2025 National Taiwan University - Population Pharmacokinetics workshop

1 Load Packages

```
library(renv)
```

```
.
. Attaching package: 'renv'
```

```
. The following objects are masked from 'package:stats':
.
.     embed, update
```

```
. The following objects are masked from 'package:utils':
.
.     history, upgrade
```

```
. The following objects are masked from 'package:base':
.
.     autoload, load, remove, use
```

```
library(tidyverse)
```

```
. ── Attaching core tidyverse packages ──────────────────────── tidyverse 2.0.0 ──
. ✔ dplyr     1.1.4     ✔ readr     2.1.5
. ✔ forcats   1.0.0     ✔ stringr   1.5.1
. ✔ ggplot2   3.5.2     ✔ tibble    3.2.1
. ✔ lubridate 1.9.4     ✔ tidyr     1.3.1
. ✔ purrr     1.0.4
```

```
. ── Conflicts ────────────────────────────────────────── tidyverse_conflicts() ──
. ✖ dplyr::filter() masks stats::filter()
. ✖ dplyr::lag()    masks stats::lag()
. ✖ purrr::modify() masks renv::modify()
. ℹ Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts t
o become errors
```

```
library(ggplot2)
library(nlmixr2)
```

```
. Loading required package: nlmixr2data
```

```
library(xpose4)
```

```
. Loading required package: lattice
```

```
library(xpose.nlmixr2)
```

```
. Loading required package: xpose
.
. Attaching package: 'xpose'
.
. The following object is masked from 'package:stats':
.
.     filter
```

```
library(rxode2)
```

```
. rxode2 3.0.4 using 1 threads (see ?getRxThreads)
.   no cache: create with `rxCreateCache()`
. ========================================
. rxode2 has not detected OpenMP support and will run in single-threaded mode
. This is a Mac. Please read https://mac.r-project.org/openmp/
. ========================================
```

```
library(gridExtra)
```

```
.
. Attaching package: 'gridExtra'
.
. The following object is masked from 'package:dplyr':
.
.     combine
```

```
library(ggPMX)
```

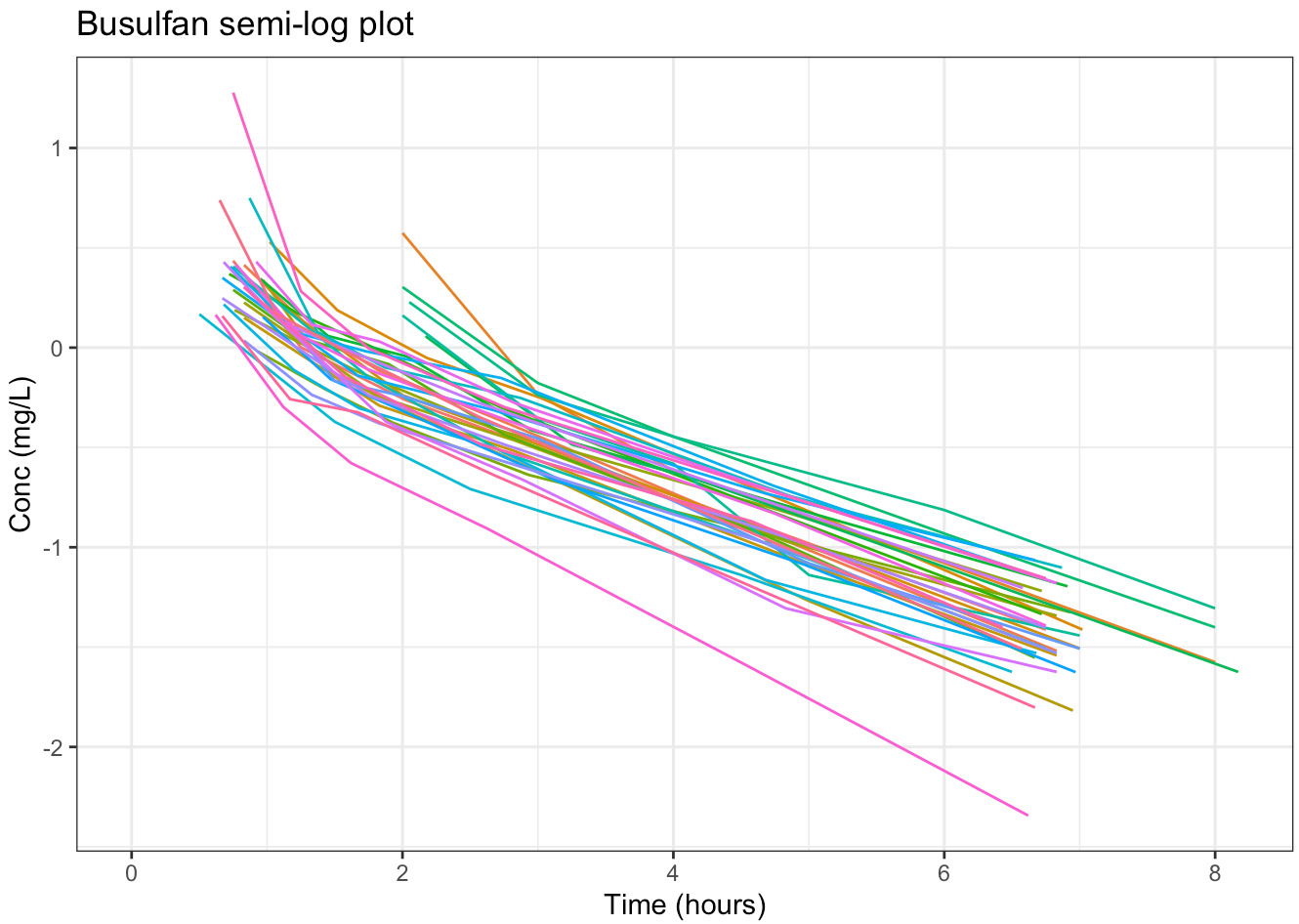
```
. Registered S3 method overwritten by 'GGally':
.   method from
.   +.gg   ggplot2
.
. Attaching package: 'ggPMX'
.
. The following object is masked from 'package:xpose':
.
.     get_data
```

```
library(ggpubr)
```

2 Data exploration

```
# Import busulfan two compartment dataset
busulfan_dataset <- read.csv("dataset/busulfan_Test_Dose.csv", na.strings = ".")

# Plasma drug concentration decline in two phases shown in semi-log plot
ggplot(busulfan_dataset, aes(TIME/60, log(DV), group = ID, color = as.factor(ID))) +
  geom_line() +
  theme_bw() +
  labs(title = "Busulfan semi-log plot", x = "Time (hours)", y = "Conc (mg/L)") +
  theme(legend.position = "blank")
```



3 Showcase 1. 1-cmt vs 2-cmt

3.1 Fitting with 1-cmt vs 2-cmt

```
# One compartment model structure
busulfan_1cmt_base_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(5)
    tvv1  <- log(50)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0322
    eta_v1  ~ 0.0222

    # Residual variability
    add.error <-  0.0955
  })

  model({
    # Individual value
    cl <- exp(tvcl + eta_cl)
    v1 <- exp(tvv1 + eta_v1)

    # Conversion
    k10 <- cl / v1

    # ODEs
    d / dt(central) = -k10 * central

    # Concentration
    cp = central / v1

    # Error model
    IPRED = cp
    IPRED ~ add(add.error)
  })
}

# Two compartment model structure
busulfan_2cmt_base_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(0.187)
    tvv1  <- log(29)
    tvq   <- log(0.41)
    tvv2  <- log(17.3)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0222
    eta_v1  ~ 0.0222
    eta_v2  ~ 0.0241

    # Residual variability
```

```
    prop.err <-  0.0955
  })

  model({
    # Individual parameters
    cl <- exp(tvcl + eta_cl)
    v1 <- exp(tvv1 + eta_v1)
    q  <- exp(tvq)
    v2 <- exp(tvv2 + eta_v2)

    # Conversion
    k10 <- cl / v1
    k12 <- q / v1
    k21 <- q / v2

    # ODEs
    d / dt(central) = -k10 * central - k12 * central + k21 * peripheral
    d / dt(peripheral) = -k21 * peripheral + k12 * central

    # Concentration
    cp = central / v1

    # Error model
    IPRED = cp
    IPRED ~ prop(prop.err)
  })
}

# 1 compartment model fitting
one_cmt_pk_fit <- nlmixr2(
  busulfan_1cmt_base_model,
  busulfan_dataset,
  "focei",
  table = list(cwres = TRUE)
)
```

```
. ℹ parameter labels from comments are typically ignored in non-interactive mode
```

```
. ℹ Need to run with the source intact to parse comments
```

```
. → loading into symengine environment...
