
## 36         -0.005874402         -0.52782665
## 37         -0.167586082         -0.85586465
## 38         -0.880496500          1.11525565
## 39         -0.850022627          0.34550758
## 40          0.603712075          0.55675376
## 41          0.717693587          0.48933584
## 42         -0.891476503         -0.71765946
## 43          1.452813085         -0.38621015
## 44         -0.172106621         -0.15426059
## 45         -1.746025869          0.04932196
## 46         -0.110305564         -1.44827979
## 47          0.309491446          0.07208363
## 48          1.402682523          1.07596767
## 49          1.246925668          1.88313445
## 50         -1.303305884          0.59132831
## 51         -0.609206504         -0.92473134
## 52          1.052400158          0.05805470
## 53         -0.280377158         -0.01560072
## 54          0.669993410          1.09545711
## 55         -1.665599340         -1.84309269
## 56         -1.453267264          0.01817025
## 57         -0.450813769          0.62959328
## 58         -1.928965610          2.48510706
## 59         -0.498097324          0.86860280
## 60          2.055743186          0.38346351
## 61         -0.639235925         -0.35209522
## 62         -0.890454104          0.84133620
## 63         -0.986356614         -0.80124446
## 64          0.786862434          1.73029567
## 65          1.258414258          0.03571403
## 66          0.182239581         -1.07479291
```

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## 67                        0.819613981                       -1.05593879
## 68                        0.160529547                       -0.39043582
## 69                        0.922400830                       -0.03698444
## 70                        1.258104175                        1.71184156
## 71                        0.974415214                       -0.50914318
## 72                        1.375614546                        0.49056108
## 73                       -0.599944387                       -1.11752442
## 74                       -0.212269551                        1.12445324
## 75                        1.339951086                       -1.38137547
## 76                       -0.664138303                        0.31386925
## 77                        0.576713339                        0.61917258
## 78                       -0.042488650                       -0.50538362
## 79                       -1.732944674                        1.22173030
## 80                        2.063021065                       -1.47619743
## 81                        0.055363977                       -0.14934203
## 82                        1.249742417                       -1.12460899
## 83                        0.578433390                        0.14391192
## 84                        0.056833630                       -0.11945706
## 85                       -0.213483651                       -1.30314850
## 86                        0.529332334                        0.69775620
## 87                       -0.720915622                        2.31434327
## 88                       -0.359075891                       -1.08208332
## 89                       -0.397699766                        0.94146407
## 90                       -0.627594336                       -0.65599252
## 91                        0.798010981                        0.61122594
## 92                        2.288736759                       -0.25250603
## 93                       -0.634745653                       -2.29363461
## 94                        0.678692016                        0.46180443
## 95                        1.883889269                        0.64520445
## 96                        0.396248054                        2.11450346
## 97                        0.705938670                        2.34922031
##    log_srel_apap_sul_Chan1997_1.4_0 log_s0_apap_sul_Chan1997_1.4_0
## 1                       -2.558385457                      -1.18576967
## 2                        0.205621359                      -1.40488821
## 3                       -0.520681492                      -3.09527617
## 4                        1.701868086                      -2.42486076
## 5                       -1.929015264                      -0.84411275
## 6                        0.675441132                       0.66587901
## 7                       -1.063718214                      -0.33099271
## 8                        0.029160618                       0.37793870
## 9                        0.746507128                      -0.35986349
## 10                       1.026083349                      -0.48821122
## 11                       1.609349283                       0.04279710
## 12                      -0.450927265                      -3.98692304
## 13                       0.087557669                       0.04390998
## 14                       1.982381441                      -0.87599964
## 15                       0.321755183                      -1.35662296
## 16                       1.272898550                       0.33924378
## 17                       0.080045474                      -0.41850295
## 18                       1.054898982                      -0.04003922
## 19                      -0.071022538                      -1.05232153
## 20                       0.697741841                      -0.01301185
## 21                      -0.357234898                       0.95870895
## 22                      -0.116907134                      -0.41508058
```

```
## 23          0.102998117          -0.46760908
## 24          0.444467587          -0.04295653
## 25         -0.858851916           0.48469726
## 26          0.460996483           0.57175328
## 27         -0.044175285          -0.90716764
## 28         -0.357795113           0.12100659
## 29         -1.527958424          -0.42110828
## 30          0.302192333          -0.16623565
## 31          0.600768011           0.29057425
## 32         -0.993931424          -0.98208670
## 33          1.416350719           0.23225508
## 34          0.929188845          -0.28278321
## 35         -0.459345605          -0.22378628
## 36          0.578668508          -0.18242091
## 37          0.695120628           0.71199773
## 38         -0.626699185          -1.65333162
## 39         -0.378747326           0.42117950
## 40         -1.013696990          -0.13790724
## 41         -0.754373969          -1.76955971
## 42         -0.947996095           0.29068496
## 43          1.229120117           0.39874885
## 44          0.878495211           1.05365119
## 45         -1.291331791           0.01593288
## 46          0.762511514          -1.76356551
## 47          0.138269508          -0.97802212
## 48         -0.338898431          -1.24451075
## 49         -0.283727141          -1.59076336
## 50          0.782842398           0.88840217
## 51         -1.313018040           1.36376835
## 52          0.827976431          -0.22988092
## 53          0.820929879          -2.08889788
## 54          1.317849046          -1.16001561
## 55          0.821872765           0.14596395
## 56         -1.401209675          -0.52959558
## 57         -1.499508340           0.31144399
## 58          0.139535407           1.25686751
## 59         -1.564147024          -1.06983651
## 60          1.357232675           0.54923592
## 61         -0.448875482          -1.77948666
## 62         -0.174496155           0.60734307
## 63         -0.424060997           0.18855865
## 64         -0.641469988          -1.25831478
## 65         -0.166383339           0.03160547
## 66         -1.712133512          -1.10726950
## 67         -1.175734894           0.04915420
## 68         -0.606378904           0.15798196
## 69         -0.664252726           0.37216002
## 70          0.393182776           0.55186026
## 71         -0.360323340          -0.37850458
## 72          2.307043931          -0.79267148
## 73         -1.230110790           1.31346781
## 74         -0.689974880          -0.37737584
## 75          0.077493433           1.31565924
## 76         -0.216590859           0.69939818
```

```
## 77                       0.525941517                      0.32109292
## 78                      -1.129696597                      0.30634918
## 79                      -1.602293267                     -1.30881769
## 80                       0.883242707                      0.06376804
## 81                      -0.259234421                      1.46005780
## 82                       0.003901447                      0.66191296
## 83                      -0.685874855                      0.90651249
## 84                      -2.974145373                     -0.31286430
## 85                       2.180352414                      0.55773566
## 86                       0.453660830                     -1.24427790
## 87                      -1.214492385                     -0.69664079
## 88                       0.718740929                     -1.31912273
## 89                      -0.017970780                      0.93771879
## 90                      -0.005541669                      0.38347588
## 91                       0.963095998                     -0.64235580
## 92                       0.108633307                      1.04068483
## 93                       0.961992912                     -0.22696412
## 94                      -0.528846882                      0.10019804
## 95                       0.507767376                     -0.19387491
## 96                      -1.501420562                     -1.04527234
## 97                      -1.053876313                      0.68923151
##    log_srel_apap_cys_Chan1997_1.4_0 log_s0_apap_cys_Chan1997_1.4_0
## 1                       -0.80413329                    -1.763841005
## 2                       -1.03467092                    -2.639128818
## 3                        0.12948514                    -0.068312294
## 4                       -1.23494485                    -0.354655096
## 5                       -1.45640160                    -2.216841706
## 6                       -0.08965077                    -2.189677284
## 7                        0.50259103                     0.557900042
## 8                        0.72395388                    -0.018196615
## 9                       -0.71569830                     0.029928661
## 10                      -1.17495333                    -1.771546368
## 11                       0.78579054                    -0.135950299
## 12                      -0.20874881                    -0.529516717
## 13                       0.35836739                    -0.698633254
## 14                      -0.33643339                     0.039919324
## 15                      -1.64816165                    -0.610039791
## 16                       0.71642199                    -1.565261546
## 17                      -1.93520639                     0.005348448
## 18                      -0.17720841                    -1.153315893
## 19                       0.45579459                    -2.684434468
## 20                      -0.94036430                    -2.348863027
## 21                      -0.17765532                    -0.119202775
## 22                       0.92006243                    -0.008128718
## 23                      -0.81070110                    -0.261331904
## 24                      -0.99681265                    -0.716378907
## 25                      -0.83899301                     0.651356917
## 26                      -0.38949788                     0.247364809
## 27                      -1.01891845                     0.370356531
## 28                      -0.02974985                    -0.777127873
## 29                       0.02369316                    -1.159190053
## 30                       0.15829686                    -0.672086891
## 31                       1.11359069                     0.440803829
## 32                      -1.53610205                     0.125954693
```

```
## 33   1.36251224 -1.005132021
## 34  -0.57499754 -0.131278959
## 35  -1.48639088  0.282207661
## 36   0.47636297 -0.856043498
## 37   0.34097678 -0.302646620
## 38  -1.89209216 -0.586867884
## 39  -1.20794521  1.902730643
## 40  -1.34528055 -0.398259552
## 41  -0.31403049  0.923720228
## 42  -0.92543839  2.087052516
## 43   0.64500247  0.759208825
## 44   0.26597584 -1.835617061
## 45   0.45151330 -0.663821197
## 46  -0.39026474  1.114689621
## 47   1.28843737 -0.441672740
## 48  -0.33664170  1.900314310
## 49  -0.20483466 -0.482553335
## 50  -0.49353878  0.448155505
## 51  -0.80324961  0.702124378
## 52  -1.54175800  0.287660766
## 53   0.11477685 -0.009699415
## 54   0.46294870  0.273210176
## 55   1.17444041 -1.652274127
## 56  -0.30654849  0.797509309
## 57   2.44058261 -1.466785715
## 58   1.26579459  0.463986156
## 59   1.91361429  1.067331455
## 60   0.16740129  0.117738080
## 61  -0.28478379  0.434970761
## 62  -0.51767121 -0.462322964
## 63  -0.33175457  0.807084732
## 64  -0.06013592  1.137497249
## 65   0.12223590  0.845662529
## 66   0.55872882  0.210552793
## 67   1.30869536  0.031813803
## 68  -0.94196750 -0.328340692
## 69  -0.71745077 -0.633035847
## 70  -0.59690241 -0.034560194
## 71  -0.64056005  1.252604113
## 72   0.49843243 -1.192274648
## 73   0.11896940  0.158937542
## 74  -0.17841434  0.683094609
## 75  -0.87971913  0.094805112
## 76   0.36166905 -0.196810766
## 77   0.51478842 -0.076858072
## 78   0.98437688  0.382258934
## 79  -1.96138276  1.178785725
## 80  -1.38116432 -0.855717590
## 81   0.85653018 -1.023440307
## 82   1.14963702  1.658407350
## 83  -0.85667363 -0.893594090
## 84   0.84570704 -0.103304221
## 85   1.11291243 -0.043354389
## 86  -0.75673967  1.378459035
```

```
## 87                       0.29034713                    0.456541048
## 88                       1.15397939                   -2.082716273
## 89                       0.27823124                    0.284791371
## 90                      -1.12941179                    0.472598770
## 91                      -1.17439737                    0.566496384
## 92                       1.56103855                    0.837709679
## 93                       0.71987398                    1.961199510
## 94                      -0.11306432                   -0.572762961
## 95                       2.47918504                    1.315612397
## 96                       1.38752075                   -1.717981714
## 97                      -1.22388169                    0.431344048
##    log_scale_apap_Chiew2010_5.6_0 log_scale_apap_glu_Chiew2010_5.6_0
## 1                      -0.73225919                        0.29875836
## 2                       0.07746059                       -0.75638815
## 3                      -0.41557105                        0.66860572
## 4                      -0.34446349                       -0.09935669
## 5                      -0.06790696                        0.17262465
## 6                      -0.36695303                        0.98236576
## 7                      -0.20316975                       -1.71612635
## 8                      -0.05272563                        0.36797886
## 9                       1.20784817                        1.53336776
## 10                     -0.07727595                        0.52309051
## 11                     -0.89161284                        1.04813343
## 12                      0.41842033                        0.17491809
## 13                     -0.63579126                       -1.47691028
## 14                      0.41960659                       -0.88379809
## 15                      0.46262316                       -1.27403311
## 16                      2.06020784                        1.15642440
## 17                     -0.39310210                        0.15255923
## 18                      0.51090442                        0.98948890
## 19                     -2.01589079                        0.02181736
## 20                      0.96256138                        0.42452793
## 21                      0.04355088                       -0.35075250
## 22                     -1.54684644                       -0.76358940
## 23                      0.13915376                        0.39629386
## 24                     -0.30274311                       -1.64712935
## 25                      0.82980777                        1.28329768
## 26                     -0.36979746                       -0.89386121
## 27                     -3.28345526                        0.05140343
## 28                     -2.85501376                        0.73358334
## 29                     -0.30913314                       -1.44870902
## 30                     -1.06250321                        2.18957853
## 31                      1.97998194                       -1.14137791
## 32                      0.07313358                        1.24518655
## 33                      1.24926210                        0.01940895
## 34                      0.94031121                       -1.31878587
## 35                      0.18809450                       -0.76413537
## 36                      0.95155721                        0.97623286
## 37                     -0.37971322                        1.07785952
## 38                      1.83962290                        0.35310598
## 39                      0.48690697                        1.04760334
## 40                      1.08264724                       -0.63634023
## 41                     -1.08303770                        0.32368494
## 42                      0.13729849                        1.14183635
```

```
## 43   0.59820226  -0.21825180
## 44  -0.21552875   0.42104601
## 45  -2.38017247  -0.70528256
## 46   0.79729800   0.52216063
## 47   1.75406693   0.10058816
## 48  -1.76776751   0.42440567
## 49  -0.37329239   0.13884988
## 50  -0.02523469  -1.52231146
## 51  -0.60831374  -0.40262163
## 52   0.62549199   1.61782083
## 53   0.64792783  -0.48676209
## 54  -1.61461373  -1.24158223
## 55   0.57169872   0.68016541
## 56   0.57971735  -1.76674252
## 57   0.79577814   0.73437332
## 58  -1.23042589  -0.45665655
## 59  -2.18636423  -1.52350881
## 60  -1.29494751   0.17448167
## 61   0.68755600  -0.57013852
## 62   0.47399068   0.16845214
## 63  -0.27175062   1.31909777
## 64  -2.83502888   1.01072579
## 65   0.30091615  -0.55699392
## 66   0.06326618  -0.26563589
## 67  -0.42786371  -1.05417209
## 68  -0.55712499  -0.18845438
## 69   2.07398604  -0.32200928
## 70  -0.67566333   0.23130121
## 71  -0.22857112   0.82128340
## 72  -0.67316982   1.63817544
## 73  -0.74302294   0.38798577
## 74  -0.60755993   0.75288786
## 75   1.40554561   1.19081077
## 76  -0.11800745   0.26682895
## 77   0.34167106  -0.17785142
## 78  -0.28390117   0.15180409
## 79   0.56824103  -0.33258076
## 80   0.14401508  -1.02840930
## 81   0.84143881   0.49209575
## 82   0.41941779   0.43869822
## 83   0.67120494   0.43988156
## 84   1.00775619  -0.26191981
## 85   0.59813734   1.03064676
## 86  -1.80976958   0.37284241
## 87   0.98058175   0.12922081
## 88   0.83829596  -1.57252628
## 89   0.40965852   3.12584627
## 90  -1.52059327  -0.32318360
## 91  -0.40134270  -0.94407261
## 92   0.35187976   1.95488779
## 93  -2.45863632  -1.15477239
## 94   2.08191902   1.02552100
## 95   0.15642796   0.76002779
## 96  -0.14623194   1.61553471
```

```
## 97                      1.83993571                          -0.87996436
##    log_scale_apap_sul_Chiew2010_5.6_0 log_srel_apap_Chiew2010_5.6_0
## 1                         -0.275135270                  0.2001657519
## 2                         -0.885373074                 -1.1763804798
## 3                         -1.457981737                  1.4459862405
## 4                          1.901383885                 -1.1825723354
## 5                          0.895795663                  0.4329236655
## 6                         -0.528503413                 -1.6273735639
## 7                          0.211567753                 -0.1872415042
## 8                          0.926717211                 -0.9794197595
## 9                         -0.228976150                  0.4907897294
## 10                        -0.685741265                 -0.3560753836
## 11                         0.671535095                  1.8548395497
## 12                         0.553761190                 -0.2597733035
## 13                        -0.255918072                  1.0349027001
## 14                        -0.903755019                  0.7725728284
## 15                        -0.752352180                 -0.0002527427
## 16                         0.548627417                  0.0651575655
## 17                         3.183402644                 -1.4597986484
## 18                         1.837753801                  0.0643406957
## 19                        -0.570371410                  0.4978717785
## 20                        -0.924887292                 -1.3975441179
## 21                         0.571100877                  0.0134458742
## 22                         1.181058764                 -0.6817150047
## 23                         0.042034846                 -1.5848831583
## 24                         2.246339114                  0.0728273584
## 25                        -0.910705800                 -1.1490717892
## 26                        -2.860762256                  1.1364683363
## 27                        -0.985156649                 -0.8879258545
## 28                         0.290272637                  0.4191348989
## 29                        -1.050275848                 -0.0621588880
## 30                        -0.647996458                  1.5018235453
## 31                         0.345956665                  0.0545707123
## 32                        -0.694371127                 -0.0262513843
## 33                        -0.390431616                  0.2779420923
## 34                        -0.148326009                 -1.1299465109
## 35                        -1.447458908                  0.8426373594
## 36                        -0.065036810                 -1.0370825285
## 37                         0.642107173                 -1.1296591965
## 38                         1.487782266                  0.4716451150
## 39                        -1.092139875                 -2.1660945745
## 40                         0.497095383                  0.7577528211
## 41                        -0.233316265                  0.4721543065
## 42                         1.493890884                  0.7850705875
## 43                        -1.389094560                 -0.3323931526
## 44                         0.451430822                  0.0474648934
## 45                        -0.661299218                 -0.3796484732
## 46                         0.009596086                  0.6502766225
## 47                        -2.503559665                  0.0090864514
## 48                        -1.909973533                 -0.7365990873
## 49                        -1.314887549                 -0.2165657146
## 50                        -1.928138981                 -0.2213237837
## 51                        -0.338937886                  0.4936612900
## 52                        -0.180868090                  1.0158480899
```

```
## 53                        0.751046335                  0.5476597422
## 54                       -0.137178004                 -0.1420098252
## 55                        0.032099257                  0.7984397880
## 56                       -0.876592880                 -0.8677726630
## 57                       -1.089984990                 -0.4884362079
## 58                       -1.100868934                  2.3663721282
## 59                        0.141905610                  1.2999998704
## 60                        0.592417566                 -1.7049539733
## 61                        0.372759798                  0.7413233832
## 62                       -1.340742120                  0.0006302381
## 63                       -1.340717564                  1.0999901356
## 64                       -0.894420796                 -0.2100487506
## 65                        1.416304707                  0.1913218370
## 66                        0.064836926                  0.0026125660
## 67                        0.491005365                 -0.4122634597
## 68                       -0.031385325                 -0.6743202909
## 69                        0.956238257                  0.2218533364
## 70                        1.111515292                 -0.1870539397
## 71                        1.493463802                  0.0494826553
## 72                       -0.507687058                 -0.4985697878
## 73                        0.521731587                 -1.2359509014
## 74                        1.036961678                  0.7261687140
## 75                       -1.165936016                 -0.8222473430
## 76                        1.650612494                 -0.8238515620
## 77                       -1.966762906                  1.1615142115
## 78                       -0.503943021                  0.6646236520
## 79                        0.168195699                  0.5139856871
## 80                       -0.565219020                 -1.4841721505
## 81                       -0.842414289                 -1.2103412373
## 82                       -2.707329383                 -0.8054780157
## 83                       -1.651332802                  0.3140811354
## 84                       -0.119035284                 -0.5195209772
## 85                        0.012859283                 -0.8141151004
## 86                       -0.283837388                  0.7515143988
## 87                       -0.426863987                  0.2449823369
## 88                        0.860154484                 -2.2747368407
## 89                        0.374224373                 -0.8095381742
## 90                       -0.668820866                 -2.2035527895
## 91                       -0.063731145                 -0.7731558528
## 92                       -1.813728878                 -0.3454808315
## 93                        0.767948833                 -1.7414582682
## 94                       -1.779098498                  0.1570948747
## 95                        0.253670245                  0.3341615668
## 96                        0.508119164                  0.6216701366
## 97                        0.293330626                 -0.3893186738
##    log_s0_apap_Chiew2010_5.6_0 log_srel_apap_glu_Chiew2010_5.6_0
## 1                -1.308380061                          0.25376786
## 2                -0.991073460                          0.47811542
## 3                -1.349576993                         -0.24564407
## 4                -0.492206840                         -0.49255895
## 5                 1.276083741                          1.45518686
## 6                -1.441961055                         -2.24275143
## 7                 2.400252540                         -1.19054321
## 8                -1.548225694                          1.66760158
```

```
## 9              0.437930535              0.58340829
## 10             1.654683024             -0.26212575
## 11            -0.002380268             -0.43585637
## 12            -0.985580674              0.81296829
## 13             0.480794564             -0.09516957
## 14            -1.288813420              2.27211738
## 15            -1.567818294              0.11548195
## 16             0.910194082             -0.04099498
## 17            -0.242411486             -2.34692331
## 18             0.249475526             -2.87088405
## 19            -0.667515974              0.22088334
## 20             1.193155860              0.31887591
## 21            -0.043120661              0.93515092
## 22            -2.298252443              0.17554713
## 23             1.909790167              0.76692594
## 24             0.516086518              0.28498872
## 25            -0.886663783              0.97577983
## 26            -0.059659246             -1.06825590
## 27             1.872528949              0.44541405
## 28            -1.438992443              1.47941300
## 29            -0.098733920              1.13465268
## 30            -0.330090050              0.71094076
## 31             0.225838297              0.21862259
## 32             0.258355347              0.48721584
## 33             0.377746246             -0.27022209
## 34            -0.978242172              1.08961792
## 35            -1.286099436              1.91567206
## 36             0.703260781              0.46223282
## 37             0.412355277             -1.16474202
## 38             0.057856965             -1.50625178
## 39             0.204290332              0.80384371
## 40             1.593689010              0.34023124
## 41             0.248481118              0.71998241
## 42             0.091698252             -0.59187301
## 43             0.774956893             -1.25193219
## 44            -0.235182369             -1.61631061
## 45             0.177170426             -0.66317982
## 46             0.663245859             -0.15070229
## 47             2.314998609             -0.65954921
## 48             0.295866960             -0.81749003
## 49            -1.620977375             -0.40125914
## 50             0.354711670              0.23096033
## 51             0.775297198             -1.58445502
## 52             0.180769160              1.02296773
## 53             1.228970298             -2.80211154
## 54            -0.087808678             -0.30319128
## 55             0.541068733             -1.69893001
## 56            -0.393362214             -1.55996884
## 57             1.171215443             -0.44757701
## 58            -0.821784319             -0.01970898
## 59             0.305690910             -0.09979971
## 60            -1.095497747             -1.72377808
## 61             1.164130850              1.05573595
## 62            -0.234214467              0.14021121
```

```
## 63                 0.098479659                        0.28379001
## 64                -1.051906960                       -0.24025308
## 65                -0.858812930                       -0.41842410
## 66                -0.391414971                        1.31540702
## 67                 0.734220932                        1.20310267
## 68                 0.440167375                        1.30155150
## 69                -0.185358574                       -0.78311410
## 70                -1.237197702                        0.15574186
## 71                 0.952262841                       -1.48415679
## 72                 1.187887846                       -0.44737975
## 73                 0.147136524                        1.54589831
## 74                -0.962118966                        0.85014832
## 75                 1.080090433                        0.11588125
## 76                -0.531404789                        0.60540272
## 77                 0.584289119                        1.95881609
## 78                 1.688754520                        0.52680935
## 79                 0.348585998                       -0.45197784
## 80                -0.683508295                       -1.60913475
## 81                 1.021776198                       -0.60988277
## 82                -1.890168859                        0.22217376
## 83                -0.057403895                        1.67043943
## 84                 1.875423785                        0.27335413
## 85                 0.972972930                       -0.22950778
## 86                -0.124181514                        0.64173965
## 87                -1.045837083                       -0.24739741
## 88                 1.618453398                        0.18392249
## 89                 1.109501737                       -0.92106550
## 90                 0.364712498                       -1.62948573
## 91                -0.629267022                        1.57135526
## 92                 0.061922044                       -1.32204187
## 93                 0.282787609                        0.95028413
## 94                -1.072622104                       -0.64472677
## 95                -0.464323640                       -2.50737327
## 96                 2.118962119                       -0.48128951
## 97                -0.099671846                       -0.85170781
##    log_s0_apap_glu_Chiew2010_5.6_0 log_srel_apap_sul_Chiew2010_5.6_0
## 1                      -0.991707410                         0.30899346
## 2                      -0.132242630                         0.20086298
## 3                      -2.450067355                         1.13602514
## 4                      -2.151377827                         0.97349583
## 5                       0.328540947                         0.09686059
## 6                      -1.171831585                        -0.32388955
## 7                       0.471801287                        -1.14218345
## 8                      -2.301573460                         0.45209239
## 9                      -1.068274942                         1.10391683
## 10                     -1.461065451                        -0.18394592
## 11                     -0.367634785                        -1.25585401
## 12                      0.769091439                         0.59592528
## 13                     -0.794010411                         0.11745745
## 14                      0.077055140                         0.65755264
## 15                      0.706162889                        -0.63644674
## 16                      0.470133114                        -0.23708367
## 17                     -0.394265649                        -0.68715195
## 18                     -1.999005679                         0.94465600
```

```
## 19   0.862572290   0.65775665
## 20  -1.862581499   1.92691861
## 21  -1.424307735   1.03109486
## 22   0.482037865   0.89863521
## 23   1.174506320   0.23205136
## 24   0.224838078   0.53472054
## 25  -1.310974750  -1.30774603
## 26   0.436715157   0.77737254
## 27  -0.638042363   0.13233756
## 28  -0.408832602  -0.43347761
## 29  -1.773736697   0.08164061
## 30   0.967798083   0.19112522
## 31  -1.982934374  -1.11112764
## 32   0.348189092   1.09864146
## 33   0.292246140   1.15874525
## 34   0.238863369  -1.03435802
## 35  -0.429331449   0.56330676
## 36   0.553842087   0.30479879
## 37  -1.688336868   0.27650405
## 38   0.003685104   0.88328764
## 39  -0.760816567  -1.31863580
## 40  -1.759330102   0.08977671
## 41  -0.288837536  -0.57013539
## 42  -1.196639868   0.24348550
## 43   0.510206452  -0.98525711
## 44   1.025676729   1.79450898
## 45   0.556545316  -0.71458710
## 46   0.354019088   0.25378921
## 47  -0.402307744  -0.14676923
## 48  -0.040308026  -0.79602214
## 49  -0.728441973  -0.21322136
## 50   0.024120353   1.37802461
## 51  -0.861701196   0.64199722
## 52   0.682256089  -0.55028127
## 53  -0.081733329   0.57692730
## 54   1.232188451   1.71220894
## 55  -1.297078849   0.26098071
## 56   1.251344347  -1.00589085
## 57  -0.629372057  -1.71939425
## 58   0.085540938  -1.92195812
## 59   0.052330319   0.37049155
## 60   0.257276619   0.07468501
## 61   1.293040722   0.60990836
## 62  -0.013335780  -0.69362289
## 63  -0.359634108  -0.75710254
## 64   0.409228334  -0.49970865
## 65   0.312926370  -0.24099977
## 66   0.128579710  -0.44319801
## 67   1.031302602   0.93517036
## 68   1.027091338  -0.22604184
## 69   1.709261092   0.44151022
## 70  -0.633200118  -0.66011812
## 71   0.404870904   1.24736543
## 72  -0.325597989   0.69429599
```

```
## 73                    -0.023546941                      0.59209265
## 74                    -0.503467834                      0.09587515
## 75                     0.110435751                     -1.42520611
## 76                     0.874039060                     -1.24732554
## 77                    -0.458177736                      1.19310587
## 78                     0.429623317                     -1.23173931
## 79                     1.530129781                     -0.58709482
## 80                     0.117725834                     -1.53204539
## 81                     0.046102501                      0.79141859
## 82                    -0.120916557                      0.64763597
## 83                     0.018689255                      0.69557780
## 84                    -0.392854028                     -0.09372652
## 85                     1.592546564                      2.54438936
## 86                     2.126157602                      0.30484874
## 87                     0.711467467                      1.58590907
## 88                     0.594857957                     -0.88280688
## 89                    -0.766681538                      2.12364652
## 90                     1.480838892                     -0.02797373
## 91                     0.732931319                     -1.07340244
## 92                     0.792576804                      0.88539959
## 93                     1.035691243                     -1.42308384
## 94                     1.256982439                      0.47372795
## 95                     0.620083727                     -0.74060054
## 96                    -1.003509300                      1.16628288
## 97                     1.512587923                     -0.47542972
##    log_s0_apap_sul_Chiew2010_5.6_0 log_scale_apap_Critchley2005_1.4_0
## 1                       -0.23179204                       0.75661973
## 2                       -0.10806720                       0.40330247
## 3                       -1.25388912                      -1.84876130
## 4                        0.59701072                       0.09984706
## 5                        0.33779519                      -1.08319140
## 6                       -0.95797870                       0.15268520
## 7                       -0.51522330                       0.56201992
## 8                        1.03100066                       0.29899082
## 9                        1.23390962                      -0.52688576
## 10                      -0.94283679                      -0.26581901
## 11                      -1.10448765                       0.29334436
## 12                      -0.87193569                      -0.72218849
## 13                      -1.56224155                      -1.04214103
## 14                       0.49842432                       2.52965517
## 15                      -0.23388576                       1.22886094
## 16                      -0.99048452                       1.09754004
## 17                      -1.87143588                      -0.84150990
## 18                      -0.45116934                      -0.83488947
## 19                       0.44107818                      -0.83754445
## 20                      -0.72181831                       0.32228690
## 21                       1.87883771                       2.30479130
## 22                       0.71073759                      -0.14517903
## 23                      -0.01348691                      -1.42923521
## 24                       0.38126333                       0.25924505
## 25                      -0.08638036                      -0.25251569
## 26                      -0.68208827                       0.80295658
## 27                      -0.04129931                      -0.90571556
## 28                      -0.89409382                      -0.43567426
```

```
## 29   0.15515877   0.75465129
## 30  -0.08668392   1.54885582
## 31   0.25516669   1.03890540
## 32   1.94753052   0.68623613
## 33   1.22804724   0.43542204
## 34  -0.31724308  -2.10774802
## 35  -1.11200733   0.22250747
## 36  -1.94405117   1.02624847
## 37   1.10811794  -0.55831789
## 38  -1.26599879  -0.88023222
## 39   0.82833966   0.56521113
## 40   1.28587705   0.13783391
## 41   0.82768677   0.45433154
## 42  -1.22369852   0.31884491
## 43  -0.40843218  -1.03544396
## 44  -0.56054935  -0.85796479
## 45  -2.12639377  -0.70896480
## 46   1.00829857   0.35336806
## 47  -0.26428486   0.41619230
## 48  -1.68052178  -1.64215009
## 49  -0.24431852   0.24871352
## 50   1.23145811  -0.93785965
## 51  -1.17899927   1.67441999
## 52  -1.10562537  -0.30269563
## 53  -1.33036081   1.36668690
## 54  -0.07545473  -1.16872284
## 55  -1.70857545   0.52929011
## 56   0.06201465   1.45927043
## 57  -1.64519812   0.84150950
## 58  -0.96287348  -1.69502471
## 59   2.00836596   1.59071307
## 60  -1.25287985  -0.07445540
## 61   0.30230365   0.63053064
## 62  -0.05827024  -0.45023638
## 63  -0.14909375   1.23494296
## 64   1.42037255   0.31402042
## 65  -0.75182633   1.65299676
## 66   0.88218400   0.13782309
## 67  -0.04170860  -0.36387544
## 68   2.16054655  -0.56337015
## 69  -0.19584723   0.22373845
## 70   0.21738215   1.40660856
## 71  -1.73232609   0.95239022
## 72  -0.86802313  -0.80570604
## 73  -0.92824296   0.04722774
## 74   1.34190599  -0.08149965
## 75  -0.58378457  -0.02737008
## 76  -0.86308150   1.21334265
## 77  -1.92429108   0.87850484
## 78  -0.38154408  -0.51923168
## 79  -0.15383536   0.82847713
## 80  -0.60610298   1.14409366
## 81   1.52366311  -0.96659017
## 82   0.83420870   1.57121214
```

```
## 83                     -0.51009911                      3.11213449
## 84                     -0.74556696                     -0.50596363
## 85                     -0.56886601                     -0.76058122
## 86                      1.63612777                      1.36377137
## 87                      2.29789869                     -0.11755259
## 88                     -1.01395490                     -0.66718019
## 89                     -0.90910008                      1.54046444
## 90                     -0.19834120                     -0.05286602
## 91                      0.48793830                     -0.75762349
## 92                      1.32985967                     -0.90286002
## 93                     -0.06425434                     -0.53655130
## 94                     -0.87383371                     -0.32943514
## 95                      1.71276896                     -0.71167285
## 96                      1.66749779                     -0.55395909
## 97                     -0.39800849                      0.51796744
##    log_scale_apap_glu_Critchley2005_1.4_0
## 1                             -1.607509252
## 2                             -0.420393690
## 3                             -0.408971373
## 4                              0.632283902
## 5                              0.539646047
## 6                              0.690980347
## 7                             -0.105357238
## 8                              0.045894694
## 9                              1.766939373
## 10                             1.730967568
## 11                            -0.119318867
## 12                            -0.700916454
## 13                             0.255753669
## 14                             0.542943918
## 15                            -0.653055469
## 16                             0.196311430
## 17                            -0.377192653
## 18                             1.089480845
## 19                            -0.706583395
## 20                             0.571140132
## 21                             0.973517821
## 22                             1.205292414
## 23                            -0.363806011
## 24                            -1.638258659
## 25                            -1.310217732
## 26                            -1.790466289
## 27                            -1.795972505
## 28                            -0.866173584
## 29                            -0.306095392
## 30                            -0.406533123
## 31                            -1.272774162
## 32                            -0.162144241
## 33                            -0.879096205
## 34                             0.286308740
## 35                             1.334770626
## 36                             0.048944897
## 37                             0.294266225
## 38                             0.700048787
```

```
## 39                          1.900483473
## 40                         -0.044259984
## 41                         -0.709833325
## 42                         -1.189239254
## 43                         -0.784705971
## 44                         -1.852351162
## 45                          0.690784005
## 46                          0.387406971
## 47                         -1.447065837
## 48                          1.031845963
## 49                          0.272487860
## 50                         -1.278585171
## 51                          0.561874806
## 52                         -0.392774105
## 53                          0.149539031
## 54                         -0.241909434
## 55                         -0.639659931
## 56                          0.213613445
## 57                         -0.641785721
## 58                          0.840286281
## 59                         -1.488887343
## 60                         -1.372982561
## 61                          0.319519387
## 62                         -1.008557225
## 63                         -1.146422396
## 64                         -1.141484047
## 65                          1.338561790
## 66                          1.175205604
## 67                          0.144141330
## 68                          0.789226431
## 69                          0.419578966
## 70                          0.157556363
## 71                         -0.383895075
## 72                         -1.161884718
## 73                          1.067878882
## 74                         -0.007370942
## 75                         -0.187304063
## 76                          1.037312380
## 77                          0.518463238
## 78                          0.148244148
## 79                          0.792454364
## 80                          0.207629790
## 81                         -0.064931599
## 82                         -0.446676325
## 83                         -0.713303305
## 84                         -0.028721069
## 85                          1.019765021
## 86                          0.617331497
## 87                         -0.920403427
## 88                          0.422487024
## 89                          1.367943045
## 90                          1.125139101
## 91                          0.865074622
## 92                          0.713548757
```

```
## 93                             1.181509978
## 94                            -0.136315707
## 95                             0.883810696
## 96                            -0.580564354
## 97                            -1.664425430
##    log_scale_apap_sul_Critchley2005_1.4_0
## 1                              1.120058550
## 2                              1.377211590
## 3                             -0.821941819
## 4                             -0.100523256
## 5                             -1.110497385
## 6                             -0.408609150
## 7                             -0.027865835
## 8                              1.915635277
## 9                             -0.786854027
## 10                             0.353292172
## 11                            -0.100982902
## 12                             0.039617472
## 13                             1.675530820
## 14                             0.079104936
## 15                            -1.608713614
## 16                            -0.309007442
## 17                            -0.202609900
## 18                            -0.532374953
## 19                             0.944140003
## 20                            -1.004158405
## 21                             0.671977206
## 22                            -0.234652911
## 23                             0.259612102
## 24                            -0.566863019
## 25                            -0.075080269
## 26                            -0.422801900
## 27                             0.686075515
## 28                            -0.868652520
## 29                            -0.718246415
## 30                             1.899146440
## 31                            -1.830568340
## 32                            -0.513190623
## 33                            -0.644410039
## 34                             0.195256335
## 35                             0.924465121
## 36                            -2.258582157
## 37                            -0.072393526
## 38                            -0.802313976
## 39                            -1.705475268
## 40                            -1.736641096
## 41                             0.091068175
## 42                            -0.783604376
## 43                            -1.029884675
## 44                            -1.088184381
## 45                             0.535125289
## 46                             1.610728546
## 47                             0.293630873
## 48                             0.305195093
```

```
## 49                            -0.920984459
## 50                             0.631909113
## 51                            -0.566236216
## 52                            -0.612417738
## 53                             0.294525060
## 54                             2.345604270
## 55                            -0.402366751
## 56                            -1.414805585
## 57                            -0.006250964
## 58                             2.209654700
## 59                             1.630798648
## 60                             1.142530024
## 61                             1.090019528
## 62                            -1.501211048
## 63                            -0.410908797
## 64                            -0.512974541
## 65                             0.859708781
## 66                            -0.437636857
## 67                             1.298216959
## 68                             0.651304581
## 69                             2.563753079
## 70                             1.229885107
## 71                             0.477941181
## 72                             0.370534755
## 73                            -0.961432110
## 74                             0.106036081
## 75                            -0.531880500
## 76                             1.709078912
## 77                            -0.230070321
## 78                             0.778880851
## 79                            -0.858625762
## 80                            -0.971670790
## 81                            -0.236846279
## 82                             0.389107755
## 83                             0.817329484
## 84                            -0.090860788
## 85                            -0.713528080
## 86                            -0.059585388
## 87                             0.509371505
## 88                            -0.450797198
## 89                             0.685309420
## 90                            -1.156564737
## 91                            -1.484269611
## 92                             1.541091147
## 93                            -0.277014956
## 94                            -0.838331239
## 95                            -1.743471619
## 96                            -1.478912444
## 97                             0.219022378
##    log_scale_apap_cys_Critchley2005_1.4_0
## 1                               0.79146268
## 2                              -0.22060324
## 3                              -0.70284940
## 4                              -0.34422962
```

```
## 5                          -0.77642415
## 6                          -1.22190397
## 7                          -0.64159905
## 8                          -0.42487849
## 9                          -0.94158573
## 10                          0.26907981
## 11                         -1.77666524
## 12                          0.82824870
## 13                         -0.53532784
## 14                         -0.54192704
## 15                         -0.34917880
## 16                         -1.98384249
## 17                         -0.40482907
## 18                         -1.43072665
## 19                          0.92132484
## 20                         -0.72235664
## 21                          0.75737032
## 22                         -1.37285797
## 23                         -0.47156974
## 24                          0.75904198
## 25                          1.32729065
## 26                         -0.79550039
## 27                          1.94575471
## 28                          0.21335422
## 29                         -2.42426692
## 30                         -0.96844266
## 31                          0.67771438
## 32                          1.09501536
## 33                         -0.84351406
## 34                         -0.55602323
## 35                         -1.11403319
## 36                          0.13574632
## 37                          0.59518300
## 38                         -0.38125868
## 39                          0.96877943
## 40                         -0.77889102
## 41                         -0.08310551
## 42                         -0.36803606
## 43                         -2.53058534
## 44                         -0.17147720
## 45                         -0.05810961
## 46                         -0.01353234
## 47                          0.14743764
## 48                         -0.71769515
## 49                         -2.01139041
## 50                          0.17645775
## 51                          0.21826471
## 52                         -0.68273001
## 53                         -0.02947630
## 54                          1.11614617
## 55                          0.90084101
## 56                         -0.47067691
## 57                         -0.26017818
## 58                         -0.75385154
```

```
## 59                              0.53684322
## 60                             -0.08623198
## 61                              0.18420859
## 62                             -0.65428547
## 63                             -0.03228487
## 64                              0.38258341
## 65                              0.45611078
## 66                             -1.71097109
## 67                             -1.32064412
## 68                             -0.43836451
## 69                             -1.26650490
## 70                             -1.00948490
## 71                              0.82884355
## 72                             -1.01406520
## 73                              0.74099178
## 74                             -0.86661508
## 75                             -1.27108052
## 76                             -0.36349411
## 77                              0.32366317
## 78                              1.06425320
## 79                              2.07678027
## 80                              0.17891151
## 81                              0.19065035
## 82                             -0.28958151
## 83                             -0.84988555
## 84                             -0.37652473
## 85                             -0.16531676
## 86                             -1.02300809
## 87                              0.07420040
## 88                              0.75680700
## 89                             -0.06388893
## 90                              2.05905432
## 91                             -0.28413825
## 92                             -1.34911219
## 93                              0.86234474
## 94                             -0.13819326
## 95                              0.76083712
## 96                             -0.94010141
## 97                             -0.09030007
##    log_srel_apap_Critchley2005_1.4_0 log_s0_apap_Critchley2005_1.4_0
## 1                         0.522948413                      2.88859953
## 2                         1.709308515                      0.27696231
## 3                        -0.416275573                      1.96685999
## 4                        -1.522463548                      0.46966809
## 5                        -1.506560397                     -0.11204321
## 6                        -0.409650024                      2.00071389
## 7                         0.373697267                     -3.01898110
## 8                         0.637839088                     -0.39064465
## 9                         0.688491456                      1.18029152
## 10                        1.069998810                     -0.23546922
## 11                        0.475834378                      1.27280418
## 12                       -0.647859319                      1.37197842
## 13                        0.886269230                      0.42368938
## 14                        0.822445195                      0.82930257
```

```
## 15  -0.334879054   1.85689885
## 16   1.648138817  -0.34050107
## 17  -1.185609800  -0.26088559
## 18   0.895524316   1.48123503
## 19  -0.432085757   1.07752924
## 20  -0.033329261   0.80296678
## 21   0.292590739  -1.10363116
## 22  -0.591812598  -1.28466179
## 23   3.115462247  -0.10834243
## 24  -1.387796638  -0.96633710
## 25   0.246958923   1.66072585
## 26   1.211919843   1.01567726
## 27   1.248605241  -0.34273497
## 28   0.073346775  -0.09466370
## 29   0.794752935   0.32995065
## 30  -0.759364282   0.72640432
## 31   0.738904940  -0.67646794
## 32  -1.016199322  -1.07384152
## 33  -1.357758328  -0.47473579
## 34   1.280649572   0.76818292
## 35  -0.020725631   1.12105632
## 36  -0.737954466  -0.28408470
## 37  -0.849725886   1.63012222
## 38  -1.112684049  -1.05100636
## 39   0.006865968  -1.11029845
## 40   3.167950423  -0.18298315
## 41   0.139244723  -1.08921219
## 42  -2.340557044  -0.14434323
## 43  -1.420881541   0.22612992
## 44   0.511333328   1.50660852
## 45  -0.655129032   1.16033784
## 46   0.883765774  -0.35637900
## 47   2.210026549  -1.38787404
## 48   0.563547016  -2.35702795
## 49   1.346947366  -1.32143835
## 50  -1.105151514  -1.58840586
## 51  -1.508563500   0.87747928
## 52  -1.721579167   0.61886469
## 53  -1.608464187  -0.22117268
## 54  -0.830722334   0.06375129
## 55  -0.902344057   0.21846096
## 56  -0.427823792  -1.35191747
## 57  -0.563515861  -1.05133646
## 58  -1.697004569   0.62860501
## 59  -0.875449088   1.28940805
## 60  -0.855904675   1.54780294
## 61  -0.763203521   0.25091597
## 62  -0.052329573   0.79779734
## 63  -0.950696955   0.75952755
## 64  -0.778446838   1.54523266
## 65   0.673127469   0.04598376
## 66  -0.182503608   0.30087649
## 67   0.294533091   0.48435488
## 68   0.432095784  -0.71543671
```

```
## 69                       -1.980531042                       0.15144016
## 70                        0.271892087                       1.40617126
## 71                        0.275605975                       0.70697007
## 72                        0.332527813                       0.14637877
## 73                       -0.793881077                       0.75856793
## 74                       -1.067261378                       0.07077657
## 75                        0.198929989                      -1.07284960
## 76                        0.028179767                       1.02483689
## 77                       -0.064174034                      -0.13540047
## 78                        0.188828235                      -0.42388787
## 79                        0.915589329                       0.69287707
## 80                        0.664737188                      -0.47595105
## 81                        0.721950110                      -0.16721335
## 82                        1.340725295                      -0.34549703
## 83                        0.763121588                       1.77044185
## 84                        0.683289321                       1.61619631
## 85                       -0.795670370                       1.77942626
## 86                       -0.038983966                      -1.55480917
## 87                        0.561562104                      -0.41485080
## 88                       -1.263246457                       0.93269267
## 89                       -2.016598531                       0.65773121
## 90                       -1.095116099                       0.52342616
## 91                        1.318711056                       1.94821674
## 92                        0.549814867                       0.77797115
## 93                       -0.409660471                       1.45569809
## 94                       -1.831373456                       1.02122792
## 95                       -1.468781586                       0.50998716
## 96                        0.619678851                       1.67517090
## 97                       -0.365230107                       0.01930949
##    log_srel_apap_glu_Critchley2005_1.4_0
## 1                            -0.69587318
## 2                             1.61130133
## 3                             0.88165708
## 4                             0.61906464
## 5                             0.97729180
## 6                            -1.20273995
## 7                            -2.41834302
## 8                            -0.28830913
## 9                            -1.26653212
## 10                           -0.11402867
## 11                            0.99675418
## 12                            0.12998510
## 13                            1.37999150
## 14                            1.00477010
## 15                           -0.12350666
## 16                            1.11454338
## 17                           -1.78694212
## 18                           -0.37844413
## 19                           -0.33901257
## 20                            0.59253664
## 21                           -0.65736110
## 22                           -0.06988253
## 23                           -0.75195180
## 24                           -0.13965216
```

```
## 25                        -0.46495763
## 26                         0.74995309
## 27                        -0.04532367
## 28                         0.35338981
## 29                        -0.03091481
## 30                        -1.24094698
## 31                        -2.14939871
## 32                        -2.42097139
## 33                         0.53463667
## 34                         0.95342123
## 35                         1.38121522
## 36                        -1.75127897
## 37                        -0.62347127
## 38                         0.09687853
## 39                         0.66019375
## 40                        -1.32272214
## 41                         0.14350875
## 42                        -0.29925215
## 43                        -1.71415812
## 44                        -0.25423250
## 45                        -0.51348836
## 46                         1.31988241
## 47                         0.86175701
## 48                         0.96664132
## 49                         1.93159222
## 50                        -1.31573278
## 51                        -0.09880012
## 52                        -0.23805165
## 53                         0.53208697
## 54                        -1.58110558
## 55                         0.39764877
## 56                         1.09901611
## 57                        -2.14201112
## 58                         1.71648560
## 59                        -0.23744592
## 60                         0.02831160
## 61                         0.59007258
## 62                         0.82693102
## 63                         0.32086134
## 64                         0.92831063
## 65                         0.54021115
## 66                         0.03869330
## 67                        -0.93207619
## 68                         0.90139416
## 69                        -0.56017757
## 70                        -0.32091159
## 71                         0.58924319
## 72                        -0.71951717
## 73                        -0.38097575
## 74                         0.56602396
## 75                         0.46801350
## 76                        -0.82837612
## 77                         0.28938276
## 78                        -0.53025814
```

```
## 79                            -0.49208205
## 80                            -0.11066750
## 81                             1.71272269
## 82                            -1.23431655
## 83                            -0.81058550
## 84                            -0.84310406
## 85                             0.52962634
## 86                             0.36881243
## 87                            -1.08540847
## 88                            -1.98657321
## 89                            -0.21875264
## 90                             1.27873387
## 91                            -0.64401746
## 92                             0.08334345
## 93                             0.48578996
## 94                            -1.96676937
## 95                             0.72280675
## 96                            -0.96402657
## 97                             0.65886752
##    log_s0_apap_glu_Critchley2005_1.4_0
## 1                           -1.462525446
## 2                           -0.876828265
## 3                           -2.072184801
## 4                           -0.374247260
## 5                           -0.093214581
## 6                            0.005710159
## 7                            0.203633372
## 8                           -0.587695031
## 9                           -0.482651948
## 10                          -1.198278965
## 11                          -1.476583871
## 12                           1.131188577
## 13                           0.254145603
## 14                          -0.017581426
## 15                          -1.436491861
## 16                          -0.032157311
## 17                          -1.651176305
## 18                           0.654813925
## 19                          -0.568654808
## 20                           1.786732925
## 21                           0.618692490
## 22                          -0.807254318
## 23                           2.308840315
## 24                          -0.776324293
## 25                           0.018062597
## 26                          -1.801950915
## 27                          -0.094051438
## 28                           0.517297326
## 29                           0.513327656
## 30                          -0.373881071
## 31                           0.432910444
## 32                          -0.608175129
## 33                           1.266839143
## 34                           1.331283649
```

```
## 35                      -0.843996412
## 36                      -1.078258500
## 37                       0.449456048
## 38                      -0.189913630
## 39                      -0.627673185
## 40                      -0.457637203
## 41                      -1.666184015
## 42                       0.033905438
## 43                       0.105008608
## 44                       0.132224130
## 45                      -0.154695513
## 46                      -0.254663314
## 47                      -0.121504499
## 48                       0.741676338
## 49                      -0.768415655
## 50                      -0.447065765
## 51                      -1.689291863
## 52                       0.107480303
## 53                       0.737623928
## 54                      -0.577696236
## 55                       1.013296725
## 56                      -1.413088093
## 57                       1.971574481
## 58                      -0.609504186
## 59                      -1.206315202
## 60                      -0.177286206
## 61                       0.430442584
## 62                       0.696931483
## 63                      -0.348796523
## 64                      -1.510967199
## 65                       1.070973524
## 66                      -0.368865407
## 67                       0.646514031
## 68                       0.521432322
## 69                       0.292984717
## 70                       0.345335049
## 71                       0.820658601
## 72                       0.368647983
## 73                       0.531834672
## 74                       0.570214855
## 75                       0.568346420
## 76                      -0.040774982
## 77                       0.447159734
## 78                      -0.335353238
## 79                      -0.152310201
## 80                       1.501879988
## 81                      -0.390866492
## 82                      -0.191549976
## 83                       0.959600284
## 84                       1.366580453
## 85                       0.425003748
## 86                       0.122860847
## 87                       0.736324964
## 88                       1.029817334
```

```
## 89                          -0.400687487
## 90                           1.783943881
## 91                           1.261178661
## 92                           1.457712238
## 93                           0.521600780
## 94                           1.651032017
## 95                           1.351755483
## 96                           1.647901913
## 97                          -0.015294223
##    log_srel_apap_sul_Critchley2005_1.4_0
## 1                              0.09474047
## 2                              1.05831194
## 3                              1.37006018
## 4                              0.49068959
## 5                             -0.15389290
## 6                             -0.21423115
## 7                              0.55038587
## 8                             -0.74129708
## 9                              0.33825561
## 10                             0.87837646
## 11                             0.13506246
## 12                             0.62160710
## 13                            -0.54562079
## 14                             0.84642076
## 15                            -0.68258421
## 16                             0.02805551
## 17                            -0.49490726
## 18                             1.17126546
## 19                             1.48280480
## 20                            -1.24575867
## 21                             0.47725684
## 22                             0.69784433
## 23                            -0.18881995
## 24                             0.90176345
## 25                            -0.99761734
## 26                             0.33181229
## 27                             0.77238656
## 28                             0.91097859
## 29                            -0.46257951
## 30                             0.34037742
## 31                             0.53247499
## 32                             0.39674425
## 33                             0.05568052
## 34                             1.49697540
## 35                             1.08210815
## 36                             0.09698620
## 37                            -1.18339916
## 38                            -1.94236715
## 39                            -0.02092297
## 40                             0.48453199
## 41                             0.30263428
## 42                             0.80018452
## 43                             0.42133096
## 44                             0.20675044
```