```

```
. → pruning branches (`if`/`else`) of full model...
```

```
. ✔ done
```

```
. → calculate jacobian
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → calculate sensitivities
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → calculate ∂(f)/∂(η)
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → calculate ∂(R²)/∂(η)
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → finding duplicate expressions in inner model...
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → optimizing duplicate expressions in inner model...
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → finding duplicate expressions in EBE model...
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → optimizing duplicate expressions in EBE model...
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → compiling inner model...
```

```
. using C compiler: 'Apple clang version 16.0.0 (clang-1600.0.26.6)'
. using SDK: 'MacOSX15.2.sdk'
```

```
. ✔ done
```

```
. → finding duplicate expressions in FD model...
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → optimizing duplicate expressions in FD model...
```

```
. [====|====|====|====|====|====|====|====|====|====] 0:00:00
```

```
. → compiling EBE model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. → compiling events FD model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. Key: U: Unscaled Parameters; X: Back-transformed parameters; G: Gill difference gradie
nt approximation
. F: Forward difference gradient approximation
. C: Central difference gradient approximation
. M: Mixed forward and central difference gradient approximation
. Unscaled parameters for Omegas=chol(solve(omega));
. Diagonals are transformed, as specified by foceiControl(diagXform=)
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    #| Objective Fun |      tvcl |      tvv1 | add.error |        o1 |
. |.....................|        o2 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    1|     7978.9543 |   -0.2066 |     1.000 |    -1.000 |    0.1870 |
. |.....................|    0.3076 |...........|...........|...........|
. |    U|     7978.9543 |     1.609 |     3.912 |   0.09550 |     2.361 |
. |.....................|     2.591 |...........|...........|...........|
. |    X|     7978.9543 |     5.000 |     50.00 |   0.09550 |     2.361 |
. |.....................|     2.591 |...........|...........|...........|
. |    G|    Gill Diff. |     4507. |     908.1 |    -3446. |     3563. |
. |.....................|     144.5 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    2|     3101.1849 |   -0.8731 |    0.8657 |   -0.4904 |   -0.3399 |
. |.....................|    0.2862 |...........|...........|...........|
. |    U|     3101.1849 |    0.9429 |     3.778 |    0.1198 |     2.137 |
. |.....................|     2.582 |...........|...........|...........|
. |    X|     3101.1849 |     2.568 |     43.72 |    0.1198 |     2.137 |
. |.....................|     2.582 |...........|...........|...........|
. |    F| Forward Diff. |     2652. |     649.3 |    -924.1 |     1890. |
. |.....................|     81.44 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    3|     687.05929 |    -1.642 |    0.6774 |   -0.2224 |   -0.8880 |
. |.....................|    0.2626 |...........|...........|...........|
. |    U|     687.05929 |    0.1737 |     3.589 |    0.1326 |     1.905 |
. |.....................|     2.573 |...........|...........|...........|
. |    X|     687.05929 |     1.190 |     36.21 |    0.1326 |     1.905 |
. |.....................|     2.573 |...........|...........|...........|
. |    F| Forward Diff. |     1288. |     264.1 |    -195.3 |     775.7 |
. |.....................|     36.90 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    4|    -243.74462 |    -2.556 |    0.5704 |   -0.3658 |    -1.252 |
. |.....................|    0.2399 |...........|...........|...........|
. |    U|    -243.74462 |   -0.7401 |     3.482 |    0.1258 |     1.751 |
. |.....................|     2.565 |...........|...........|...........|
. |    X|    -243.74462 |    0.4771 |     32.54 |    0.1258 |     1.751 |
. |.....................|     2.565 |...........|...........|...........|
. |    F| Forward Diff. |     470.5 |    -50.96 |    -51.75 |     143.8 |
. |.....................|     32.24 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    5|    -287.43862 |    -3.424 |     1.042 |   -0.2903 |    -1.171 |
. |.....................|    0.1312 |...........|...........|...........|
. |    U|    -287.43862 |    -1.608 |     3.954 |    0.1294 |     1.785 |
. |.....................|     2.523 |...........|...........|...........|
. |    X|    -287.43862 |    0.2002 |     52.15 |    0.1294 |     1.785 |
```

```
. |.....................|     2.523 |.....|.....|.....|
. |    F| Forward Diff. |     23.22 |     777.3 |    -57.15 |    -13.71 |
. |.....................|     100.8 |.....|.....|.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    6|    -153.84500 |    -3.629 |   0.08971 |   -0.1955 |    -1.067 |
. |.....................|  -0.04521 |.....|.....|.....|
. |    U|      -153.845 |    -1.813 |     3.002 |    0.1339 |     1.830 |
. |.....................|     2.454 |.....|.....|.....|
. |    X|      -153.845 |    0.1631 |     20.12 |    0.1339 |     1.830 |
. |.....................|     2.454 |.....|.....|.....|
. |    7|    -447.43888 |    -3.437 |    0.6209 |   -0.2594 |    -1.164 |
. |.....................|   0.07662 |.....|.....|.....|
. |    U|    -447.43888 |    -1.621 |     3.533 |    0.1309 |     1.788 |
. |.....................|     2.502 |.....|.....|.....|
. |    X|    -447.43888 |    0.1977 |     34.22 |    0.1309 |     1.788 |
. |.....................|     2.502 |.....|.....|.....|
. |    F| Forward Diff. |    -30.64 |    -31.69 |    -12.78 |    -13.32 |
. |.....................|     31.19 |.....|.....|.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    8|    -450.66469 |    -3.263 |    0.7010 |   -0.1408 |    -1.183 |
. |.....................|   -0.2846 |.....|.....|.....|
. |    U|    -450.66469 |    -1.447 |     3.613 |    0.1365 |     1.780 |
. |.....................|     2.362 |.....|.....|.....|
. |    X|    -450.66469 |    0.2353 |     37.08 |    0.1365 |     1.780 |
. |.....................|     2.362 |.....|.....|.....|
. |    F| Forward Diff. |     79.99 |     111.8 |    -2.235 |    -10.41 |
. |.....................|     27.34 |.....|.....|.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    9|    -467.23936 |    -3.450 |    0.6550 |  -0.05368 |    -1.049 |
. |.....................|   -0.6296 |.....|.....|.....|
. |    U|    -467.23936 |    -1.634 |     3.567 |    0.1407 |     1.837 |
. |.....................|     2.229 |.....|.....|.....|
. |    X|    -467.23936 |    0.1952 |     35.41 |    0.1407 |     1.837 |
. |.....................|     2.229 |.....|.....|.....|
. |    F| Forward Diff. |    -35.65 |     15.08 |     7.287 |    -12.37 |
. |.....................|     20.17 |.....|.....|.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   10|    -463.81837 |    -3.222 |    0.5689 |   -0.1992 |   -0.9364 |
. |.....................|   -0.9271 |.....|.....|.....|
. |    U|    -463.81837 |    -1.406 |     3.481 |    0.1337 |     1.885 |
. |.....................|     2.114 |.....|.....|.....|
. |    X|    -463.81837 |    0.2451 |     32.49 |    0.1337 |     1.885 |
. |.....................|     2.114 |.....|.....|.....|
. |   11|    -467.87088 |    -3.311 |    0.5963 |  -0.08203 |    -1.001 |
. |.....................|   -0.7081 |.....|.....|.....|
. |    U|    -467.87088 |    -1.495 |     3.508 |    0.1393 |     1.857 |
. |.....................|     2.199 |.....|.....|.....|
. |    X|    -467.87088 |    0.2243 |     33.39 |    0.1393 |     1.857 |
. |.....................|     2.199 |.....|.....|.....|
. |    F| Forward Diff. |     49.76 |    -47.24 |     5.839 |    -11.03 |
. |.....................|     18.97 |.....|.....|.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
```

```
. |   12|    -472.64316 |    -3.381 |    0.6844 |   -0.1021 |   -0.9468 |
. |.....................|   -0.8346 |...........|...........|...........|
. |    U|    -472.64316 |    -1.565 |     3.596 |    0.1384 |     1.880 |
. |.....................|     2.150 |...........|...........|...........|
. |    X|    -472.64316 |    0.2092 |     36.47 |    0.1384 |     1.880 |
. |.....................|     2.150 |...........|...........|...........|
. |    F| Forward Diff. |     12.09 |     53.21 |     5.686 |    -11.81 |
. |.....................|     17.95 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   13|    -476.76920 |    -3.383 |    0.6159 |   -0.1539 |   -0.8884 |
. |.....................|   -0.9801 |...........|...........|...........|
. |    U|     -476.7692 |    -1.566 |     3.528 |    0.1359 |     1.905 |
. |.....................|     2.094 |...........|...........|...........|
. |    X|     -476.7692 |    0.2088 |     34.05 |    0.1359 |     1.905 |
. |.....................|     2.094 |...........|...........|...........|
. |    F| Forward Diff. |     6.042 |    -26.17 |     3.803 |    -11.24 |
. |.....................|     14.95 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   14|    -479.68632 |    -3.369 |    0.6593 |   -0.1715 |   -0.8118 |
. |.....................|    -1.134 |...........|...........|...........|
. |    U|    -479.68632 |    -1.553 |     3.571 |    0.1351 |     1.938 |
. |.....................|     2.034 |...........|...........|...........|
. |    X|    -479.68632 |    0.2117 |     35.56 |    0.1351 |     1.938 |
. |.....................|     2.034 |...........|...........|...........|
. |    F| Forward Diff. |     20.97 |     19.99 |     3.071 |    -10.25 |
. |.....................|     12.35 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   15|    -482.24525 |    -3.377 |    0.6143 |   -0.1994 |   -0.7115 |
. |.....................|    -1.272 |...........|...........|...........|
. |    U|    -482.24525 |    -1.561 |     3.526 |    0.1337 |     1.980 |
. |.....................|     1.981 |...........|...........|...........|
. |    X|    -482.24525 |    0.2099 |     34.00 |    0.1337 |     1.980 |
. |.....................|     1.981 |...........|...........|...........|
. |    F| Forward Diff. |     12.87 |    -23.92 |     1.852 |    -9.253 |
. |.....................|     9.845 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   16|    -485.79465 |    -3.391 |    0.6449 |   -0.2738 |   -0.3716 |
. |.....................|    -1.347 |...........|...........|...........|
. |    U|    -485.79465 |    -1.575 |     3.557 |    0.1302 |     2.124 |
. |.....................|     1.952 |...........|...........|...........|
. |    X|    -485.79465 |    0.2070 |     35.06 |    0.1302 |     2.124 |
. |.....................|     1.952 |...........|...........|...........|
. |    F| Forward Diff. |     6.255 |     3.138 |    -3.755 |    -5.504 |
. |.....................|     8.865 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   17|    -487.71033 |    -3.402 |    0.6265 |   -0.1076 |   -0.1036 |
. |.....................|    -1.514 |...........|...........|...........|
. |    U|    -487.71033 |    -1.586 |     3.539 |    0.1381 |     2.238 |
. |.....................|     1.887 |...........|...........|...........|
. |    X|    -487.71033 |    0.2048 |     34.42 |    0.1381 |     2.238 |
. |.....................|     1.887 |...........|...........|...........|
. |    F| Forward Diff. |    -5.895 |    -13.68 |     7.446 |    -3.618 |
```

```
. |                  |     5.476 |           |           |           |           |
. |-----+------------+-----------+-----------+-----------+-----------|
. |   18|    -484.99057 |    -3.315 |    0.6461 |   -0.1425 | -0.003931 |
. |                  |    -1.844 |           |           |           |
. |    U|    -484.99057 |    -1.498 |     3.558 |    0.1364 |     2.280 |
. |                  |     1.760 |           |           |           |
. |    X|    -484.99057 |    0.2235 |     35.10 |    0.1364 |     2.280 |
. |                  |     1.760 |           |           |           |
. |   19|    -487.86213 |    -3.371 |    0.6656 |   -0.1332 |  -0.07615 |
. |                  |    -1.588 |           |           |           |
. |    U|    -487.86213 |    -1.555 |     3.578 |    0.1369 |     2.249 |
. |                  |     1.859 |           |           |           |
. |    X|    -487.86213 |    0.2112 |     35.79 |    0.1369 |     2.249 |
. |                  |     1.859 |           |           |           |
. |    F| Forward Diff. |     33.34 |     18.48 |     5.590 |    -3.130 |
. |                  |     4.074 |           |           |           |
. |-----+------------+-----------+-----------+-----------+-----------|
. |   20|    -488.74314 |    -3.408 |    0.6502 |   -0.1788 |  -0.09404 |
. |                  |    -1.661 |           |           |           |
. |    U|    -488.74314 |    -1.592 |     3.562 |    0.1347 |     2.242 |
. |                  |     1.831 |           |           |           |
. |    X|    -488.74314 |    0.2035 |     35.24 |    0.1347 |     2.242 |
. |                  |     1.831 |           |           |           |
. |    F| Forward Diff. |    -10.07 |     3.778 |     3.058 |    -3.538 |
. |                  |     2.491 |           |           |           |
. |-----+------------+-----------+-----------+-----------+-----------|
. |   21|    -488.98772 |    -3.387 |    0.6262 |   -0.1896 |  -0.04325 |
. |                  |    -1.736 |           |           |           |
. |    U|    -488.98772 |    -1.571 |     3.538 |    0.1342 |     2.263 |
. |                  |     1.802 |           |           |           |
. |    X|    -488.98772 |    0.2079 |     34.41 |    0.1342 |     2.263 |
. |                  |     1.802 |           |           |           |
. |    F| Forward Diff. |     13.35 |    -10.88 |     2.287 |    -3.114 |
. |                  |    0.8868 |           |           |           |
. |-----+------------+-----------+-----------+-----------+-----------|
. |   22|    -489.40513 |    -3.392 |    0.6418 |   -0.2295 |   0.04124 |