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## 45                              0.27353044
## 46                              1.00653235
## 47                              0.39986082
## 48                              0.18297528
## 49                              1.81798700
## 50                              1.54341380
## 51                              0.33171418
## 52                              1.56868363
## 53                             -0.15146383
## 54                              1.66184484
## 55                             -2.12329681
## 56                             -0.34341752
## 57                             -0.34624355
## 58                              1.06565942
## 59                              1.23526181
## 60                             -2.66910022
## 61                              1.87876169
## 62                              0.45525243
## 63                             -0.40217872
## 64                             -0.72361765
## 65                             -0.95499785
## 66                              0.70487417
## 67                              0.96968337
## 68                              1.86661156
## 69                              0.63051665
## 70                              0.90836842
## 71                              0.39768020
## 72                             -1.58815531
## 73                             -0.40613033
## 74                             -0.04934150
## 75                              0.03857000
## 76                              2.04675497
## 77                              0.32973013
## 78                              1.80201354
## 79                              0.14554655
## 80                              0.02922803
## 81                             -0.39091938
## 82                             -0.33738328
## 83                             -0.78277834
## 84                             -0.71665847
## 85                              0.12960303
## 86                             -0.57716799
## 87                             -1.43827595
## 88                             -1.28160145
## 89                              1.82214582
## 90                              1.04251985
## 91                              1.40237811
## 92                             -0.78555842
## 93                             -2.99069617
## 94                              1.22960940
## 95                              2.18407863
## 96                             -0.20489570
## 97                             -0.82769822
##    log_s0_apap_sul_Critchley2005_1.4_0
```