. |                  |    -1.755 |           |           |           |
. |    U|    -489.40513 |    -1.576 |     3.554 |    0.1323 |     2.299 |
. |                  |     1.794 |           |           |           |
. |    X|    -489.40513 |    0.2067 |     34.95 |    0.1323 |     2.299 |
. |                  |     1.794 |           |           |           |
. |    F| Forward Diff. |     8.814 |   -0.7967 |   -0.7533 |    -2.419 |
. |                  |    0.5717 |           |           |           |
. |-----+------------+-----------+-----------+-----------+-----------|
. |   23|    -489.53028 |    -3.408 |    0.6414 |   -0.2162 |    0.1324 |
. |                  |    -1.730 |           |           |           |
. |    U|    -489.53028 |    -1.592 |     3.553 |    0.1329 |     2.338 |
. |                  |     1.804 |           |           |           |
. |    X|    -489.53028 |    0.2035 |     34.93 |    0.1329 |     2.338 |
. |                  |     1.804 |           |           |           |
. |    F| Forward Diff. |    -10.70 |    -2.479 |  -0.04722 |    -1.837 |
. |                  |     1.257 |           |           |           |
```

```
. |-----+--------------+----------+----------+----------+----------|
. |   24|    -489.71800 |    -3.403 |    0.6423 |   -0.2091 |    0.2283 |
. |.....................|    -1.721 |..........|..........|..........|
. |    U|      -489.718 |    -1.587 |     3.554 |    0.1333 |     2.378 |
. |.....................|     1.808 |..........|..........|..........|
. |    X|      -489.718 |    0.2046 |     34.96 |    0.1333 |     2.378 |
. |.....................|     1.808 |..........|..........|..........|
. |   25|    -489.81628 |    -3.395 |    0.6433 |   -0.1929 |    0.4439 |
. |.....................|    -1.699 |..........|..........|..........|
. |    U|    -489.81628 |    -1.579 |     3.555 |    0.1340 |     2.469 |
. |.....................|     1.816 |..........|..........|..........|
. |    X|    -489.81628 |    0.2061 |     35.00 |    0.1340 |     2.469 |
. |.....................|     1.816 |..........|..........|..........|
. |    F| Forward Diff. |     7.535 |   -0.2361 |    0.3679 |  -0.01366 |
. |.....................|     2.198 |..........|..........|..........|
. |-----+--------------+----------+----------+----------+----------|
. |   26|    -489.62850 |    -3.413 |    0.6501 |   -0.1992 |    0.5306 |
. |.....................|    -1.916 |..........|..........|..........|
. |    U|     -489.6285 |    -1.597 |     3.562 |    0.1337 |     2.506 |
. |.....................|     1.732 |..........|..........|..........|
. |    X|     -489.6285 |    0.2025 |     35.24 |    0.1337 |     2.506 |
. |.....................|     1.732 |..........|..........|..........|
. |   27|    -489.92511 |    -3.398 |    0.6455 |   -0.1933 |    0.4763 |
. |.....................|    -1.783 |..........|..........|..........|
. |    U|    -489.92511 |    -1.582 |     3.557 |    0.1340 |     2.483 |
. |.....................|     1.784 |..........|..........|..........|
. |    X|    -489.92511 |    0.2056 |     35.07 |    0.1340 |     2.483 |
. |.....................|     1.784 |..........|..........|..........|
. |    F| Forward Diff. |     4.480 |    0.7810 |    0.2832 |   0.04761 |
. |.....................|    0.4054 |..........|..........|..........|
. |-----+--------------+----------+----------+----------+----------|
. |   28|    -489.92380 |    -3.401 |    0.6442 |   -0.2000 |    0.4719 |
. |.....................|    -1.801 |..........|..........|..........|
. |    U|     -489.9238 |    -1.585 |     3.556 |    0.1337 |     2.481 |
. |.....................|     1.777 |..........|..........|..........|
. |    X|     -489.9238 |    0.2049 |     35.03 |    0.1337 |     2.481 |
. |.....................|     1.777 |..........|..........|..........|
. |   29|    -489.92511 |    -3.398 |    0.6455 |   -0.1933 |    0.4763 |
. |.....................|    -1.783 |..........|..........|..........|
. |    U|    -489.92511 |    -1.582 |     3.557 |    0.1340 |     2.483 |
. |.....................|     1.784 |..........|..........|..........|
. |    X|    -489.92511 |    0.2056 |     35.07 |    0.1340 |     2.483 |
. |.....................|     1.784 |..........|..........|..........|
. calculating covariance matrix
. done
```

```
. → Calculating residuals/tables
. ✔ done
```

```
. → compress origData in nlmixr2 object, save 13504
```

```
. → compress parHistData in nlmixr2 object, save 3840
```

```
# 2 compartment model fitting
two_cmt_pk_fit <- nlmixr2(
  busulfan_2cmt_base_model,
  busulfan_dataset,
  "focei",
  table = list(cwres = TRUE)
)
```

```
. ℹ parameter labels from comments are typically ignored in non-interactive mode
```

```
. ℹ Need to run with the source intact to parse comments
```

```
. → loading into symengine environment...
```

```
. → pruning branches (`if`/`else`) of full model...
```

```
. ✔ done
```

```
. → calculate jacobian
```

```
. → calculate sensitivities
```

```
. → calculate ∂(f)/∂(η)
```

```
. → calculate ∂(R²)/∂(η)
```

```
. → finding duplicate expressions in inner model...
```

```
. → optimizing duplicate expressions in inner model...
```

```
. → finding duplicate expressions in EBE model...
```

```
. → optimizing duplicate expressions in EBE model...
```

```
. → compiling inner model...
```

```
. using C compiler: 'Apple clang version 16.0.0 (clang-1600.0.26.6)'
. using SDK: 'MacOSX15.2.sdk'
```

```
. ✔ done
```

```
. → finding duplicate expressions in FD model...
```

```
. → optimizing duplicate expressions in FD model...
```

```
. → compiling EBE model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. → compiling events FD model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. Key: U: Unscaled Parameters; X: Back-transformed parameters; G: Gill difference gradie
nt approximation
. F: Forward difference gradient approximation
. C: Central difference gradient approximation
. M: Mixed forward and central difference gradient approximation
. Unscaled parameters for Omegas=chol(solve(omega));
. Diagonals are transformed, as specified by foceiControl(diagXform=)
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    #| Objective Fun |      tvcl |      tvv1 |       tvq |      tvv2 |
. |.....................|  prop.err |        o1 |        o2 |        o3 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    1|    -687.19730 |    -1.000 |     1.000 |   -0.6887 |    0.7952 |
. |.....................|   -0.2973 |    0.6921 |    0.6921 |    0.6712 |
. |    U|     -687.1973 |    -1.677 |     3.367 |   -0.8916 |     2.851 |
. |.....................|   0.09550 |     2.591 |     2.591 |     2.538 |
. |    X|     -687.1973 |    0.1870 |     29.00 |    0.4100 |     17.30 |
. |.....................|   0.09550 |     2.591 |     2.591 |     2.538 |
. |    G|    Gill Diff. |     117.4 |     352.9 |     67.30 |     176.3 |
. |.....................|     4.447 |     19.22 |     48.61 |     8.219 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    2|    -136.30715 |    -1.279 |    0.1606 |   -0.8488 |    0.3757 |
. |.....................|   -0.3079 |    0.6463 |    0.5764 |    0.6516 |
. |    U|    -136.30715 |    -1.956 |     2.528 |    -1.052 |     2.431 |
. |.....................|   0.09499 |     2.573 |     2.546 |     2.530 |
. |    X|    -136.30715 |    0.1414 |     12.53 |    0.3493 |     11.37 |
. |.....................|   0.09499 |     2.573 |     2.546 |     2.530 |
. |    3|    -727.55825 |    -1.060 |    0.8183 |   -0.7234 |    0.7044 |
. |.....................|   -0.2996 |    0.6822 |    0.6670 |    0.6670 |
. |    U|    -727.55825 |    -1.737 |     3.186 |   -0.9262 |     2.760 |
. |.....................|   0.09539 |     2.587 |     2.581 |     2.536 |
. |    X|    -727.55825 |    0.1760 |     24.18 |    0.3960 |     15.80 |
. |.....................|   0.09539 |     2.587 |     2.581 |     2.536 |
. |    F| Forward Diff. |    -47.71 |    -36.77 |     23.80 |    -19.12 |
. |.....................|     20.27 |     16.73 |     35.26 |     3.864 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    4|    -720.24461 |   -0.9410 |    0.8406 |   -0.8164 |    0.7179 |
. |.....................|   -0.3648 |    0.6242 |    0.5428 |    0.6526 |
. |    U|    -720.24461 |    -1.618 |     3.208 |    -1.019 |     2.773 |
. |.....................|   0.09228 |     2.564 |     2.533 |     2.531 |
. |    X|    -720.24461 |    0.1984 |     24.73 |    0.3609 |     16.01 |
. |.....................|   0.09228 |     2.564 |     2.533 |     2.531 |
. |    5|    -729.23038 |    -1.017 |    0.8520 |   -0.7451 |    0.7219 |
. |.....................|   -0.3182 |    0.6668 |    0.6348 |    0.6634 |
. |    U|    -729.23038 |    -1.693 |     3.219 |   -0.9480 |     2.777 |
. |.....................|   0.09450 |     2.581 |     2.569 |     2.535 |
. |    X|    -729.23038 |    0.1839 |     25.01 |    0.3875 |     16.08 |
. |.....................|   0.09450 |     2.581 |     2.569 |     2.535 |
. |    F| Forward Diff. |     81.17 |     20.05 |     21.82 |     27.95 |
. |.....................|     20.23 |     17.30 |     36.23 |     3.998 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    6|    -732.81133 |    -1.065 |    0.8553 |   -0.7685 |    0.7093 |
. |.....................|   -0.3406 |    0.6482 |    0.5958 |    0.6592 |
```

```
. |    U|    -732.81133 |    -1.742 |     3.223 |   -0.9714 |     2.765 |
. |.....................|   0.09343 |     2.574 |     2.554 |     2.533 |
. |    X|    -732.81133 |    0.1752 |     25.09 |    0.3786 |     15.88 |
. |.....................|   0.09343 |     2.574 |     2.554 |     2.533 |
. |    F| Forward Diff. |    -59.49 |     17.79 |     25.46 |     15.70 |
. |.....................|     22.60 |     16.97 |     36.85 |     3.751 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    7|    -735.65784 |    -1.024 |    0.8417 |   -0.7936 |    0.6902 |
. |.....................|   -0.3662 |    0.6296 |    0.5559 |    0.6553 |
. |    U|    -735.65784 |    -1.701 |     3.209 |   -0.9965 |     2.746 |
. |.....................|   0.09221 |     2.567 |     2.538 |     2.532 |
. |    X|    -735.65784 |    0.1825 |     24.75 |    0.3692 |     15.58 |
. |.....................|   0.09221 |     2.567 |     2.538 |     2.532 |
. |    F| Forward Diff. |     61.63 |    -31.08 |     14.45 |     1.175 |
. |.....................|     23.32 |     16.75 |     37.62 |     3.515 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    8|    -739.53472 |    -1.055 |    0.8711 |   -0.8119 |    0.6858 |
. |.....................|   -0.3953 |    0.6096 |    0.5111 |    0.6512 |
. |    U|    -739.53472 |    -1.732 |     3.238 |    -1.015 |     2.741 |
. |.....................|   0.09082 |     2.559 |     2.521 |     2.530 |
. |    X|    -739.53472 |    0.1769 |     25.49 |    0.3625 |     15.51 |
. |.....................|   0.09082 |     2.559 |     2.521 |     2.530 |
. |    F| Forward Diff. |    -30.20 |     16.67 |     24.01 |     12.73 |
. |.....................|     24.82 |     16.55 |     38.46 |     3.499 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    9|    -746.23258 |    -1.017 |    0.8756 |   -0.8625 |    0.6667 |
. |.....................|   -0.4662 |    0.5666 |    0.4089 |    0.6430 |
. |    U|    -746.23258 |    -1.694 |     3.243 |    -1.065 |     2.722 |
. |.....................|   0.08744 |     2.542 |     2.481 |     2.527 |
. |    X|    -746.23258 |    0.1839 |     25.61 |    0.3446 |     15.21 |
. |.....................|   0.08744 |     2.542 |     2.481 |     2.527 |
. |    F| Forward Diff. |     82.24 |    -5.377 |     13.50 |     13.99 |
. |.....................|     26.33 |     17.04 |     40.19 |     3.363 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   10|    -760.28519 |    -1.062 |    0.8478 |   -0.9224 |    0.6057 |
. |.....................|   -0.6324 |    0.4871 |    0.2014 |    0.6313 |
. |    U|    -760.28519 |    -1.738 |     3.215 |    -1.125 |     2.661 |
. |.....................|   0.07950 |     2.512 |     2.401 |     2.522 |
. |    X|    -760.28519 |    0.1758 |     24.90 |    0.3245 |     14.31 |
. |.....................|   0.07950 |     2.512 |     2.401 |     2.522 |
. |    F| Forward Diff. |    -37.97 |    -90.51 |     8.400 |    -45.01 |
. |.....................|     28.75 |     16.20 |     44.79 |     3.534 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   11|    -777.34521 |    -1.058 |    0.9369 |   -0.9683 |    0.6228 |
. |.....................|   -0.7929 |    0.4103 |  -0.01093 |    0.6186 |
. |    U|    -777.34521 |    -1.735 |     3.304 |    -1.171 |     2.678 |
. |.....................|   0.07183 |     2.482 |     2.319 |     2.517 |
. |    X|    -777.34521 |    0.1764 |     27.23 |    0.3100 |     14.56 |
. |.....................|   0.07183 |     2.482 |     2.319 |     2.517 |
. |    F| Forward Diff. |    -24.62 |     60.82 |     15.10 |     21.39 |
. |.....................|     22.15 |     15.94 |     44.98 |     4.232 |
. |-----+---------------+-----------+-----------+-----------+-----------|
```

```
. |   12|    -791.89549 |    -1.049 |    0.8649 |   -0.9954 |    0.6014 |
. |.....................|   -0.9410 |    0.3347 |   -0.2409 |    0.6032 |
. |    U|    -791.89549 |    -1.725 |     3.232 |    -1.198 |     2.657 |
. |.....................|   0.06476 |     2.453 |     2.231 |     2.511 |
. |    X|    -791.89549 |    0.1781 |     25.33 |    0.3017 |     14.25 |
. |.....................|   0.06476 |     2.453 |     2.231 |     2.511 |
. |    F| Forward Diff. |     7.281 |    -59.64 |    -13.52 |    -12.83 |
. |.....................|     15.34 |     15.22 |     45.63 |     4.856 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   13|    -804.13218 |    -1.069 |    0.9348 |   -0.9556 |    0.5855 |
. |.....................|    -1.060 |    0.2561 |   -0.4847 |    0.5826 |
. |    U|    -804.13218 |    -1.745 |     3.302 |    -1.158 |     2.641 |
. |.....................|   0.05910 |     2.422 |     2.136 |     2.503 |
. |    X|    -804.13218 |    0.1746 |     27.17 |    0.3140 |     14.03 |
. |.....................|   0.05910 |     2.422 |     2.136 |     2.503 |