```
## 1                          -1.543602178
## 2                          -1.978723870
## 3                           1.161174618
## 4                          -0.572233626
## 5                          -0.760490075
## 6                          -0.526363381
## 7                          -0.840952402
## 8                          -0.783071595
## 9                          -0.400919967
## 10                          0.993673845
## 11                          0.290194572
## 12                         -0.260475663
## 13                         -0.216888969
## 14                         -1.350264314
## 15                          0.350708865
## 16                         -1.271311257
## 17                         -0.462667526
## 18                         -1.244851775
## 19                         -0.406609375
## 20                         -1.095501272
## 21                         -1.240433755
## 22                          0.574207354
## 23                         -2.150320749
## 24                         -0.419445838
## 25                         -1.458507474
## 26                         -1.333313925
## 27                         -0.441465795
## 28                          0.724510949
## 29                          0.376139004
## 30                         -0.794570587
## 31                          0.484721297
## 32                          1.655029376
## 33                         -0.512885016
## 34                         -0.441724665
## 35                         -0.142839264
## 36                         -0.001710237
## 37                         -0.312734271
## 38                          0.423782635
## 39                         -1.074867816
## 40                          0.577637944
## 41                         -0.569221337
## 42                         -1.399965432
## 43                         -0.430936395
## 44                          0.066471049
## 45                          1.111102806
## 46                          0.102489861
## 47                          1.288461789
## 48                         -0.386112222
## 49                          1.161481892
## 50                          0.147139038
## 51                         -0.164859995
## 52                          0.557489288
## 53                          0.926711319
## 54                          0.640672535
```