. |    F| Forward Diff. |    -47.14 |     52.63 |     21.04 |    -25.17 |
. |.....................|     1.374 |     14.56 |     42.80 |     6.007 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   14|    -813.34314 |    -1.033 |    0.8573 |   -0.9634 |    0.6847 |
. |.....................|    -1.098 |    0.1772 |   -0.7328 |    0.5531 |
. |    U|    -813.34314 |    -1.710 |     3.225 |    -1.166 |     2.740 |
. |.....................|   0.05729 |     2.392 |     2.041 |     2.491 |
. |    X|    -813.34314 |    0.1809 |     25.14 |    0.3115 |     15.49 |
. |.....................|   0.05729 |     2.392 |     2.041 |     2.491 |
. |    F| Forward Diff. |     52.15 |    -19.12 |    -45.01 |     88.77 |
. |.....................|    -3.606 |     13.45 |     37.57 |     6.134 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   15|    -823.11576 |    -1.053 |    0.8292 |   -0.8810 |    0.5741 |
. |.....................|    -1.090 |   0.09631 |   -0.9760 |    0.5178 |
. |    U|    -823.11576 |    -1.730 |     3.197 |    -1.084 |     2.630 |
. |.....................|   0.05764 |     2.361 |     1.947 |     2.478 |
. |    X|    -823.11576 |    0.1773 |     24.45 |    0.3383 |     13.87 |
. |.....................|   0.05764 |     2.361 |     1.947 |     2.478 |
. |    F| Forward Diff. |    -9.040 |    -44.09 |     27.20 |    -89.39 |
. |.....................|     12.41 |     11.42 |     32.75 |     6.460 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   16|    -832.09763 |    -1.095 |    0.8801 |   -0.8851 |    0.6839 |
. |.....................|    -1.111 |   0.01264 |    -1.223 |    0.4709 |
. |    U|    -832.09763 |    -1.772 |     3.247 |    -1.088 |     2.739 |
. |.....................|   0.05666 |     2.328 |     1.851 |     2.459 |
. |    X|    -832.09763 |    0.1701 |     25.72 |    0.3369 |     15.48 |
. |.....................|   0.05666 |     2.328 |     1.851 |     2.459 |
. |    F| Forward Diff. |    -84.87 |     23.16 |    -11.54 |     53.76 |
. |.....................|     9.641 |     11.19 |     25.27 |     4.844 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   17|    -832.09217 |   -0.9543 |    0.8239 |   -0.8498 |    0.6600 |
. |.....................|    -1.144 |  -0.07273 |    -1.450 |    0.4203 |
. |    U|    -832.09217 |    -1.631 |     3.191 |    -1.053 |     2.715 |
. |.....................|   0.05506 |     2.295 |     1.764 |     2.439 |
. |    X|    -832.09217 |    0.1957 |     24.32 |    0.3490 |     15.11 |
. |.....................|   0.05506 |     2.295 |     1.764 |     2.439 |
. |   18|    -833.59484 |   -0.9898 |    0.8474 |   -0.8672 |    0.6321 |
```

```
. |.....................|    -1.127 |  -0.01636 |    -1.297 |    0.4552 |
. |    U|    -833.59484 |    -1.666 |     3.215 |    -1.070 |     2.688 |
. |.....................|   0.05590 |     2.317 |     1.823 |     2.453 |
. |    X|    -833.59484 |    0.1889 |     24.90 |    0.3430 |     14.70 |
. |.....................|   0.05590 |     2.317 |     1.823 |     2.453 |
. |    F| Forward Diff. |     124.7 |    -8.315 |     4.045 |    -13.91 |
. |.....................|     9.862 |     11.93 |     23.44 |     4.997 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   19|    -840.36413 |    -1.067 |    0.8364 |   -0.8692 |    0.6388 |
. |.....................|    -1.174 |  -0.06488 |    -1.399 |    0.4323 |
. |    U|    -840.36413 |    -1.743 |     3.204 |    -1.072 |     2.694 |
. |.....................|   0.05362 |     2.298 |     1.783 |     2.444 |
. |    X|    -840.36413 |    0.1749 |     24.62 |    0.3423 |     14.80 |
. |.....................|   0.05362 |     2.298 |     1.783 |     2.444 |
. |    F| Forward Diff. |    -28.24 |    -10.84 |   -0.4673 |    -11.23 |
. |.....................|    0.2568 |     8.737 |     21.44 |     5.272 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   20|    -842.93827 |    -1.034 |    0.8375 |   -0.8515 |    0.6763 |
. |.....................|    -1.168 |   -0.1163 |    -1.523 |    0.3992 |
. |    U|    -842.93827 |    -1.711 |     3.205 |    -1.054 |     2.732 |
. |.....................|   0.05391 |     2.279 |     1.736 |     2.431 |
. |    X|    -842.93827 |    0.1807 |     24.65 |    0.3484 |     15.36 |
. |.....................|   0.05391 |     2.279 |     1.736 |     2.431 |
. |    F| Forward Diff. |     36.93 |    -1.845 |    -12.19 |     32.27 |
. |.....................|     2.757 |     8.006 |     17.87 |     4.705 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   21|    -844.69654 |    -1.057 |    0.8338 |   -0.8225 |    0.6490 |
. |.....................|    -1.178 |   -0.2286 |    -1.531 |    0.3245 |
. |    U|    -844.69654 |    -1.734 |     3.201 |    -1.025 |     2.705 |
. |.....................|   0.05343 |     2.235 |     1.732 |     2.401 |
. |    X|    -844.69654 |    0.1766 |     24.56 |    0.3587 |     14.95 |
. |.....................|   0.05343 |     2.235 |     1.732 |     2.401 |
. |    F| Forward Diff. |    -9.284 |    -3.388 |     13.31 |    -16.08 |
. |.....................|     3.269 |     5.511 |     18.55 |     4.502 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   22|    -845.29467 |    -1.052 |    0.8398 |   -0.8985 |    0.6330 |
. |.....................|    -1.206 |   -0.3189 |    -1.531 |    0.2420 |
. |    U|    -845.29467 |    -1.728 |     3.207 |    -1.101 |     2.689 |
. |.....................|   0.05212 |     2.200 |     1.732 |     2.369 |
. |    X|    -845.29467 |    0.1776 |     24.71 |    0.3324 |     14.71 |
. |.....................|   0.05212 |     2.200 |     1.732 |     2.369 |
. |    F| Forward Diff. |     2.681 |    -10.97 |    -15.65 |   -0.4906 |
. |.....................|    -6.394 |     3.832 |     17.19 |     4.570 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   23|    -846.01453 |    -1.057 |    0.8688 |   -0.8580 |    0.6516 |
. |.....................|    -1.157 |   -0.3962 |    -1.531 |    0.1393 |
. |    U|    -846.01453 |    -1.734 |     3.236 |    -1.061 |     2.707 |
. |.....................|   0.05446 |     2.171 |     1.732 |     2.328 |
. |    X|    -846.01453 |    0.1767 |     25.43 |    0.3461 |     14.99 |
. |.....................|   0.05446 |     2.171 |     1.732 |     2.328 |
. |    F| Forward Diff. |    -7.114 |     13.30 |     1.796 |     6.863 |
. |.....................|     9.889 |     2.311 |     17.29 |     3.183 |
```

```
. |-----+---------------+----------+----------+----------+----------|
. |   24|    -845.74058 |   -1.033 |   0.8271 |  -0.8063 |   0.6565 |
. |.....................|   -1.241 |  -0.4396 |   -1.531 |  0.05064 |
. |    U|    -845.74058 |   -1.710 |    3.194 |   -1.009 |    2.712 |
. |.....................|  0.05044 |    2.154 |    1.732 |    2.294 |
. |    X|    -845.74058 |   0.1809 |    24.40 |   0.3645 |    15.06 |
. |.....................|  0.05044 |    2.154 |    1.732 |    2.294 |
. |   25|    -846.20315 |   -1.038 |   0.8333 |  -0.8505 |   0.6389 |
. |.....................|   -1.195 |  -0.4101 |   -1.531 |   0.1139 |
. |    U|    -846.20315 |   -1.714 |    3.201 |   -1.053 |    2.694 |