```
## 55                          -0.177074584
## 56                           0.462401888
## 57                           1.680043476
## 58                          -2.029537482
## 59                           0.320328605
## 60                          -0.355090642
## 61                           0.426335369
## 62                          -1.329143852
## 63                          -0.639902172
## 64                           0.144577246
## 65                          -0.470748625
## 66                           2.172048181
## 67                          -0.288530342
## 68                          -0.466616055
## 69                          -0.712007661
## 70                          -0.360303923
## 71                           0.170078361
## 72                           0.885668022
## 73                           1.110290403
## 74                           0.796832382
## 75                           0.571369293
## 76                          -0.092468041
## 77                           1.147667836
## 78                           1.051726419
## 79                          -0.604223998
## 80                           0.541915388
## 81                           0.438439285
## 82                           0.514215768
## 83                          -0.584285837
## 84                           0.863575825
## 85                          -1.133269730
## 86                           0.134493444
## 87                          -0.317973156
## 88                           1.535514418
## 89                          -0.396495604
## 90                          -0.412487030
## 91                           0.603211324
## 92                           0.635847623
## 93                           1.044514010
## 94                           1.223725587
## 95                          -0.010817924
## 96                           0.989658999
## 97                           1.130807651
##    log_srel_apap_cys_Critchley2005_1.4_0
## 1                             0.63466916
## 2                            -0.97888417
## 3                            -1.78315231
## 4                             0.61565799
## 5                            -1.31464357
## 6                             0.45757371
## 7                             0.44698562
## 8                             0.55815505
## 9                            -1.62691250
## 10                           -1.31054042
```

```
## 11                          0.32769121
## 12                         -0.01689208
## 13                         -0.69261160
## 14                         -0.41588489
## 15                         -0.70654568
## 16                         -1.46296032
## 17                          0.02930375
## 18                         -0.84523401
## 19                         -0.75981514
## 20                         -0.70129207
## 21                          0.57901767
## 22                          1.39885662
## 23                          0.53560135
## 24                          0.02953265
## 25                          0.69777751
## 26                          0.58872179
## 27                          1.33767804
## 28                         -0.64446047
## 29                         -0.56224457
## 30                         -0.32451698
## 31                          0.99340432
## 32                          1.71205890
## 33                         -0.04182765
## 34                         -0.14412954
## 35                          1.04687845
## 36                         -1.84967605
## 37                         -0.44726342
## 38                          1.79152696
## 39                          0.10948796
## 40                         -0.07330467
## 41                          0.21511592
## 42                          0.42489410
## 43                         -0.90223930
## 44                         -1.55341633
## 45                         -0.85344610
## 46                          0.59794549
## 47                          0.62500560
## 48                          0.51852817
## 49                          0.46072081
## 50                          1.01916252
## 51                          0.42383732
## 52                         -0.01047933
## 53                         -0.16063034
## 54                         -0.38072143
## 55                         -0.61886321
## 56                          0.36569660
## 57                         -0.30075551
## 58                          0.18297933
## 59                          0.47901528
## 60                         -0.63021022
## 61                          0.43167360
## 62                          1.86039622
## 63                          0.26699767
## 64                          0.50307632
```

```
## 65                            -0.05096364
## 66                            -0.48229115
## 67                             1.09143442
## 68                             1.18793321
## 69                            -0.87445031
## 70                            -0.38984191
## 71                            -1.00224925
## 72                             0.35179849
## 73                             0.18092926
## 74                             0.79800951
## 75                             0.75193950
## 76                             0.76081609
## 77                             1.23125149
## 78                             0.91930385
## 79                            -0.19157743
## 80                            -0.21615894
## 81                             0.20191798
## 82                            -0.87529768
## 83                            -0.75762596
## 84                             1.67278275
## 85                             1.79448457
## 86                             1.16944906
## 87                             0.33210361
## 88                            -0.65226311
## 89                             0.43840506
## 90                            -0.17667916
## 91                            -1.27695169
## 92                             0.01831596
## 93                             1.40964593
## 94                            -1.46803660
## 95                            -0.57483183
## 96                             1.03047916
## 97                            -0.75755840
##    log_s0_apap_cys_Critchley2005_1.4_0 log_scale_apap_Rawlins1977_0_1
## 1                            0.497725958                   0.0216218888
## 2                           -0.619817108                   0.0218450111
## 3                           -1.837539315                   0.0086990868
## 4                           -1.224160898                   0.0221330866
## 5                           -1.109198103                   0.0260124292
## 6                           -0.111073301                   0.0242574707
## 7                            1.103310902                  -0.0005920975
## 8                            0.667660306                   0.0043161215
## 9                           -2.501459873                  -0.0141626512
## 10                          -0.534340984                   0.0171955223
## 11                           0.341496601                   0.0259726760
## 12                           0.641478927                   0.0158987920
## 13                          -2.197105684                   0.0218602353
## 14                           0.210175359                   0.0226623899
## 15                          -0.467572320                   0.0266154962
## 16                           0.727235132                   0.0223879827
## 17                           1.738779470                   0.0211569562
## 18                           1.456056159                   0.0060088241
## 19                          -0.101767872                   0.0263255773
## 20                          -0.370001905                   0.0205963285
```

```
## 21          -0.002162368          0.0278215485
## 22          -0.045840132          0.0212866784
## 23          -1.437202719          0.0218172638
## 24           0.446798439          0.0217893811
## 25          -1.327050907         -0.0142176669
## 26          -0.401076184          0.0218393104
## 27           0.331199828          0.0207141015
## 28          -1.659480238          0.0154765636
## 29           1.564288931          0.0219443910
## 30          -0.831451844         -0.0094564365
## 31          -1.139204984          0.0276652350
## 32          -1.436278568         -0.0151967148
## 33          -0.643148140          0.0222690940
## 34           1.483864238          0.0255276526
## 35          -0.520215042          0.0263574047
## 36           0.362679640          0.0216178516
## 37          -0.559733413          0.0005603733
## 38           0.063877440          0.0278871945
## 39          -1.356970608         -0.0082093862
## 40          -0.504684405          0.0221458322
## 41           1.815153486          0.0217425867
## 42           1.992543669          0.0125458858
## 43          -0.579926569          0.0219134369
## 44          -1.444477603          0.0219637621
## 45          -1.292140206          0.0264071838
## 46           0.014550524          0.0218331985
## 47          -2.487278773          0.0221483712
## 48           0.239396953          0.0214200020
## 49           0.930665972          0.0260580869
## 50          -0.296994072          0.0218494261
## 51           2.348042335          0.0263731910
## 52          -1.356776419          0.0053438579
## 53           0.776487663          0.0262805628
## 54           0.288991936          0.0218922992
## 55           3.192067382          0.0216167790
## 56          -0.392465922          0.0222709919
## 57           0.009049857          0.0262279886
## 58          -0.312705417          0.0218426119
## 59          -0.904762147          0.0219090071
## 60           1.521631748          0.0218479759
## 61          -0.211957183          0.0264840885
## 62           0.979619175          0.0219201806
## 63           1.535636682          0.0074341138
## 64          -1.043782885          0.0217146056
## 65           0.453933502          0.0220932408
## 66          -0.431108155          0.0103319118
## 67           0.201981809          0.0273510892
## 68          -0.804155485          0.0259513657
## 69           0.802118792          0.0287782681
## 70           0.496661128          0.0217385229
## 71          -0.717801884          0.0219432402
## 72          -0.017355119          0.0062122423
## 73          -0.934619069          0.0215860719
## 74           0.350102276          0.0211875950
```

```
## 75                          0.185369172                  0.0215485059
## 76                          0.100044745                  0.0223273074
## 77                          1.333060275                  0.0215349899
## 78                         -0.331722676                  0.0219407925
## 79                         -0.673909293                  0.0219424682
## 80                          0.359899483                  0.0219147106
## 81                          0.680856972                  0.0217671318
## 82                          2.101694396                  0.0219234092
## 83                          1.159663783                  0.0265855126
## 84                          0.215178433                  0.0263513571
## 85                          1.259715274                  0.0217144698
## 86                         -1.622323409                  0.0222080104
## 87                         -0.478987622                  0.0271845812
## 88                          2.086970818                  0.0218577754
## 89                          1.953712219                 -0.0224458309
## 90                          0.057782689                  0.0178750785
## 91                          0.258842368                  0.0220983237
## 92                         -0.558736256                  0.0216580833
## 93                          1.228352999                  0.0036135389
## 94                         -0.265337713                  0.0317937992
## 95                          1.291522385                  0.0218832155
## 96                          0.721429290                 -0.0118225164
## 97                          0.484008716                  0.0274636855
##    log_srel_apap_Rawlins1977_0_1 log_s0_apap_Rawlins1977_0_1
## 1                       2.454559                   -8.977730
## 2                       2.454535                   -8.977814
## 3                       2.483257                   -8.996088
## 4                       2.453265                   -8.974551
## 5                       2.437694                   -8.941497
## 6                       2.442176                   -8.947284
## 7                       2.493275                   -8.964653
## 8                       2.485495                   -8.969410
## 9                       2.527556                   -9.000267
## 10                      2.465515                   -8.985132
## 11                      2.437852                   -8.941467
## 12                      2.466290                   -8.980374
## 13                      2.454122                   -8.977741
## 14                      2.449009                   -8.970499
## 15                      2.434839                   -8.935748
## 16                      2.452215                   -8.971670
## 17                      2.456473                   -8.977701
## 18                      2.489469                   -8.998206
## 19                      2.436498                   -8.939115
## 20                      2.458204                   -8.982238
## 21                      2.430114                   -8.927483
## 22                      2.450881                   -8.957947
## 23                      2.441552                   -8.932818
## 24                      2.454749                   -8.976566
## 25                      2.530583                   -9.005380
## 26                      2.454971                   -8.978381
## 27                      2.452268                   -8.964331
## 28                      2.469361                   -8.987036
## 29                      2.454637                   -8.977026
## 30                      2.519190                   -8.997410
```

```
## 31                2.431588                -8.929844
## 32                2.528269                -8.994749
## 33                2.453711                -8.975322
## 34                2.439859                -8.946387
## 35                2.436490                -8.939003
## 36                2.455769                -8.977156
## 37                2.499748                -8.996584
## 38                2.430126                -8.926006
## 39                2.518187                -9.003691
## 40                2.453743                -8.974839
## 41                2.455279                -8.978064
## 42                2.475766                -8.991003
## 43                2.455411                -8.977674
## 44                2.452458                -8.973638
## 45                2.435630                -8.937089
## 46                2.456595                -8.980960
## 47                2.453300                -8.975109
## 48                2.455044                -8.977823
## 49                2.438436                -8.945176
## 50                2.454298                -8.976893
## 51                2.436666                -8.939296
## 52                2.490148                -8.993408
## 53                2.436354                -8.938028
## 54                2.454365                -8.977027
## 55                2.454860                -8.979385
## 56                2.453043                -8.973662
## 57                2.437066                -8.940337
## 58                2.453969                -8.975807
## 59                2.454066                -8.977338
## 60                2.454440                -8.977411
## 61                2.432734                -8.927925
## 62                2.454321                -8.972108
## 63                2.485979                -8.993410
## 64                2.454716                -8.977536
## 65                2.453570                -8.975734
## 66                2.473428                -8.967355
## 67                2.430804                -8.926981
## 68                2.437199                -8.939218
## 69                2.427093                -8.920197
## 70                2.454428                -8.976703
## 71                2.454647                -8.978755
## 72                2.482706                -8.971576
## 73                2.455744                -8.981424
## 74                2.455804                -8.979219
## 75                2.456343                -8.978674
## 76                2.453421                -8.972737
## 77                2.445965                -8.943955
## 78                2.453619                -8.974963
## 79                2.454131                -8.976959
## 80                2.454180                -8.976915
## 81                2.454171                -8.976715
## 82                2.448264                -8.959147
## 83                2.434810                -8.935671
## 84                2.436323                -8.938827
```

```
## 85                      2.454858                   -8.977986
## 86                      2.452962                   -8.974400
## 87                      2.433554                   -8.931122
## 88                      2.454745                   -8.976424
## 89                      2.546981                   -9.015551
## 90                      2.462774                   -8.981036
## 91                      2.453468                   -8.975162
## 92                      2.455231                   -8.979135
## 93                      2.493944                   -8.993341
## 94                      2.413198                   -8.893687
## 95                      2.454240                   -8.977016
## 96                      2.525584                   -9.007234
## 97                      2.431843                   -8.928370
##    log_scale_apap_Rawlins1977_1_0 log_srel_apap_Rawlins1977_1_0
## 1                       0.16782732                     2.582696
## 2                       0.16921289                     2.581302
## 3                       0.13889913                     2.595842
## 4                       0.16922141                     2.580949
## 5                       0.23075452                     2.589881
## 6                       0.22038424                     2.591367
## 7                       0.11307916                     2.607424
## 8                       0.13046663                     2.608944
## 9                       0.09005204                     2.622542
## 10                      0.15828380                     2.587212
## 11                      0.23159759                     2.590261
## 12                      0.15644895                     2.587605
## 13                      0.16935136                     2.580648
## 14                      0.17064171                     2.578947
## 15                      0.23320559                     2.588998
## 16                      0.17325219                     2.578989
## 17                      0.16753447                     2.581330
## 18                      0.13359424                     2.599844
## 19                      0.23185999                     2.589611
## 20                      0.16454643                     2.583637
## 21                      0.23545651                     2.588052
## 22                      0.16113660                     2.577828
## 23                      0.17075572                     2.577511
## 24                      0.16980240                     2.579243
## 25                      0.09055341                     2.622353
## 26                      0.16956383                     2.581297
## 27                      0.16911214                     2.586117
## 28                      0.15430368                     2.588266
## 29                      0.16938203                     2.581291
## 30                      0.10026238                     2.608921
## 31                      0.23511867                     2.588377
## 32                      0.08788647                     2.625006
## 33                      0.17146560                     2.577108
## 34                      0.21017559                     2.588791
## 35                      0.23232168                     2.589617
## 36                      0.16701493                     2.579870
## 37                      0.12221347                     2.604032
## 38                      0.23542524                     2.587850
## 39                      0.10377101                     2.616330
## 40                      0.16973473                     2.580662
```

```
## 41                0.16847171                2.581096
## 42                0.14783482                2.592766
## 43                0.16999852                2.581342
## 44                0.16691468                2.580951
## 45                0.23289835                2.589739
## 46                0.16996804                2.580719
## 47                0.16894679                2.580851
## 48                0.16808085                2.582801
## 49                0.23216860                2.590065
## 50                0.16925318                2.580459
## 51                0.23271705                2.590143
## 52                0.13312393                2.600031
## 53                0.22898644                2.588406
## 54                0.16951129                2.580847
## 55                0.16782624                2.581964
## 56                0.16853671                2.580937
## 57                0.23229176                2.589985
## 58                0.16946424                2.580514
## 59                0.16938772                2.581304
## 60                0.16925256                2.580882
## 61                0.23292041                2.589329
## 62                0.16754087                2.576978
## 63                0.13733201                2.597904
## 64                0.16857172                2.580446
## 65                0.16953719                2.581038
## 66                0.14226659                2.583450
## 67                0.22834638                2.586812
## 68                0.22350100                2.587730
## 69                0.23712094                2.586980
## 70                0.16822388                2.579886
## 71                0.16996208                2.580919
## 72                0.14448939                2.610939
## 73                0.16770238                2.581372
## 74                0.16613006                2.581080
## 75                0.16756799                2.581574
## 76                0.17386856                2.581786
## 77                0.16678433                2.574519
## 78                0.16754025                2.582024
## 79                0.17001714                2.580969
## 80                0.16879202                2.581083
## 81                0.16935264                2.580173
## 82                0.17337761                2.580002
## 83                0.23320212                2.590021
## 84                0.23188880                2.589564
## 85                0.16877776                2.580674
## 86                0.16782912                2.581836
## 87                0.23430405                2.589159
## 88                0.16914698                2.580286
## 89                0.07266373                2.632989
## 90                0.16042122                2.581592
## 91                0.17047225                2.580485
## 92                0.16829825                2.581522
## 93                0.12936722                2.600253
## 94                0.24273910                2.583837
```

```
## 95                     0.16990093                      2.581246
## 96                     0.09628072                      2.619491
## 97                     0.23482526                      2.588503
##    log_s0_apap_Rawlins1977_1_0 log_scale_apap_Rawlins1977_2_0
## 1                    -14.66563                       0.4137086
## 2                    -16.05141                       0.4157914
## 3                    -15.53460                       0.3500338
## 4                    -15.71205                       0.4157741
## 5                    -16.02509                       0.4775457
## 6                    -15.33039                       0.4570333
## 7                    -13.51082                       0.2853663
## 8                    -13.25004                       0.3046008
## 9                    -14.21216                       0.2346549
## 10                   -15.58290                       0.3945947
## 11                   -17.30717                       0.4787135
## 12                   -15.09383                       0.3881685
## 13                   -15.67752                       0.4157907
## 14                   -14.71660                       0.4171021
## 15                   -18.00419                       0.4806140
## 16                   -14.57677                       0.4195779
## 17                   -14.83662                       0.4120757
## 18                   -16.24514                       0.3399182
## 19                   -16.31517                       0.4789166
## 20                   -16.35044                       0.4086098
## 21                   -18.81025                       0.4830196
## 22                   -13.38427                       0.4039720
## 23                   -14.07814                       0.4161627
## 24                   -14.37996                       0.4155987
## 25                   -15.73659                       0.2361933
## 26                   -16.38386                       0.4162206
## 27                   -14.22472                       0.4121055
## 28                   -15.14448                       0.3863912
## 29                   -15.93106                       0.4159597
## 30                   -13.07100                       0.2580564
## 31                   -17.66994                       0.4826423
## 32                   -14.34396                       0.2273847
## 33                   -13.93857                       0.4171997
## 34                   -16.46453                       0.4571142
## 35                   -16.60123                       0.4795406
## 36                   -14.19932                       0.4121472
## 37                   -14.22388                       0.3133825
## 38                   -16.45282                       0.4829313
## 39                   -15.60040                       0.2702146
## 40                   -15.35626                       0.4162106
## 41                   -15.49333                       0.4148576
## 42                   -16.38986                       0.3732218
## 43                   -16.29091                       0.4166568
## 44                   -15.01671                       0.4130945
## 45                   -19.29026                       0.4803023
## 46                   -15.60635                       0.4164704
## 47                   -15.46695                       0.4154332
## 48                   -15.11335                       0.4132930
## 49                   -18.96679                       0.4794921
## 50                   -15.00564                       0.4155258
```

```
## 51                   -18.33062                    0.4801213
## 52                   -15.31169                    0.3386793
## 53                   -14.68067                    0.4750125
## 54                   -15.48190                    0.4159739
## 55                   -15.90048                    0.4141847
## 56                   -15.16604                    0.4149225
## 57                   -17.53956                    0.4795646
## 58                   -15.31662                    0.4158227
## 59                   -16.94411                    0.4160887
## 60                   -15.39750                    0.4156720
## 61                   -17.63022                    0.4803005
## 62                   -13.57523                    0.4118489
## 63                   -15.66901                    0.3489778
## 64                   -14.78427                    0.4146538
## 65                   -16.03427                    0.4161555
## 66                   -12.60790                    0.3522350
## 67                   -14.38435                    0.4745735
## 68                   -14.16782                    0.4683454
## 69                   -16.49949                    0.4847344
## 70                   -14.42889                    0.4140736
## 71                   -16.18074                    0.4165603
## 72                   -14.39728                    0.3316923
## 73                   -15.81425                    0.4140544
## 74                   -14.59544                    0.4112069
## 75                   -14.69687                    0.4132512
## 76                   -20.85497                    0.4205491
## 77                   -12.85422                    0.4082155
## 78                   -16.51605                    0.4141971
## 79                   -15.80257                    0.4166188
## 80                   -15.56262                    0.4152530
## 81                   -14.78158                    0.4153893
## 82                   -15.56062                    0.4201834
## 83                   -19.18350                    0.4806277
## 84                   -16.29508                    0.4789443
## 85                   -14.99048                    0.4149867
## 86                   -18.46578                    0.4142114
## 87                   -18.58913                    0.4817776
## 88                   -14.93917                    0.4153302
## 89                   -15.90717                    0.1916635
## 90                   -15.82598                    0.3956943
## 91                   -15.40826                    0.4169774
## 92                   -15.86351                    0.4147330
## 93                   -14.42044                    0.3293995
## 94                   -15.72322                    0.4906757
## 95                   -16.35213                    0.4165781
## 96                   -15.36388                    0.2510329
## 97                   -18.58908                    0.4823568
##    log_srel_apap_Rawlins1977_2_0 log_s0_apap_Rawlins1977_2_0
## 1                       2.341414                   -15.33500
## 2                       2.341451                   -16.63546
## 3                       2.347062                   -16.04883
## 4                       2.341416                   -16.30266
## 5                       2.346485                   -16.51624
## 6                       2.347016                   -15.82922
```

```
## 7                2.352994                -14.54699
## 8                2.354453                -14.66307
## 9                2.359070                -15.38712
## 10               2.343733                -16.12531
## 11               2.346533                -17.75980
## 12               2.343672                -15.71837
## 13               2.341545                -16.31812
## 14               2.342435                -15.51425
## 15               2.346191                -18.48386
## 16               2.340608                -15.23927
## 17               2.341836                -15.33723
## 18               2.347867                -16.86310
## 19               2.346353                -16.79007
## 20               2.342501                -17.24545
## 21               2.346735                -19.44322
## 22               2.343685                -14.51235
## 23               2.348891                -14.89598
## 24               2.340522                -14.94247
## 25               2.356468                -16.24648
## 26               2.341251                -16.91750
## 27               2.343567                -15.32927
## 28               2.344305                -15.74159
## 29               2.341357                -16.48006
## 30               2.353132                -14.10389
## 31               2.345767                -18.28221
## 32               2.361091                -15.16419
## 33               2.340770                -14.60239
## 34               2.345464                -17.01241
## 35               2.346298                -17.08485
## 36               2.341775                -14.91900
## 37               2.350637                -15.01231
## 38               2.345562                -17.09608
## 39               2.354624                -16.53017
## 40               2.341386                -15.90668
## 41               2.341321                -16.12123
## 42               2.345436                -16.92384
## 43               2.341260                -16.84115
## 44               2.341711                -15.54981
## 45               2.346137                -19.74029
## 46               2.344055                -16.20135
## 47               2.341529                -16.12295
## 48               2.341436                -15.72515
## 49               2.346916                -19.39571
## 50               2.341524                -15.62032
## 51               2.346734                -18.76891
## 52               2.348194                -16.07779
## 53               2.346393                -15.32375
## 54               2.341390                -16.07153
## 55               2.341900                -16.42831
## 56               2.341406                -15.92857
## 57               2.346388                -18.02961
## 58               2.341920                -15.96782
## 59               2.341375                -17.48559
## 60               2.341488                -16.04262
```

```
## 61                      2.349767                   -18.09709
## 62                      2.341258                   -14.39027
## 63                      2.347421                   -16.34611
## 64                      2.341627                   -15.47392
## 65                      2.341388                   -16.61640
## 66                      2.348168                   -13.64099
## 67                      2.325939                   -13.63411
## 68                      2.346642                   -14.71252
## 69                      2.345355                   -17.27193
## 70                      2.341639                   -15.16872
## 71                      2.341561                   -16.73892
## 72                      2.353554                   -15.11824
## 73                      2.342111                   -16.32161
## 74                      2.341143                   -15.09663
## 75                      2.341933                   -15.22402
## 76                      2.339925                   -20.65470
## 77                      2.344304                   -13.47310
## 78                      2.342090                   -17.08796
## 79                      2.341042                   -16.39113
## 80                      2.341494                   -16.15270
## 81                      2.341361                   -15.27222
## 82                      2.342262                   -16.28162
## 83                      2.345371                   -19.68879
## 84                      2.346466                   -16.75173
## 85                      2.341514                   -15.65717
## 86                      2.342045                   -18.72447
## 87                      2.346767                   -19.13222
## 88                      2.342252                   -15.48870
## 89                      2.362110                   -16.38791
## 90                      2.351434                   -15.43936
## 91                      2.341192                   -16.03709
## 92                      2.341695                   -16.44193
## 93                      2.350350                   -15.51621
## 94                      2.343998                   -17.23703
## 95                      2.341366                   -16.88660
## 96                      2.355867                   -16.38018
## 97                      2.345465                   -19.16399
##    log_scale_apap_Rawlins1977_0.5_0 log_srel_apap_Rawlins1977_0.5_0
## 1                      -1.590025287                      1.93450843
## 2                      -0.213742346                      0.22367602
## 3                       0.862739527                      0.61019512
## 4                       1.114981812                     -0.50999605
## 5                      -0.408943750                      1.06474462
## 6                      -0.115551104                      0.71247453
## 7                       0.251265084                     -0.33733632
## 8                       1.659424182                     -0.17393247
## 9                       0.630532271                      0.40173659
## 10                     -0.174886291                      1.63956804
## 11                     -0.802038369                     -0.78368118
## 12                      1.283851072                      0.37264564
## 13                     -0.511779585                     -1.18769309
## 14                      0.394263758                      1.98837264
## 15                      0.201246210                     -0.83882892
## 16                     -0.234042778                     -0.92743386
```

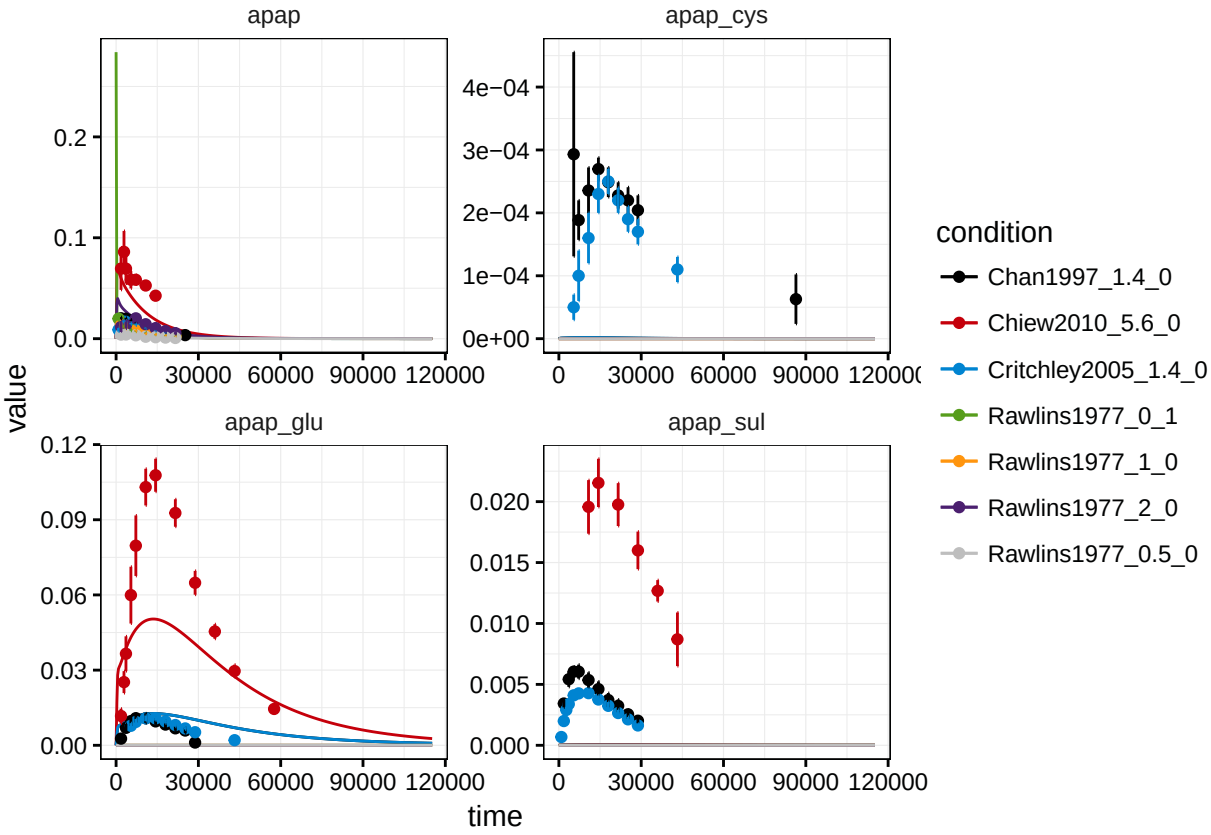
```
## 17  -0.215859360  2.14695600
## 18  -1.109491624  0.98877841
## 19   1.636542129 -0.85592278
## 20   0.387077909  0.44543929
## 21  -0.645652740  1.39145937
## 22  -0.633569856  0.33428851
## 23   1.689717814 -0.89240243
## 24   2.363738072 -1.59439448
## 25  -1.199963304 -1.18946785
## 26   0.638642539 -1.83682994
## 27   1.526045636 -1.83925868
## 28  -0.074635367 -0.58875573
## 29   0.909111786  0.27358517
## 30  -1.099091205 -0.71908482
## 31  -0.408323385  0.02022961
## 32   1.703312244 -0.76129587
## 33  -1.032827334 -0.41508400
## 34   0.106054706 -1.03797934
## 35  -1.251673436  1.31712329
## 36  -1.030008364 -0.31761397
## 37  -1.403147512  0.26064377
## 38  -0.312896260  0.07898229
## 39  -1.452912299 -0.39084219
## 40  -0.623778093 -0.24592018
## 41   0.781405161 -1.79449766
## 42   0.136584718 -0.34580836
## 43   0.057687642  1.67056995
## 44   0.744771462 -2.71086809
## 45   2.567622743  0.80141055
## 46  -0.031471329  0.19298343
## 47  -0.721875688 -0.07655351
## 48   1.440781321  1.10453737
## 49   1.452534129  0.15822359
## 50  -0.217236269 -0.03500181
## 51  -0.275200007 -1.71363276
## 52   0.291723253 -0.96546584
## 53   0.400985996  0.50526277
## 54   0.157748674 -1.07882303
## 55  -1.254283427 -0.17437388
## 56   0.190376787  0.69441558
## 57   0.671805745 -0.69439267
## 58   0.403295472  0.02108671
## 59  -0.108285414  1.07827129
## 60   1.370889286  0.69004348
## 61  -0.802189441 -0.68751590
## 62  -0.809136570 -1.78089530
## 63   0.866165660  0.15496568
## 64  -0.818906436  1.83138961
## 65   0.145638387 -0.74872222
## 66  -1.366830663 -1.55297730
## 67  -2.412566668  0.70155993
## 68  -1.520917955 -0.56028472
## 69  -1.684815158 -1.11445887
## 70  -0.368479392  0.13245904
```

```
## 71                      0.218377411                      1.07870860
## 72                     -0.170215540                     -2.09942688
## 73                     -0.129621482                     -0.02930931
## 74                     -1.827694885                      0.35886311
## 75                      1.493200469                      0.53666340
## 76                     -0.478841464                     -1.46666427
## 77                      0.223412312                      0.77213441
## 78                      0.730902590                     -1.07424369
## 79                     -0.846548139                     -0.91346213
## 80                     -0.481650312                      2.07388281
## 81                      0.994118565                      0.92481556
## 82                      0.008651297                      0.70881282
## 83                     -0.225324523                     -0.29719792
## 84                     -0.053594656                      1.18135949
## 85                      0.113826820                     -1.65786396
## 86                      0.273631088                     -0.27006334
## 87                      1.691763776                      0.36015546
## 88                      0.268646684                     -0.90194133
## 89                     -1.340612061                     -0.25774410
## 90                     -0.090969799                     -0.30515972
## 91                      0.847355128                     -0.07043823
## 92                      0.289851714                      1.95002022
## 93                     -1.207964352                      0.31458136
## 94                      0.643530343                     -0.22663892
## 95                     -0.692992794                     -1.50298783
## 96                      0.823740428                      0.02547789
## 97                     -0.323820259                      0.07326794
##    log_s0_apap_Rawlins1977_0.5_0
## 1                     -2.51992187
## 2                     -0.23450780
## 3                     -1.28198501
## 4                      1.56776108
## 5                     -0.78847261
## 6                     -0.36132767
## 7                     -1.06657661
## 8                     -0.71546488
## 9                     -0.35697483
## 10                    -1.16507219
## 11                    -1.25677562
## 12                     0.56917835
## 13                     0.68940954
## 14                    -1.47841492
## 15                     1.10162093
## 16                    -1.49669313
## 17                    -0.98566941
## 18                     0.39923168
## 19                    -1.19346846
## 20                     1.54509931
## 21                    -0.14729399
## 22                    -0.28444918
## 23                    -0.27680221
## 24                     0.74347462
## 25                    -0.88447378
## 26                    -0.01417977
```

```
## 27                0.48187815
## 28               -0.61119792
## 29                0.49328047
## 30               -0.90744422
## 31               -0.50750087
## 32               -0.10335109
## 33                0.48586088
## 34               -0.61893724
## 35                0.68984417
## 36                0.92230416
## 37               -0.25530240
## 38                1.05660569
## 39               -0.14118152
## 40               -1.50607964
## 41                1.02692758
## 42                0.63267349
## 43               -1.59836469
## 44                0.19620299
## 45                0.27029283
## 46                0.13860860
## 47                0.44591768
## 48                0.71897303
## 49                1.09700648
## 50               -1.11202648
## 51               -0.81643947
## 52               -1.12300472
## 53               -0.26588452
## 54               -0.90870520
## 55                1.41769502
## 56               -0.27738076
## 57               -0.48018082
## 58               -0.92415607
## 59               -0.41956867
## 60               -1.68689387
## 61               -1.34738971
## 62               -1.38970154
## 63                0.75432648
## 64               -0.52971686
## 65                0.19258635
## 66                0.17195118
## 67                0.74126013
## 68                1.27490342
## 69               -1.56900473
## 70               -1.33552682
## 71                0.69743395
## 72                1.06035233
## 73                0.53742880
## 74               -1.13112738
## 75                0.55537267
## 76                0.22702740
## 77                0.42968195
## 78               -0.48987566
## 79               -0.29429163
## 80                2.09611496
```

```
## 81                    0.29952507
## 82                    0.90212881
## 83                    0.34766483
## 84                   -1.25386301
## 85                    1.03811625
## 86                    0.57519426
## 87                   -0.55129651
## 88                    1.03173333
## 89                    0.48307843
## 90                   -0.14704933
## 91                    1.42909560
## 92                    1.30950426
## 93                    0.09557711
## 94                    1.53058355
## 95                   -0.27664948
## 96                    1.72661581
## 97                    0.48299060
```