. |.....................|  0.05265 |    2.165 |    1.732 |    2.318 |
. |    X|    -846.20315 |   0.1801 |    24.55 |   0.3487 |    14.80 |
. |.....................|  0.05265 |    2.165 |    1.732 |    2.318 |
. |    F| Forward Diff. |    22.59 |   -8.160 |    3.586 |   -11.66 |
. |.....................|   0.3361 |    2.172 |    18.19 |    3.449 |
. |-----+---------------+----------+----------+----------+----------|
. |   26|    -846.31100 |   -1.067 |   0.8391 |  -0.8378 |   0.6644 |
. |.....................|   -1.214 |  -0.4221 |   -1.531 |  0.07015 |
. |    U|      -846.311 |   -1.743 |    3.206 |   -1.041 |    2.720 |
. |.....................|  0.05174 |    2.161 |    1.732 |    2.301 |
. |    X|      -846.311 |   0.1750 |    24.69 |   0.3532 |    15.18 |
. |.....................|  0.05174 |    2.161 |    1.732 |    2.301 |
. |    F| Forward Diff. |   -21.05 |   0.2152 |   0.9261 |    13.05 |
. |.....................|   -5.957 |    1.902 |    18.82 |    3.053 |
. |-----+---------------+----------+----------+----------+----------|
. |   27|    -846.78696 |   -1.053 |   0.8421 |  -0.8576 |   0.6493 |
. |.....................|   -1.191 |  -0.4273 |   -1.531 |  0.01784 |
. |    U|    -846.78696 |   -1.730 |    3.209 |   -1.061 |    2.705 |
. |.....................|  0.05285 |    2.159 |    1.732 |    2.281 |
. |    X|    -846.78696 |   0.1773 |    24.76 |   0.3463 |    14.95 |
. |.....................|  0.05285 |    2.159 |    1.732 |    2.281 |
. |    F| Forward Diff. |   -1.221 |   -2.974 |   -1.511 |    3.936 |
. |.....................|    1.936 |    1.681 |    17.91 |    2.648 |
. |-----+---------------+----------+----------+----------+----------|
. |   28|    -845.75853 |   -1.041 |   0.8716 |  -0.8426 |   0.6102 |
. |.....................|   -1.210 |  -0.4440 |   -1.531 | -0.008457 |
. |    U|    -845.75853 |   -1.718 |    3.239 |   -1.046 |    2.666 |
. |.....................|  0.05193 |    2.152 |    1.732 |    2.270 |
. |    X|    -845.75853 |   0.1794 |    25.51 |   0.3515 |    14.38 |
. |.....................|  0.05193 |    2.152 |    1.732 |    2.270 |
. |   29|    -846.81535 |   -1.052 |   0.8463 |  -0.8555 |   0.6437 |
. |.....................|   -1.193 |  -0.4297 |   -1.531 |  0.01407 |
. |    U|    -846.81535 |   -1.728 |    3.214 |   -1.058 |    2.699 |
. |.....................|  0.05272 |    2.158 |    1.732 |    2.279 |
. |    X|    -846.81535 |   0.1776 |    24.87 |   0.3470 |    14.87 |
. |.....................|  0.05272 |    2.158 |    1.732 |    2.279 |
. |    F| Forward Diff. |    1.143 |  -0.4256 |    2.040 |   -2.439 |
. |.....................|    1.300 |    1.648 |    17.95 |    2.714 |
. |-----+---------------+----------+----------+----------+----------|
. |   30|    -846.83234 |   -1.054 |   0.8471 |  -0.8594 |   0.6483 |
. |.....................|   -1.196 |  -0.4328 |   -1.531 |  0.008901 |
. |    U|    -846.83234 |   -1.731 |    3.214 |   -1.062 |    2.704 |
```

```
. |.....................|   0.05260 |     2.156 |     1.732 |     2.277 |
. |    X|    -846.83234 |    0.1772 |     24.89 |    0.3457 |     14.94 |
. |.....................|   0.05260 |     2.156 |     1.732 |     2.277 |
. |    F| Forward Diff. |    -1.885 |   -0.3646 |    -1.317 |     4.266 |
. |.....................|    0.3031 |     1.637 |     17.89 |     2.639 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   31|    -846.88809 |    -1.051 |    0.8470 |   -0.8564 |    0.6441 |
. |.....................|    -1.197 |   -0.4373 |    -1.531 | -0.007871 |
. |    U|    -846.88809 |    -1.728 |     3.214 |    -1.059 |     2.700 |
. |.....................|   0.05253 |     2.155 |     1.732 |     2.270 |
. |    X|    -846.88809 |    0.1777 |     24.89 |    0.3467 |     14.87 |
. |.....................|   0.05253 |     2.155 |     1.732 |     2.270 |
. |    F| Forward Diff. |     2.310 |  -0.03225 |     1.484 |    -1.125 |
. |.....................|    0.2199 |     1.528 |     17.98 |     2.584 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   32|    -846.98063 |    -1.056 |    0.8471 |   -0.8598 |    0.6456 |
. |.....................|    -1.197 |   -0.4448 |    -1.531 |  -0.04340 |
. |    U|    -846.98063 |    -1.732 |     3.214 |    -1.063 |     2.701 |
. |.....................|   0.05253 |     2.152 |     1.732 |     2.256 |
. |    X|    -846.98063 |    0.1769 |     24.89 |    0.3455 |     14.90 |
. |.....................|   0.05253 |     2.152 |     1.732 |     2.256 |
. |   33|    -847.07685 |    -1.056 |    0.8470 |   -0.8604 |    0.6447 |
. |.....................|    -1.196 |   -0.4511 |    -1.531 |  -0.08502 |
. |    U|    -847.07685 |    -1.732 |     3.214 |    -1.063 |     2.700 |
. |.....................|   0.05257 |     2.149 |     1.732 |     2.240 |
. |    X|    -847.07685 |    0.1769 |     24.89 |    0.3453 |     14.88 |
. |.....................|   0.05257 |     2.149 |     1.732 |     2.240 |
. |   34|    -847.25956 |    -1.056 |    0.8469 |   -0.8621 |    0.6423 |
. |.....................|    -1.194 |   -0.4675 |    -1.531 |   -0.1948 |
. |    U|    -847.25956 |    -1.733 |     3.214 |    -1.065 |     2.698 |
. |.....................|   0.05266 |     2.143 |     1.732 |     2.197 |
. |    X|    -847.25956 |    0.1768 |     24.88 |    0.3447 |     14.85 |
. |.....................|   0.05266 |     2.143 |     1.732 |     2.197 |
. |    F| Forward Diff. |    -5.270 |    -1.411 |    0.2231 |    0.5662 |
. |.....................|     2.553 |    0.8642 |     17.79 |     1.124 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   35|    -845.90623 |    -1.028 |    0.8329 |   -0.8166 |    0.6874 |
. |.....................|    -1.240 |   -0.5073 |    -1.531 |   -0.3597 |
. |    U|    -845.90623 |    -1.705 |     3.200 |    -1.019 |     2.743 |
. |.....................|   0.05051 |     2.128 |     1.732 |     2.132 |
. |    X|    -845.90623 |    0.1818 |     24.54 |    0.3608 |     15.53 |
. |.....................|   0.05051 |     2.128 |     1.732 |     2.132 |
. |   36|    -847.25456 |    -1.045 |    0.8480 |   -0.8585 |    0.6454 |
. |.....................|    -1.203 |   -0.4725 |    -1.531 |   -0.2113 |
. |    U|    -847.25456 |    -1.722 |     3.215 |    -1.061 |     2.701 |
. |.....................|   0.05227 |     2.141 |     1.732 |     2.190 |
. |    X|    -847.25456 |    0.1788 |     24.91 |    0.3460 |     14.89 |
. |.....................|   0.05227 |     2.141 |     1.732 |     2.190 |
. |   37|    -847.26396 |    -1.047 |    0.8493 |   -0.8625 |    0.6413 |
. |.....................|    -1.199 |   -0.4690 |    -1.531 |   -0.1967 |
. |    U|    -847.26396 |    -1.724 |     3.217 |    -1.065 |     2.697 |
. |.....................|   0.05245 |     2.142 |     1.732 |     2.196 |
```

```
. |    X|    -847.26396 |    0.1784 |     24.94 |    0.3446 |     14.83 |
. |.....................|   0.05245 |     2.142 |     1.732 |     2.196 |
. |    F| Forward Diff. |     7.890 |    0.1311 |    0.3751 |    0.5495 |
. |.....................|     1.091 |    0.8959 |     17.81 |     1.157 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   38|    -847.29424 |    -1.053 |    0.8483 |   -0.8610 |    0.6428 |