```
# plotValues(myfit8 %>% as.parframe())+scale_y_log10()


mypred8 <- (g8*x*p8)(mytimes*4, myfit8 %>% as.parframe() %>% as.parvec %>% {names(.) <- names(.) %>% st
myplot <- plotCombined(mypred8, mydatalist, name %in% names(observables))
# plotly::ggplotly(myplot)
myplot
```



9 Introduce error model and scaling factors in the dynamic model -

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters9 <- c("APAPGLU_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPSUL_HLM_CL",  # Vmax value
                      "APAPGLU_Km",  # Km value
                      "APAPCYS_HLM_CL",  # Vmax value
                      "APAPCYS_Km",  # Km value

                      "Ka_apap"#, #"F_apap_sul"    ,
                      # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                      # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                      # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                      # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                      # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                      # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                      )

fixed_parameters9 <- pars[!(names(pars)%in%c(free_parameters9,names(f)[1]))] %>% names

mydatalist <- data  %>% select(-n) %>% as.datalist()
conditions <- mydatalist %>% attr("condition.grid")


observables9 <- c(apap = "Ave_apap/(BW*FVve)*scale_apap",
                  apap_glu = "Ave_apap_glu/(BW*FVve)*scale_apap_glu",
                  apap_sul = "Ave_apap_sul/(BW*FVve)*scale_apap_sul",
                  apap_cys = "Ave_apap_cys/(BW*FVve)*scale_apap_cys")
scale_parameters9 <- paste0("scale_apap", c("", "_glu", "_sul", "_cys")) %>% set_names(.,.)

# free_parameters9 <- c(free_parameters9, scale_parameters9)

error_model9 <- c(apap = "srel_apap*apap^2 +s0_apap",
                  apap_glu = "srel_apap_glu*apap_glu^2 +s0_apap_glu",
                  apap_sul = "srel_apap_sul*apap_sul^2 +s0_apap_sul",
                  apap_cys = "srel_apap_cys*apap_cys^2 +s0_apap_cys")
error_parameters9 <- setdiff(getSymbols(error_model9), names(error_model9)) %>% set_names(.,.)

i <- 1
p_list <- lapply(1:nrow(conditions), function(i) {
  cond <- unlist(conditions[i,])[2:3]

  trafo <- as.character(pars) %>% set_names(names(pars))
  trafo[names(cond)] <- cond
```

```
  trafo[free_parameters9] <- paste0("exp(log", free_parameters9, ")")

  scales <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", scale_parameters9, x = scale_parameter
  scales <- scales[names(scales) %>% sapply(. %>% str_detect(mydatalist[[i]][["name"]] %>% unique() %>%

  errors <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", error_parameters9, x = error_parameter
  errors <- errors[names(errors) %>% sapply(. %>% str_detect(mydatalist[[i]][["name"]] %>% unique() %>%

  trafo <- c(trafo, scales, errors)

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p9 <- NULL
for(i in 1:length(p_list)) { p9 <<- p9 + p_list[[i]]}

g9 <- Y(observables9, x)#, parameters = c(free_parameters9, scale_parameters9))
```

```
## States:
##  [1] "Ali_metc13"   "Ali_apap"     "Ali_co2c13"   "Ali_apap_glu"
##  [5] "Ali_apap_sul" "Ali_apap_cys" "Agu_apap_sul" "D_apap_sul"
##  [9] "Aki_apap_sul" "Ave_apap_sul" "Alu_apap_sul" "Aar_apap_sul"
## [13] "Are_apap_sul" "Asp_apap_sul" "Agu_apap"     "D_apap"
## [17] "Aki_apap"     "Ave_apap"     "Alu_apap"     "Aar_apap"
## [21] "Are_apap"     "Asp_apap"     "Agu_metc13"   "D_metc13"
## [25] "Aki_metc13"   "Ave_metc13"   "Alu_metc13"   "Aar_metc13"
## [29] "Are_metc13"   "Asp_metc13"   "Agu_apap_cys" "D_apap_cys"
## [33] "Aki_apap_cys" "Ave_apap_cys" "Alu_apap_cys" "Aar_apap_cys"
## [37] "Are_apap_cys" "Asp_apap_cys" "Agu_apap_glu" "D_apap_glu"
## [41] "Aki_apap_glu" "Ave_apap_glu" "Alu_apap_glu" "Aar_apap_glu"
## [45] "Are_apap_glu" "Asp_apap_glu" "Agu_co2c13"   "D_co2c13"
## [49] "Aki_co2c13"   "Ave_co2c13"   "Alu_co2c13"   "Aar_co2c13"
## [53] "Are_co2c13"   "Asp_co2c13"   "time"
## Parameters:
##  [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##  [4] "BW"               "FVli"             "fup_metc13"
##  [7] "MET2APAP_Km"      "CO"               "FQgu"
## [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
## [13] "FQsp"             "FVsp"             "Kpsp_metc13"
## [16] "FQh"              "FVar"             "Kpli_metc13"
## [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
## [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
## [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
## [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
## [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
## [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
## [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
## [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
## [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
## [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
## [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
## [52] "FVki"             "fup_apap_sul"     "FQki"
## [55] "Kpki_apap_sul"    "FQlu"             "FVve"
## [58] "FQre"             "FVre"             "Kpre_apap_sul"
```

```
## [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
## [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
## [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
## [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
## [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
## [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
## [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
## [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
## [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
## [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
## [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
## [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
## [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## Estimate:
##   [1] "Ali_metc13"       "Ali_apap"         "Ali_co2c13"
##   [4] "Ali_apap_glu"     "Ali_apap_sul"     "Ali_apap_cys"
##   [7] "Agu_apap_sul"     "D_apap_sul"       "Aki_apap_sul"
##  [10] "Ave_apap_sul"     "Alu_apap_sul"     "Aar_apap_sul"
##  [13] "Are_apap_sul"     "Asp_apap_sul"     "Agu_apap"
##  [16] "D_apap"           "Aki_apap"         "Ave_apap"
##  [19] "Alu_apap"         "Aar_apap"         "Are_apap"
##  [22] "Asp_apap"         "Agu_metc13"       "D_metc13"
##  [25] "Aki_metc13"       "Ave_metc13"       "Alu_metc13"
##  [28] "Aar_metc13"       "Are_metc13"       "Asp_metc13"
##  [31] "Agu_apap_cys"     "D_apap_cys"       "Aki_apap_cys"
##  [34] "Ave_apap_cys"     "Alu_apap_cys"     "Aar_apap_cys"
##  [37] "Are_apap_cys"     "Asp_apap_cys"     "Agu_apap_glu"
##  [40] "D_apap_glu"       "Aki_apap_glu"     "Ave_apap_glu"
##  [43] "Alu_apap_glu"     "Aar_apap_glu"     "Are_apap_glu"
##  [46] "Asp_apap_glu"     "Agu_co2c13"       "D_co2c13"
##  [49] "Aki_co2c13"       "Ave_co2c13"       "Alu_co2c13"
##  [52] "Aar_co2c13"       "Are_co2c13"       "Asp_co2c13"
##  [55] "time"             "MET2APAP_HLM_CL"  "fumic_metc13"
##  [58] "MPPGL"            "BW"               "FVli"
##  [61] "fup_metc13"       "MET2APAP_Km"      "CO"
##  [64] "FQgu"             "FVgu"             "Kpgu_metc13"
##  [67] "BP_metc13"        "FQsp"             "FVsp"
##  [70] "Kpsp_metc13"      "FQh"              "FVar"
##  [73] "Kpli_metc13"      "APAPGLU_HLM_CL"   "fumic_apap_glu"
##  [76] "fup_apap"         "APAPGLU_Km"       "APAPSUL_HLM_CL"
##  [79] "fumic_apap_sul"   "APAPSUL_Km"       "APAPCYS_HLM_CL"
##  [82] "fumic_apap_cys"   "APAPCYS_Km"       "Kpgu_apap"
##  [85] "BP_apap"          "Kpsp_apap"        "Kpli_apap"
##  [88] "Kpgu_co2c13"      "BP_co2c13"        "Kpsp_co2c13"
##  [91] "Kpli_co2c13"      "Kpgu_apap_glu"    "BP_apap_glu"
##  [94] "Kpsp_apap_glu"    "Kpli_apap_glu"    "Kpgu_apap_sul"
##  [97] "BP_apap_sul"      "Kpsp_apap_sul"    "Kpli_apap_sul"
## [100] "Kpgu_apap_cys"    "BP_apap_cys"      "Kpsp_apap_cys"
## [103] "Kpli_apap_cys"    "Ka_apap_sul"      "F_apap_sul"
## [106] "CLrenal_apap_sul" "FVki"             "fup_apap_sul"
## [109] "FQki"             "Kpki_apap_sul"    "FQlu"
## [112] "FVve"             "FQre"             "FVre"
## [115] "Kpre_apap_sul"    "FVlu"             "Kplu_apap_sul"
## [118] "Ka_apap"          "F_apap"           "CLrenal_apap"
```

```
## [121] "Kpki_apap"        "Kpre_apap"        "Kplu_apap"
## [124] "Ka_metc13"        "F_metc13"         "CLrenal_metc13"
## [127] "Kpki_metc13"      "Kpre_metc13"      "Kplu_metc13"
## [130] "Ka_apap_cys"      "F_apap_cys"       "CLrenal_apap_cys"
## [133] "fup_apap_cys"     "Kpki_apap_cys"    "Kpre_apap_cys"
## [136] "Kplu_apap_cys"    "Ka_apap_glu"      "F_apap_glu"
## [139] "CLrenal_apap_glu" "fup_apap_glu"     "Kpki_apap_glu"
## [142] "Kpre_apap_glu"    "Kplu_apap_glu"    "Ka_co2c13"
## [145] "F_co2c13"         "CLrenal_co2c13"   "fup_co2c13"
## [148] "Kpki_co2c13"      "Kpre_co2c13"      "Kplu_co2c13"
## [151] "scale_apap"       "scale_apap_glu"   "scale_apap_sul"
## [154] "scale_apap_cys"
```

```
err9 <- Y(error_model9, g9)
```

```
## States:
## [1] "apap"     "apap_glu" "apap_sul" "apap_cys" "time"
## Parameters:
##   [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##   [4] "BW"               "FVli"             "fup_metc13"
##   [7] "MET2APAP_Km"      "CO"               "FQgu"
##  [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
##  [13] "FQsp"             "FVsp"             "Kpsp_metc13"
##  [16] "FQh"              "FVar"             "Kpli_metc13"
##  [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
##  [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
##  [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
##  [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
##  [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
##  [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
##  [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
##  [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
##  [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
##  [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
##  [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
##  [52] "FVki"             "fup_apap_sul"     "FQki"
##  [55] "Kpki_apap_sul"    "FQlu"             "FVve"
##  [58] "FQre"             "FVre"             "Kpre_apap_sul"
##  [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
##  [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
##  [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
##  [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
##  [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
##  [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
##  [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
##  [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
##  [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
##  [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
##  [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
##  [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
##  [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## [100] "srel_apap"        "s0_apap"          "srel_apap_glu"
## [103] "s0_apap_glu"      "srel_apap_sul"    "s0_apap_sul"
## [106] "srel_apap_cys"    "s0_apap_cys"
## Estimate:
```

```
##   [1] "apap"             "apap_glu"         "apap_sul"
##   [4] "apap_cys"         "time"             "MET2APAP_HLM_CL"
##   [7] "fumic_metc13"     "MPPGL"            "BW"
##  [10] "FVli"             "fup_metc13"       "MET2APAP_Km"
##  [13] "CO"               "FQgu"             "FVgu"
##  [16] "Kpgu_metc13"      "BP_metc13"        "FQsp"
##  [19] "FVsp"             "Kpsp_metc13"      "FQh"
##  [22] "FVar"             "Kpli_metc13"      "APAPGLU_HLM_CL"
##  [25] "fumic_apap_glu"   "fup_apap"         "APAPGLU_Km"
##  [28] "APAPSUL_HLM_CL"   "fumic_apap_sul"   "APAPSUL_Km"
##  [31] "APAPCYS_HLM_CL"   "fumic_apap_cys"   "APAPCYS_Km"
##  [34] "Kpgu_apap"        "BP_apap"          "Kpsp_apap"
##  [37] "Kpli_apap"        "Kpgu_co2c13"      "BP_co2c13"
##  [40] "Kpsp_co2c13"      "Kpli_co2c13"      "Kpgu_apap_glu"
##  [43] "BP_apap_glu"      "Kpsp_apap_glu"    "Kpli_apap_glu"
##  [46] "Kpgu_apap_sul"    "BP_apap_sul"      "Kpsp_apap_sul"
##  [49] "Kpli_apap_sul"    "Kpgu_apap_cys"    "BP_apap_cys"
##  [52] "Kpsp_apap_cys"    "Kpli_apap_cys"    "Ka_apap_sul"
##  [55] "F_apap_sul"       "CLrenal_apap_sul" "FVki"
##  [58] "fup_apap_sul"     "FQki"             "Kpki_apap_sul"
##  [61] "FQlu"             "FVve"             "FQre"
##  [64] "FVre"             "Kpre_apap_sul"    "FVlu"
##  [67] "Kplu_apap_sul"    "Ka_apap"          "F_apap"
##  [70] "CLrenal_apap"     "Kpki_apap"        "Kpre_apap"
##  [73] "Kplu_apap"        "Ka_metc13"        "F_metc13"
##  [76] "CLrenal_metc13"   "Kpki_metc13"      "Kpre_metc13"
##  [79] "Kplu_metc13"      "Ka_apap_cys"      "F_apap_cys"
##  [82] "CLrenal_apap_cys" "fup_apap_cys"     "Kpki_apap_cys"
##  [85] "Kpre_apap_cys"    "Kplu_apap_cys"    "Ka_apap_glu"
##  [88] "F_apap_glu"       "CLrenal_apap_glu" "fup_apap_glu"
##  [91] "Kpki_apap_glu"    "Kpre_apap_glu"    "Kplu_apap_glu"
##  [94] "Ka_co2c13"        "F_co2c13"         "CLrenal_co2c13"
##  [97] "fup_co2c13"       "Kpki_co2c13"      "Kpre_co2c13"
## [100] "Kplu_co2c13"      "scale_apap"       "scale_apap_glu"
## [103] "scale_apap_sul"   "scale_apap_cys"   "srel_apap"
## [106] "s0_apap"          "srel_apap_glu"    "s0_apap_glu"
## [109] "srel_apap_sul"    "s0_apap_sul"      "srel_apap_cys"
## [112] "s0_apap_cys"
```

```
obj9 <- normL2(mydatalist, (g9*x*p9), errmodel = err9)

pouter9 <- rep(0, length(getParameters(obj9))) %>% set_names(getParameters(obj9))
pouter9[names(myfit5 %>% as.parframe() %>% {.[2,]} %>% as.parvec())] <- myfit5 %>% as.parframe() %>% {.

# obj9(pouter9)

# job9 <- runbg({myfit <- mstrust(objfun = obj9, center = pouter9, studyname = "methacetin", cores = 16

# save(job9, file = "job9.rda")

# job9$check()
#
```

10 Introduce error model only

Mistake: Don't remove the rows with sigma=NA! Stupid...

```
load("methacetin.rda")

x <- Xs(myodemodel) # make prediction function
loadDLL(x)
```

```
## The following local files were dynamically loaded: methacetin.so, methacetin_s.so
```

```
# get the only the parameters needed for x
pars <- all_pars[getParameters(x)]

free_parameters10 <- c("APAPGLU_HLM_CL",  # Vmax value
                       "APAPGLU_Km",  # Km value
                       "APAPSUL_HLM_CL",  # Vmax value
                       "APAPGLU_Km",  # Km value
                       "APAPCYS_HLM_CL",  # Vmax value
                       "APAPCYS_Km",  # Km value

                       "Ka_apap"#, #"F_apap_sul"    ,
                       # "Kpre_apap", "Kpki_apap", "Kpli_apap",
                       # "Kpre_apap_cys", "Kpki_apap_cys", "Kpli_apap_cys",
                       # "Kpre_apap_glu", "Kpki_apap_glu", "Kpli_apap_glu",
                       # "Kpre_apap_sul", "Kpre_apap_glu", "Kpli_apap_glu"#,
                       # "Kpre_co2c13", "Kpre_co2c13", "Kpli_co2c13",
                       # "Kpre_metc13", "Kpre_metc13", "Kpli_metc13"
                       )

fixed_parameters10 <- pars[!(names(pars)%in%c(free_parameters10,names(f)[1]))] %>% names

mydatalist <- data %>% select(-n) %>% as.datalist()
conditions <- mydatalist %>% attr("condition.grid")


observables10 <- c(apap = "Ave_apap/(BW*FVve)*scale_apap",
                   apap_glu = "Ave_apap_glu/(BW*FVve)*scale_apap_glu",
                   apap_sul = "Ave_apap_sul/(BW*FVve)*scale_apap_sul",
                   apap_cys = "Ave_apap_cys/(BW*FVve)*scale_apap_cys")
scale_parameters10 <- paste0("scale_apap", c("", "_glu", "_sul", "_cys")) %>% set_names(.,.)

# free_parameters10 <- c(free_parameters10, scale_parameters10)

error_model10 <- c(apap = "srel_apap*apap^2 +s0_apap",
                   apap_glu = "srel_apap_glu*apap_glu^2 +s0_apap_glu",
                   apap_sul = "srel_apap_sul*apap_sul^2 +s0_apap_sul",
                   apap_cys = "srel_apap_cys*apap_cys^2 +s0_apap_cys")
error_parameters10 <- setdiff(getSymbols(error_model10), names(error_model10)) %>% set_names(.,.)

p_list <- lapply(1:nrow(conditions), function(i) {
  cond <- unlist(conditions[i,])[2:3]

  trafo <- as.character(pars) %>% set_names(names(pars))
  trafo[names(cond)] <- cond
```

```
  trafo[free_parameters10] <- paste0("exp(log", free_parameters10, ")")

  scales <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", scale_parameters10, x = scale_parameter
  scales[1:length(scales)] <- "1"

  errors <- rownames(conditions)[i] %>% {repar("x~exp(log_x_y)", error_parameters10, x = error_parameter
  errors <- errors[names(errors) %>% sapply(. %>% str_detect(mydatalist[[i]][["name"]] %>% unique() %>%

  trafo <- c(trafo, scales, errors)

  p <- P(trafo, condition=rownames(conditions[i,]))
  return(p)
})
p10 <- NULL
for(i in 1:length(p_list)) { p10 <<- p10 + p_list[[i]]}

g10 <- Y(observables10, x)#, parameters = c(free_parameters10, scale_parameters10))
```

```
## States:
##  [1] "Ali_metc13"   "Ali_apap"     "Ali_co2c13"   "Ali_apap_glu"
##  [5] "Ali_apap_sul" "Ali_apap_cys" "Agu_apap_sul" "D_apap_sul"
##  [9] "Aki_apap_sul" "Ave_apap_sul" "Alu_apap_sul" "Aar_apap_sul"
## [13] "Are_apap_sul" "Asp_apap_sul" "Agu_apap"     "D_apap"
## [17] "Aki_apap"     "Ave_apap"     "Alu_apap"     "Aar_apap"
## [21] "Are_apap"     "Asp_apap"     "Agu_metc13"   "D_metc13"
## [25] "Aki_metc13"   "Ave_metc13"   "Alu_metc13"   "Aar_metc13"
## [29] "Are_metc13"   "Asp_metc13"   "Agu_apap_cys" "D_apap_cys"
## [33] "Aki_apap_cys" "Ave_apap_cys" "Alu_apap_cys" "Aar_apap_cys"
## [37] "Are_apap_cys" "Asp_apap_cys" "Agu_apap_glu" "D_apap_glu"
## [41] "Aki_apap_glu" "Ave_apap_glu" "Alu_apap_glu" "Aar_apap_glu"
## [45] "Are_apap_glu" "Asp_apap_glu" "Agu_co2c13"   "D_co2c13"
## [49] "Aki_co2c13"   "Ave_co2c13"   "Alu_co2c13"   "Aar_co2c13"
## [53] "Are_co2c13"   "Asp_co2c13"   "time"
## Parameters:
##  [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##  [4] "BW"               "FVli"             "fup_metc13"
##  [7] "MET2APAP_Km"      "CO"               "FQgu"
## [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
## [13] "FQsp"             "FVsp"             "Kpsp_metc13"
## [16] "FQh"              "FVar"             "Kpli_metc13"
## [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
## [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
## [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
## [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
## [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
## [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
## [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
## [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
## [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
## [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
## [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
## [52] "FVki"             "fup_apap_sul"     "FQki"
## [55] "Kpki_apap_sul"    "FQlu"             "FVve"
## [58] "FQre"             "FVre"             "Kpre_apap_sul"
```

```
## [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
## [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
## [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
## [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
## [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
## [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
## [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
## [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
## [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
## [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
## [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
## [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
## [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## Estimate:
##   [1] "Ali_metc13"       "Ali_apap"         "Ali_co2c13"
##   [4] "Ali_apap_glu"     "Ali_apap_sul"     "Ali_apap_cys"
##   [7] "Agu_apap_sul"     "D_apap_sul"       "Aki_apap_sul"
##  [10] "Ave_apap_sul"     "Alu_apap_sul"     "Aar_apap_sul"
##  [13] "Are_apap_sul"     "Asp_apap_sul"     "Agu_apap"
##  [16] "D_apap"           "Aki_apap"         "Ave_apap"
##  [19] "Alu_apap"         "Aar_apap"         "Are_apap"
##  [22] "Asp_apap"         "Agu_metc13"       "D_metc13"
##  [25] "Aki_metc13"       "Ave_metc13"       "Alu_metc13"
##  [28] "Aar_metc13"       "Are_metc13"       "Asp_metc13"
##  [31] "Agu_apap_cys"     "D_apap_cys"       "Aki_apap_cys"
##  [34] "Ave_apap_cys"     "Alu_apap_cys"     "Aar_apap_cys"
##  [37] "Are_apap_cys"     "Asp_apap_cys"     "Agu_apap_glu"
##  [40] "D_apap_glu"       "Aki_apap_glu"     "Ave_apap_glu"
##  [43] "Alu_apap_glu"     "Aar_apap_glu"     "Are_apap_glu"
##  [46] "Asp_apap_glu"     "Agu_co2c13"       "D_co2c13"
##  [49] "Aki_co2c13"       "Ave_co2c13"       "Alu_co2c13"
##  [52] "Aar_co2c13"       "Are_co2c13"       "Asp_co2c13"
##  [55] "time"             "MET2APAP_HLM_CL"  "fumic_metc13"
##  [58] "MPPGL"            "BW"               "FVli"
##  [61] "fup_metc13"       "MET2APAP_Km"      "CO"
##  [64] "FQgu"             "FVgu"             "Kpgu_metc13"
##  [67] "BP_metc13"        "FQsp"             "FVsp"
##  [70] "Kpsp_metc13"      "FQh"              "FVar"
##  [73] "Kpli_metc13"      "APAPGLU_HLM_CL"   "fumic_apap_glu"
##  [76] "fup_apap"         "APAPGLU_Km"       "APAPSUL_HLM_CL"
##  [79] "fumic_apap_sul"   "APAPSUL_Km"       "APAPCYS_HLM_CL"
##  [82] "fumic_apap_cys"   "APAPCYS_Km"       "Kpgu_apap"
##  [85] "BP_apap"          "Kpsp_apap"        "Kpli_apap"
##  [88] "Kpgu_co2c13"      "BP_co2c13"        "Kpsp_co2c13"
##  [91] "Kpli_co2c13"      "Kpgu_apap_glu"    "BP_apap_glu"
##  [94] "Kpsp_apap_glu"    "Kpli_apap_glu"    "Kpgu_apap_sul"
##  [97] "BP_apap_sul"      "Kpsp_apap_sul"    "Kpli_apap_sul"
## [100] "Kpgu_apap_cys"    "BP_apap_cys"      "Kpsp_apap_cys"
## [103] "Kpli_apap_cys"    "Ka_apap_sul"      "F_apap_sul"
## [106] "CLrenal_apap_sul" "FVki"             "fup_apap_sul"
## [109] "FQki"             "Kpki_apap_sul"    "FQlu"
## [112] "FVve"             "FQre"             "FVre"
## [115] "Kpre_apap_sul"    "FVlu"             "Kplu_apap_sul"
## [118] "Ka_apap"          "F_apap"           "CLrenal_apap"
```

```
## [121] "Kpki_apap"        "Kpre_apap"        "Kplu_apap"
## [124] "Ka_metc13"        "F_metc13"         "CLrenal_metc13"
## [127] "Kpki_metc13"      "Kpre_metc13"      "Kplu_metc13"
## [130] "Ka_apap_cys"      "F_apap_cys"       "CLrenal_apap_cys"
## [133] "fup_apap_cys"     "Kpki_apap_cys"    "Kpre_apap_cys"
## [136] "Kplu_apap_cys"    "Ka_apap_glu"      "F_apap_glu"
## [139] "CLrenal_apap_glu" "fup_apap_glu"     "Kpki_apap_glu"
## [142] "Kpre_apap_glu"    "Kplu_apap_glu"    "Ka_co2c13"
## [145] "F_co2c13"         "CLrenal_co2c13"   "fup_co2c13"
## [148] "Kpki_co2c13"      "Kpre_co2c13"      "Kplu_co2c13"
## [151] "scale_apap"       "scale_apap_glu"   "scale_apap_sul"
## [154] "scale_apap_cys"
```

```
err10 <- Y(error_model10, g10)
```

```
## States:
## [1] "apap"     "apap_glu" "apap_sul" "apap_cys" "time"
## Parameters:
##   [1] "MET2APAP_HLM_CL"  "fumic_metc13"     "MPPGL"
##   [4] "BW"               "FVli"             "fup_metc13"
##   [7] "MET2APAP_Km"      "CO"               "FQgu"
##  [10] "FVgu"             "Kpgu_metc13"      "BP_metc13"
##  [13] "FQsp"             "FVsp"             "Kpsp_metc13"
##  [16] "FQh"              "FVar"             "Kpli_metc13"
##  [19] "APAPGLU_HLM_CL"   "fumic_apap_glu"   "fup_apap"
##  [22] "APAPGLU_Km"       "APAPSUL_HLM_CL"   "fumic_apap_sul"
##  [25] "APAPSUL_Km"       "APAPCYS_HLM_CL"   "fumic_apap_cys"
##  [28] "APAPCYS_Km"       "Kpgu_apap"        "BP_apap"
##  [31] "Kpsp_apap"        "Kpli_apap"        "Kpgu_co2c13"
##  [34] "BP_co2c13"        "Kpsp_co2c13"      "Kpli_co2c13"
##  [37] "Kpgu_apap_glu"    "BP_apap_glu"      "Kpsp_apap_glu"
##  [40] "Kpli_apap_glu"    "Kpgu_apap_sul"    "BP_apap_sul"
##  [43] "Kpsp_apap_sul"    "Kpli_apap_sul"    "Kpgu_apap_cys"
##  [46] "BP_apap_cys"      "Kpsp_apap_cys"    "Kpli_apap_cys"
##  [49] "Ka_apap_sul"      "F_apap_sul"       "CLrenal_apap_sul"
##  [52] "FVki"             "fup_apap_sul"     "FQki"
##  [55] "Kpki_apap_sul"    "FQlu"             "FVve"
##  [58] "FQre"             "FVre"             "Kpre_apap_sul"
##  [61] "FVlu"             "Kplu_apap_sul"    "Ka_apap"
##  [64] "F_apap"           "CLrenal_apap"     "Kpki_apap"
##  [67] "Kpre_apap"        "Kplu_apap"        "Ka_metc13"
##  [70] "F_metc13"         "CLrenal_metc13"   "Kpki_metc13"
##  [73] "Kpre_metc13"      "Kplu_metc13"      "Ka_apap_cys"
##  [76] "F_apap_cys"       "CLrenal_apap_cys" "fup_apap_cys"
##  [79] "Kpki_apap_cys"    "Kpre_apap_cys"    "Kplu_apap_cys"
##  [82] "Ka_apap_glu"      "F_apap_glu"       "CLrenal_apap_glu"
##  [85] "fup_apap_glu"     "Kpki_apap_glu"    "Kpre_apap_glu"
##  [88] "Kplu_apap_glu"    "Ka_co2c13"        "F_co2c13"
##  [91] "CLrenal_co2c13"   "fup_co2c13"       "Kpki_co2c13"
##  [94] "Kpre_co2c13"      "Kplu_co2c13"      "scale_apap"
##  [97] "scale_apap_glu"   "scale_apap_sul"   "scale_apap_cys"
## [100] "srel_apap"        "s0_apap"          "srel_apap_glu"
## [103] "s0_apap_glu"      "srel_apap_sul"    "s0_apap_sul"
## [106] "srel_apap_cys"    "s0_apap_cys"
## Estimate:
```

```
##   [1] "apap"             "apap_glu"         "apap_sul"
##   [4] "apap_cys"         "time"             "MET2APAP_HLM_CL"
##   [7] "fumic_metc13"     "MPPGL"            "BW"
##  [10] "FVli"             "fup_metc13"       "MET2APAP_Km"
##  [13] "CO"               "FQgu"             "FVgu"
##  [16] "Kpgu_metc13"      "BP_metc13"        "FQsp"
##  [19] "FVsp"             "Kpsp_metc13"      "FQh"
##  [22] "FVar"             "Kpli_metc13"      "APAPGLU_HLM_CL"
##  [25] "fumic_apap_glu"   "fup_apap"         "APAPGLU_Km"
##  [28] "APAPSUL_HLM_CL"   "fumic_apap_sul"   "APAPSUL_Km"
##  [31] "APAPCYS_HLM_CL"   "fumic_apap_cys"   "APAPCYS_Km"
##  [34] "Kpgu_apap"        "BP_apap"          "Kpsp_apap"
##  [37] "Kpli_apap"        "Kpgu_co2c13"      "BP_co2c13"
##  [40] "Kpsp_co2c13"      "Kpli_co2c13"      "Kpgu_apap_glu"
##  [43] "BP_apap_glu"      "Kpsp_apap_glu"    "Kpli_apap_glu"
##  [46] "Kpgu_apap_sul"    "BP_apap_sul"      "Kpsp_apap_sul"
##  [49] "Kpli_apap_sul"    "Kpgu_apap_cys"    "BP_apap_cys"
##  [52] "Kpsp_apap_cys"    "Kpli_apap_cys"    "Ka_apap_sul"
##  [55] "F_apap_sul"       "CLrenal_apap_sul" "FVki"
##  [58] "fup_apap_sul"     "FQki"             "Kpki_apap_sul"
##  [61] "FQlu"             "FVve"             "FQre"
##  [64] "FVre"             "Kpre_apap_sul"    "FVlu"
##  [67] "Kplu_apap_sul"    "Ka_apap"          "F_apap"
##  [70] "CLrenal_apap"     "Kpki_apap"        "Kpre_apap"
##  [73] "Kplu_apap"        "Ka_metc13"        "F_metc13"
##  [76] "CLrenal_metc13"   "Kpki_metc13"      "Kpre_metc13"
##  [79] "Kplu_metc13"      "Ka_apap_cys"      "F_apap_cys"
##  [82] "CLrenal_apap_cys" "fup_apap_cys"     "Kpki_apap_cys"
##  [85] "Kpre_apap_cys"    "Kplu_apap_cys"    "Ka_apap_glu"
##  [88] "F_apap_glu"       "CLrenal_apap_glu" "fup_apap_glu"
##  [91] "Kpki_apap_glu"    "Kpre_apap_glu"    "Kplu_apap_glu"
##  [94] "Ka_co2c13"        "F_co2c13"         "CLrenal_co2c13"
##  [97] "fup_co2c13"       "Kpki_co2c13"      "Kpre_co2c13"
## [100] "Kplu_co2c13"      "scale_apap"       "scale_apap_glu"
## [103] "scale_apap_sul"   "scale_apap_cys"   "srel_apap"
## [106] "s0_apap"          "srel_apap_glu"    "s0_apap_glu"
## [109] "srel_apap_sul"    "s0_apap_sul"      "srel_apap_cys"
## [112] "s0_apap_cys"
```

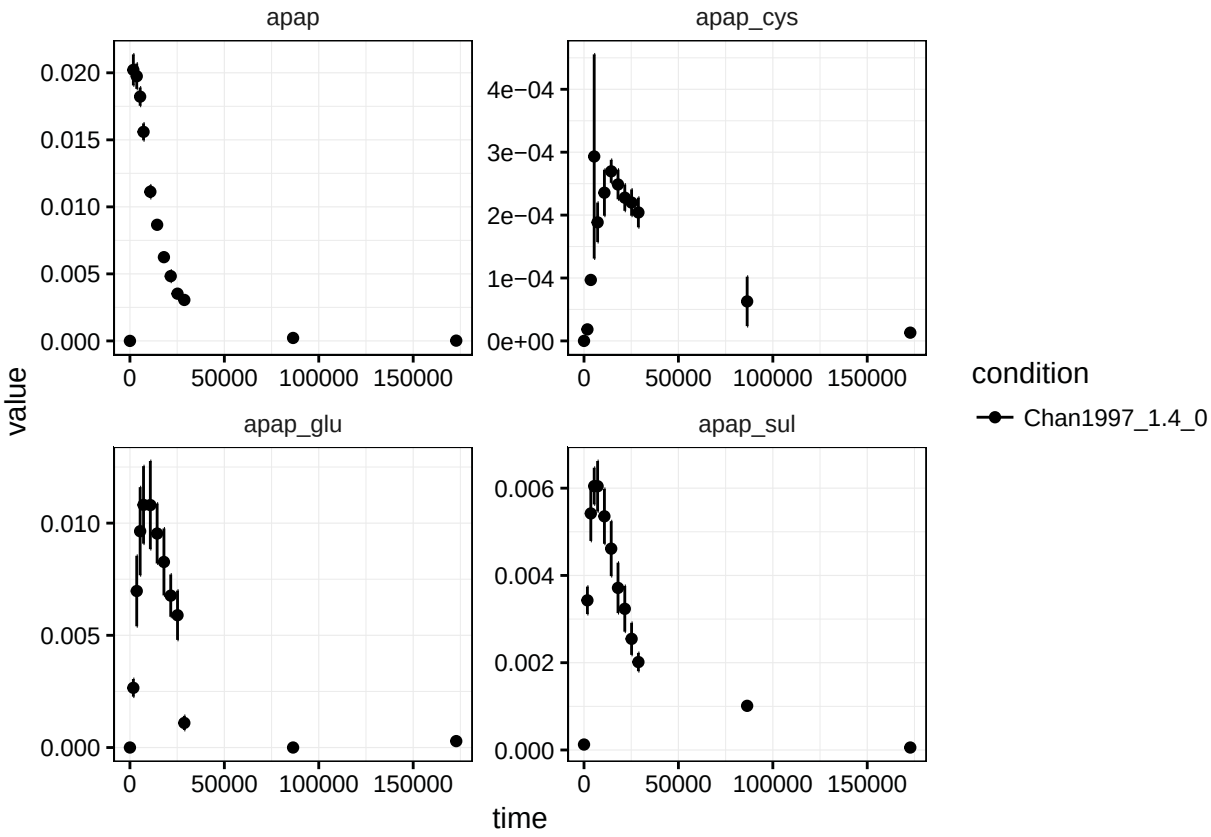
```
obj10 <- normL2(mydatalist, (g10*x*p10), errmodel = err10)


pouter10 <- rep(0, length(getParameters(obj10))) %>% set_names(getParameters(obj10))
pouter10[names(myfit5 %>% as.parframe() %>% {.[2,]} %>% as.parvec())] <- myfit5 %>% as.parframe() %>% {

# job10 <- runbg({myfit <- mstrust(objfun = obj10, center = pouter10, studyname = "methacetin", cores =

# save(job10, file = "job10.rda")

# job10$check()
```

Data revisited

Some sigmas of the data are NA, try to recover an estimate for the sigmas from the other sigmas

```
myfiles <- list.files("~/Promotion/Projects/methacetin_fitting/data/", full.names = T)

raw_data <- myfiles %>% lapply(. %>% read.table(header = T, sep = "\t", stringsAsFactors = F))

data <-
  raw_data %>%
  lapply(. %>%
           select(-contains("_mol")) %>%
           gather("name_std", "std", ends_with("_sd")) %>%
           mutate(name_std = str_replace(name_std, "_sd","")) %>%
           gather("name_sigma", "sigma", ends_with("_se")) %>%
           mutate(name_sigma = str_replace(name_sigma, "_se","")) %>%
           {gather(.,"name", "value", one_of(.$name_std))} %>%
           filter(name == name_std, name == name_sigma) %>%
           {.}) %>%
  do.call(dMod::combine,.) %>%
  mutate(D_apap = "D_apap", Ave_apap = "Ave_apap" ) %>%
  {.$D_apap[.$study=="Chan1997"] <- 1400 / 1000
  .$Ave_apap[.$study=="Chan1997"] <- 0
  .$D_apap[.$study=="Chiew2010"] <- 5600 / 1000
  .$Ave_apap[.$study=="Chiew2010"] <- 0
  .$D_apap[.$study=="Critchley2005"] <- 1400 /1000
  .$Ave_apap[.$study=="Critchley2005"] <- 0
  .$D_apap[.$study=="Rawlins1977"] <- .$dose[.$study=="Rawlins1977"] * (.$route[.$study=="Rawlins1977"]
  .$Ave_apap[.$study=="Rawlins1977"] <- .$dose[.$study=="Rawlins1977"] * (.$route[.$study=="Rawlins1977
  .
  } %>%
  mutate(time = time * 3600, value = value/1000, sigma = sigma/1000) %>%
  select(-group, -health_status, - name_std, - name_sigma, -std, -ethnicity, -route, -dose, -substance)
  # filter(!is.na(sigma)) %>%
  # as.datalist() %>%
  {.}



mydatalist <- data %>% select(-n) %>% as.datalist()

plotData(mydatalist[names(mydatalist) %>% str_detect("Chan")])
```

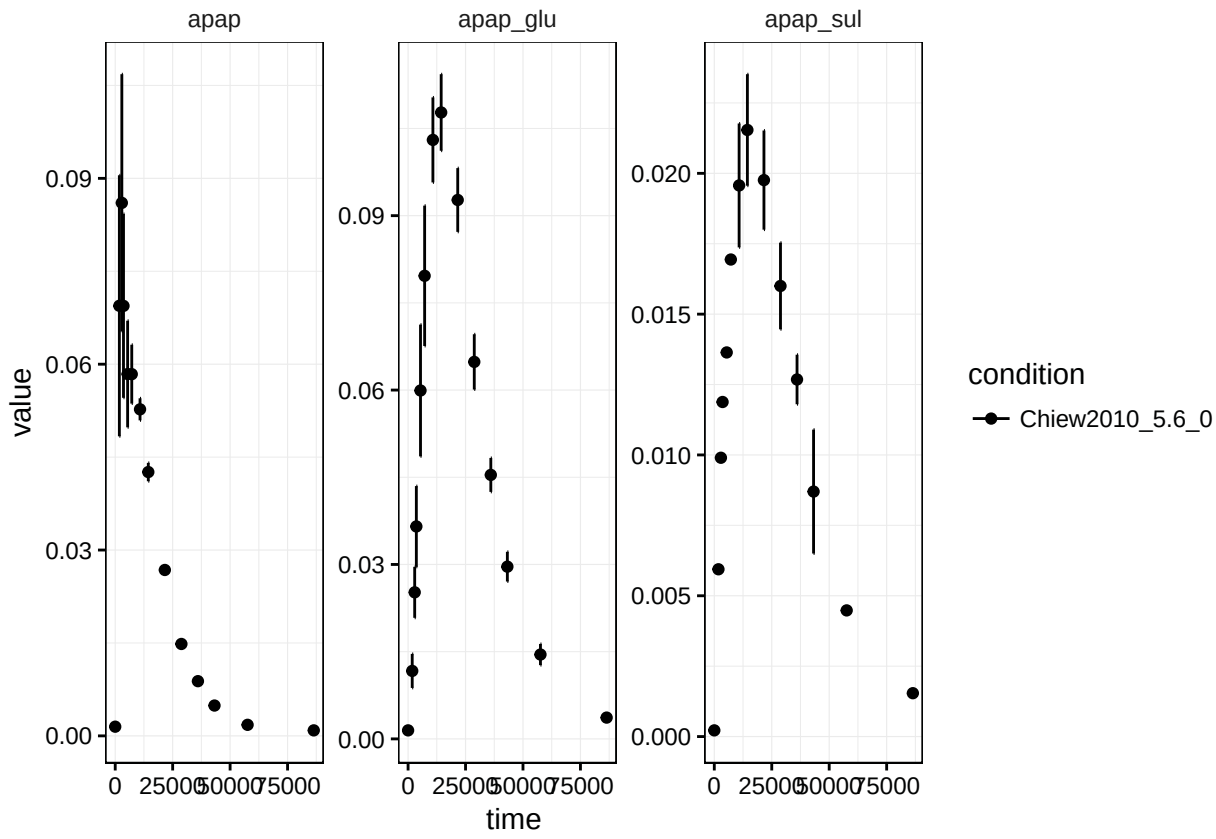
```
## Warning: Removed 15 rows containing missing values (geom_errorbar).
```



Take out some outliers for the fitting. Those are: study, name, time, reason 1. Chan1997, apap_cys, 5400, don't know what went wrong with this one, but it just doesn't fit reasonably in the time course 3. Chan1997, apap, 18000, The sigma is a few orders of magnitude lower. Mirjam said it might be that in this point less people were measured (eg 2) and they had nearly the same value. Then of course, sigma would be very smal

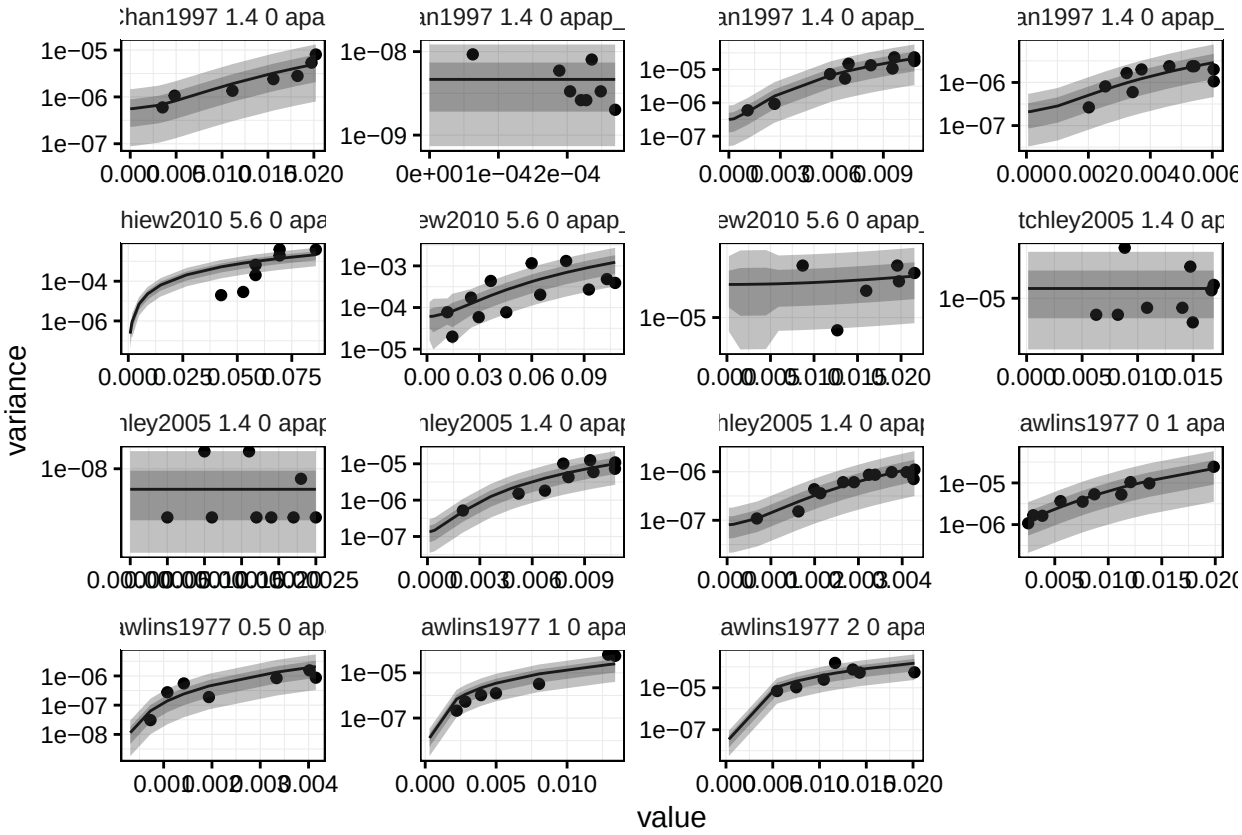
```
# data <- data %>%
#   filter(!((study %>% str_detect("Chan")) & (name %in% "apap_cys") & time == 5400)) %>%
#   filter(!((study %>% str_detect("Chan")) & (name %in% "apap") & time == 18000)) %>%
#   {.}

 data %>% select(-n) %>% filter(study %>% str_detect("Chiew"))%>% as.datalist() %>% plotData()
```

```
## Warning: Removed 17 rows containing missing values (geom_errorbar).
```




```
data_with_errors <- data %>%
  filter(!((study %>% str_detect("Chan")) & (name %in% "apap_cys") & time == 5400)) %>%
  filter(!((study %>% str_detect("Chan")) & (name %in% "apap") & time == 18000)) %>%
  fitErrorModel(factors = c("study", "D_apap", "Ave_apap", "name"), blather = T)
```

```
## Warning: Removed 56 rows containing missing values (geom_point).
```




```
data_with_errors %>% select(study, name, D_apap, s0, srel) %>% unique()
```

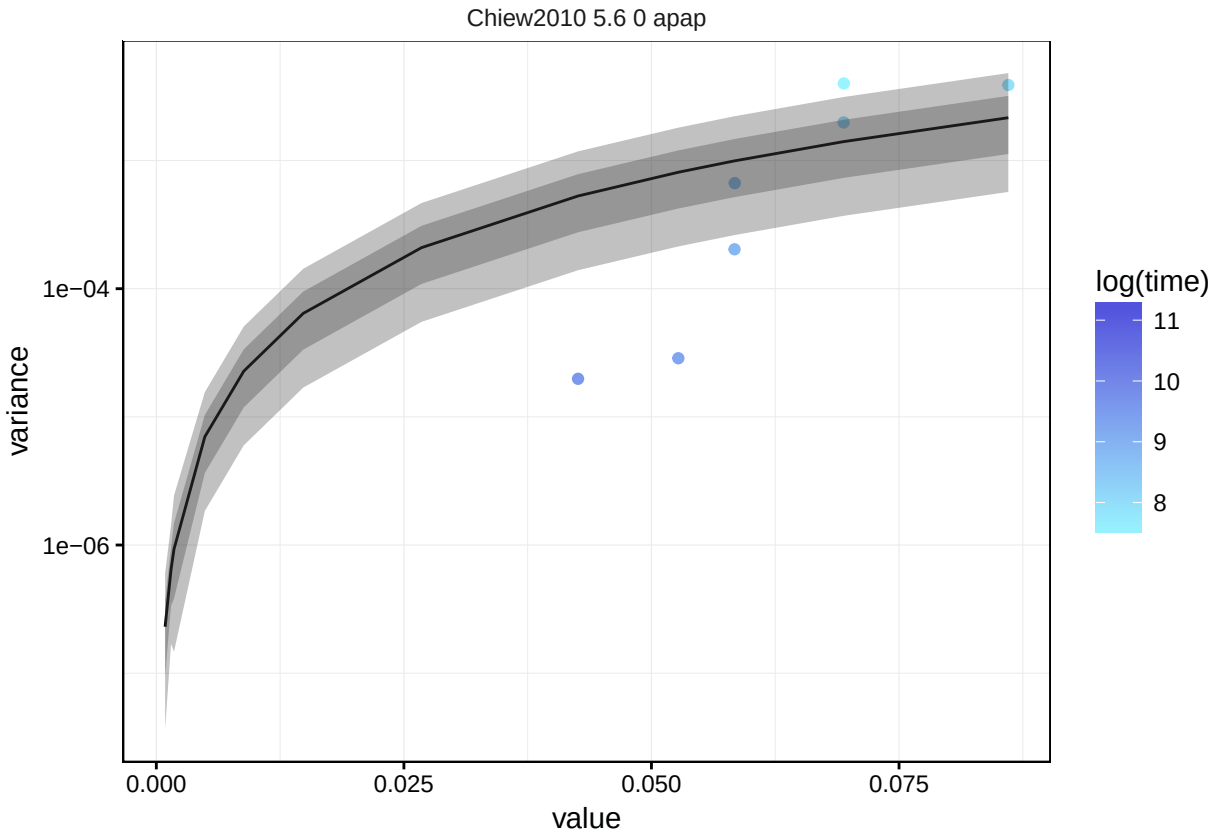
```
##             study     name D_apap         s0       srel
## 1         Chan1997     apap    1.4 -14.395145  -4.516431
## 13        Chan1997 apap_sul    1.4 -15.377176  -2.609451
## 26        Chan1997 apap_glu    1.4 -14.970003  -1.709818
## 39        Chan1997 apap_cys    1.4 -19.186945 -13.879472
## 51       Chiew2010     apap    5.6 -24.503629  -1.232431
## 65       Chiew2010 apap_glu    5.6  -9.710964  -2.303673
## 79       Chiew2010 apap_sul    5.6 -10.576758  -4.220755
## 93   Critchley2005     apap    1.4 -11.298969 -16.644666
## 108  Critchley2005 apap_sul    1.4 -16.328137  -2.802784
## 123  Critchley2005 apap_glu    1.4 -15.826025  -2.457868
## 138  Critchley2005 apap_cys    1.4 -18.851664 -18.687321
## 153    Rawlins1977     apap      0 -13.826728  -2.924789
## 163    Rawlins1977     apap      1 -28.577775  -1.968079
## 171    Rawlins1977     apap      2 -27.097492  -1.002046
## 179    Rawlins1977     apap    0.5 -27.374147  -2.115781
```

What's the problem with the Chiew-dataset? The error model doesn't work out, somehow

```
data_with_errors %>%
  filter(study %>% str_detect("Chiew"), name %in% "apap") %>%
ggplot(aes(x=value)) +
            geom_point(aes(y=sigmaLS^2*(n), color = log(time))) +
            geom_line(aes(y=sigma^2*n)) +
            geom_ribbon(aes(ymin=cbLower95, ymax=cbUpper95), alpha=.3) +
            geom_ribbon(aes(ymin=cbLower68, ymax=cbUpper68), alpha=.3) +
            ylab("variance") +
```

```
            facet_wrap(~condidnt, scales = "free") +
            scale_y_log10() +
            theme_dMod() +
            scale_color_continuous( low = "#98f5ff", high = "#4c4cdb")
```

```
## Warning: Removed 7 rows containing missing values (geom_point).
```

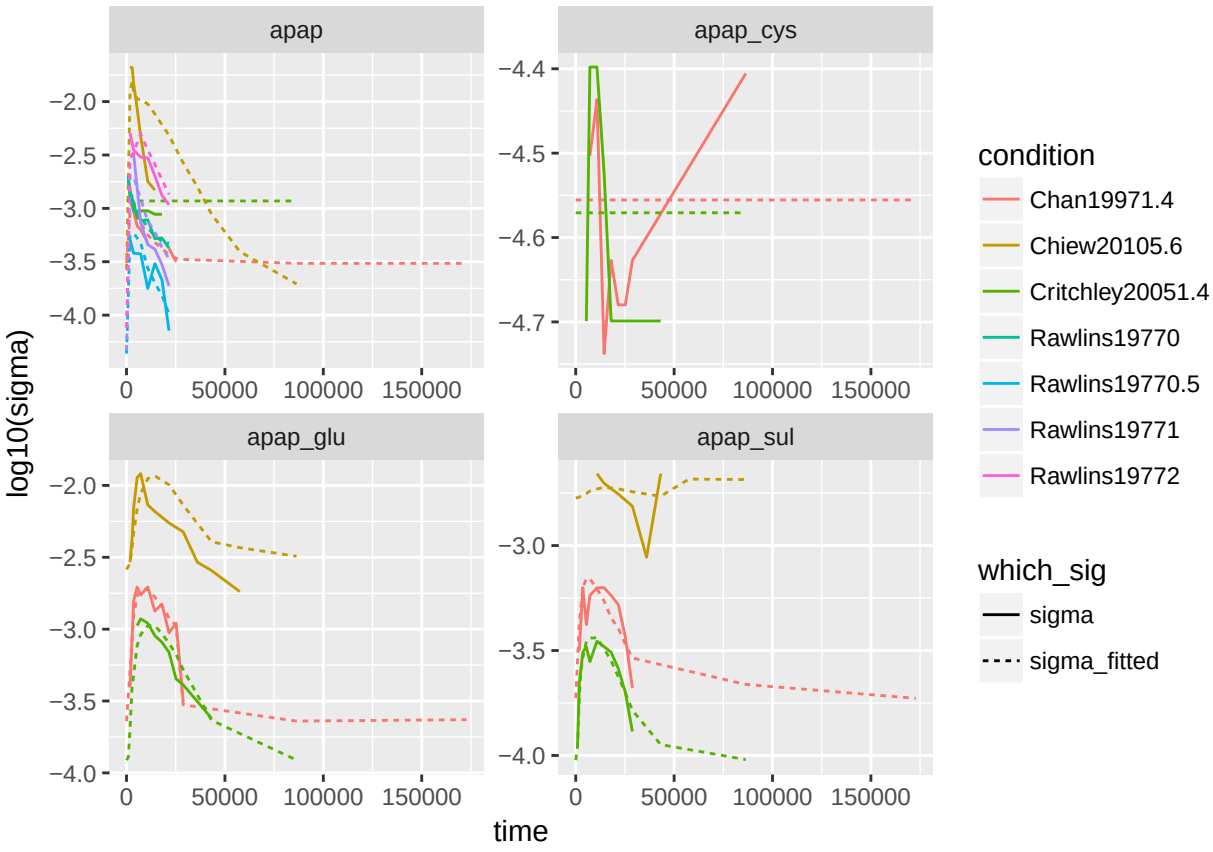



```
myplot <- data_with_errors %>%
  rename(sigma_fitted = sigma) %>%
  left_join(data) %>%
  gather("which_sig", "sigma", sigma, sigma_fitted) %>%
  mutate(condition = paste0(study, D_apap)) %>%
  ggplot(aes(x = time,y = log10(sigma))) +
  geom_line(aes(color = condition, linetype = which_sig)) +
  # geom_point(aes(color = condition, shape = which_sig))+
  facet_wrap("name", scales = "free")
```

```
## Joining, by = c("study", "n", "time", "name", "value", "D_apap", "Ave_apap")
```

```
# myplot %>% plotly::ggplotly()
myplot
```

```
## Warning: Removed 12 rows containing missing values (geom_path).
```


apap
apap_cys
apap_glu
apap_sul
log10(sigma)
time
−2.0
−2.5
−3.0
−3.5
−4.0
−4.4
−4.5
−4.6
−4.7
0
50000
100000
150000
condition
Chan19971.4
Chiew20105.6
Critchley20051.4
Rawlins19770
Rawlins19770.5
Rawlins19771
Rawlins19772
which_sig
sigma
sigma_fitted