. |.....................|    -1.201 |   -0.4715 |    -1.531 |   -0.2048 |
. |    U|    -847.29424 |    -1.730 |     3.216 |    -1.064 |     2.698 |
. |.....................|   0.05235 |     2.142 |     1.732 |     2.193 |
. |    X|    -847.29424 |    0.1773 |     24.92 |    0.3451 |     14.86 |
. |.....................|   0.05235 |     2.142 |     1.732 |     2.193 |
. |    F| Forward Diff. |    -1.081 | -0.002653 |    0.5785 |     1.309 |
. |.....................|    0.5312 |    0.7976 |     17.90 |     1.086 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   39|    -847.30549 |    -1.051 |    0.8476 |   -0.8612 |    0.6414 |
. |.....................|    -1.203 |   -0.4755 |    -1.531 |   -0.2140 |
. |    U|    -847.30549 |    -1.727 |     3.215 |    -1.064 |     2.697 |
. |.....................|   0.05224 |     2.140 |     1.732 |     2.189 |
. |    X|    -847.30549 |    0.1778 |     24.90 |    0.3451 |     14.83 |
. |.....................|   0.05224 |     2.140 |     1.732 |     2.189 |
. |    F| Forward Diff. |     2.831 |   -0.5475 |    0.7950 |    0.2088 |
. |.....................|   -0.1226 |    0.7231 |     17.93 |     1.044 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   40|    -847.32766 |    -1.052 |    0.8488 |   -0.8605 |    0.6440 |
. |.....................|    -1.205 |   -0.4821 |    -1.531 |   -0.2344 |
. |    U|    -847.32766 |    -1.729 |     3.216 |    -1.063 |     2.700 |
. |.....................|   0.05218 |     2.137 |     1.732 |     2.181 |
. |    X|    -847.32766 |    0.1775 |     24.93 |    0.3453 |     14.87 |
. |.....................|   0.05218 |     2.137 |     1.732 |     2.181 |
. |    F| Forward Diff. |    0.5377 |  -0.05560 |    0.1680 |     2.720 |
. |.....................|   -0.3913 |    0.6200 |     17.96 |    0.8566 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   41|    -847.32727 |    -1.055 |    0.8546 |   -0.8693 |    0.6328 |
. |.....................|    -1.202 |   -0.4887 |    -1.531 |   -0.2476 |
. |    U|    -847.32727 |    -1.732 |     3.222 |    -1.072 |     2.688 |
. |.....................|   0.05232 |     2.135 |     1.732 |     2.176 |
. |    X|    -847.32727 |    0.1770 |     25.07 |    0.3423 |     14.71 |
. |.....................|   0.05232 |     2.135 |     1.732 |     2.176 |
. |   42|    -847.33014 |    -1.054 |    0.8505 |   -0.8633 |    0.6361 |
. |.....................|    -1.203 |   -0.4851 |    -1.531 |   -0.2397 |
. |    U|    -847.33014 |    -1.731 |     3.218 |    -1.066 |     2.692 |
. |.....................|   0.05225 |     2.136 |     1.732 |     2.179 |
. |    X|    -847.33014 |    0.1772 |     24.97 |    0.3443 |     14.76 |
. |.....................|   0.05225 |     2.136 |     1.732 |     2.179 |
. |    F| Forward Diff. |    -1.401 |     1.876 |     2.392 |    -3.360 |
. |.....................|    0.2676 |    0.5276 |     17.86 |    0.9154 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   43|    -847.34744 |    -1.053 |    0.8504 |   -0.8689 |    0.6384 |
. |.....................|    -1.203 |   -0.4884 |    -1.531 |   -0.2479 |
. |    U|    -847.34744 |    -1.730 |     3.218 |    -1.072 |     2.694 |
. |.....................|   0.05225 |     2.135 |     1.732 |     2.176 |
. |    X|    -847.34744 |    0.1773 |     24.97 |    0.3424 |     14.79 |
```

```
. |.....................|   0.05225 |     2.135 |     1.732 |     2.176 |
. |    F| Forward Diff. |   -0.8916 |   -0.3071 |    -1.039 |    0.2173 |
. |.....................|    0.2163 |    0.6378 |     17.76 |    0.8060 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   44|    -847.35487 |    -1.051 |    0.8512 |   -0.8657 |    0.6390 |
. |.....................|    -1.203 |   -0.4963 |    -1.531 |   -0.2538 |
. |    U|    -847.35487 |    -1.727 |     3.219 |    -1.069 |     2.695 |
. |.....................|   0.05226 |     2.132 |     1.732 |     2.174 |
. |    X|    -847.35487 |    0.1778 |     24.99 |    0.3435 |     14.80 |
. |.....................|   0.05226 |     2.132 |     1.732 |     2.174 |
. |    F| Forward Diff. |     2.870 |     1.554 |    0.2748 |   -0.1228 |
. |.....................|    0.2364 |    0.3035 |     17.79 |    0.7434 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   45|    -847.36229 |    -1.052 |    0.8485 |   -0.8644 |    0.6386 |
. |.....................|    -1.204 |   -0.4966 |    -1.531 |   -0.2639 |
. |    U|    -847.36229 |    -1.729 |     3.216 |    -1.067 |     2.694 |
. |.....................|   0.05221 |     2.132 |     1.732 |     2.170 |
. |    X|    -847.36229 |    0.1775 |     24.92 |    0.3439 |     14.79 |
. |.....................|   0.05221 |     2.132 |     1.732 |     2.170 |
. |    F| Forward Diff. |    0.2997 |  -0.09757 |    0.5922 |   -0.9674 |
. |.....................|    0.1146 |    0.3288 |     17.86 |    0.6575 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   46|    -847.36230 |    -1.052 |    0.8485 |   -0.8644 |    0.6386 |
. |.....................|    -1.204 |   -0.4966 |    -1.531 |   -0.2639 |
. |    U|     -847.3623 |    -1.729 |     3.216 |    -1.067 |     2.694 |
. |.....................|   0.05221 |     2.132 |     1.732 |     2.170 |
. |    X|     -847.3623 |    0.1775 |     24.92 |    0.3439 |     14.79 |
. |.....................|   0.05221 |     2.132 |     1.732 |     2.170 |
. calculating covariance matrix
. done
```

```
. → Calculating residuals/tables
. ✔ done
```

```
. → compress origData in nlmixr2 object, save 13504
```

```
. → compress parHistData in nlmixr2 object, save 6616
```

3.2 Model diagnostics - Objective Function Values

```
# Extract Objective Functions
one_cmt_objDf <- one_cmt_pk_fit$objDf
two_cmt_objDf <- two_cmt_pk_fit$objDf


compare_obj <- rbind(one_cmt_objDf, two_cmt_objDf)
rownames(compare_obj) <- c("1-cmt", "2-cmt")
compare_obj[,1:4]
```

```
.            OBJF       AIC        BIC Log-likelihood
. 1-cmt -489.9251 -110.5118  -93.99529       60.25591
. 2-cmt -847.3623 -461.9490 -435.52256      238.97450
```

3.3 Model diagnostics - Goodness of Fit (GOF)

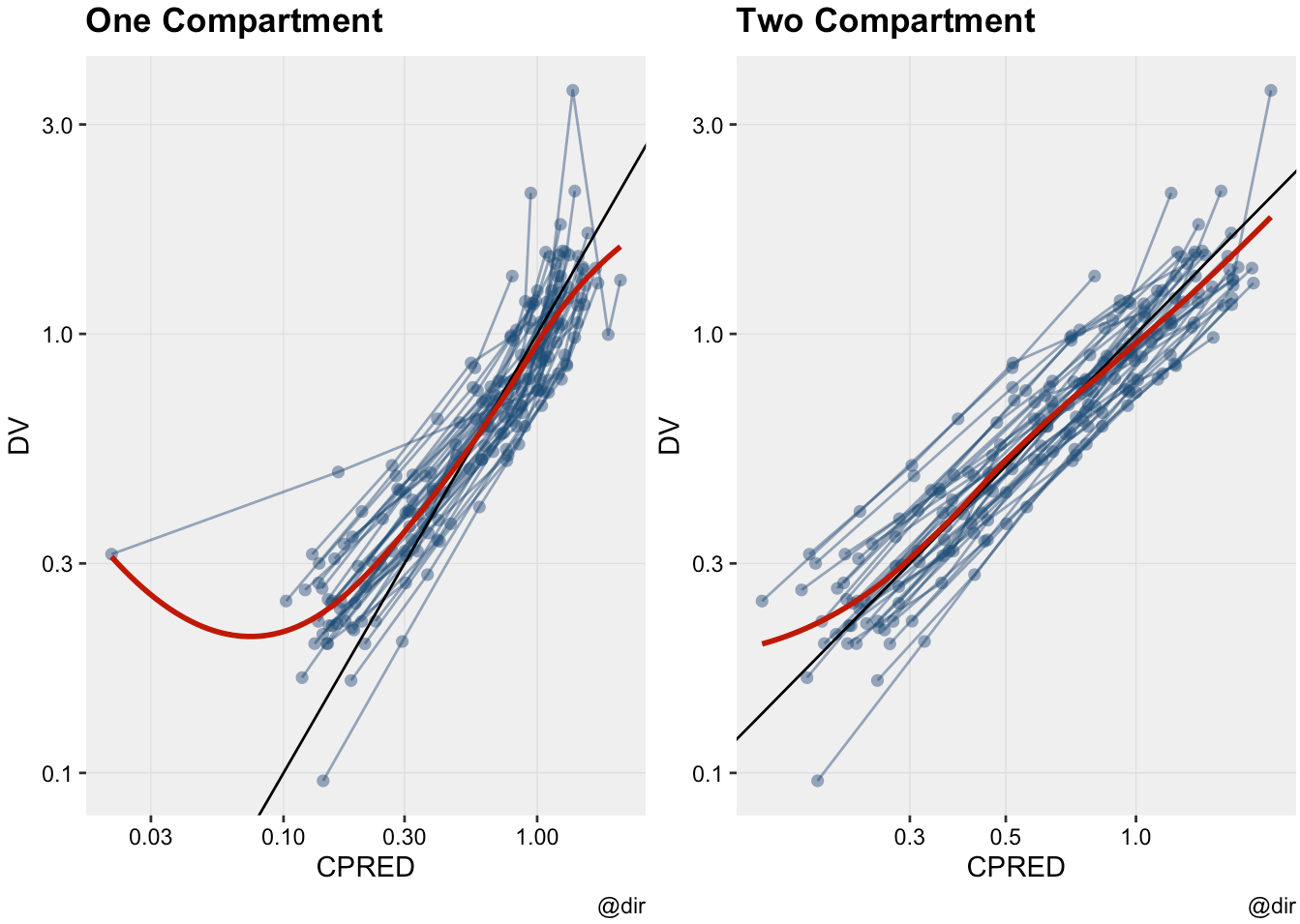
```
# Convert to XPOSE for goodness of fit
one_cmt_xpdb_pk <- xpose_data_nlmixr2(one_cmt_pk_fit,
                                      xp_theme = theme_xp_nlmixr2()
                                      )

two_cmt_xpdb_pk <- xpose_data_nlmixr2(two_cmt_pk_fit,
                                      xp_theme = theme_xp_nlmixr2()
                                      )

# observation vs population prediction plot
one_cmt_dv_pred <- dv_vs_pred(one_cmt_xpdb_pk,
                              type="pls",
                              title = "One Compartment",
                              log   = 'xy',
                              subtitle = NULL,
                              guide = TRUE)
two_cmt_dv_pred <- dv_vs_pred(two_cmt_xpdb_pk,
                              type="pls",
                              title = "Two Compartment",
                              log   = 'xy',
                              subtitle = NULL,
                              guide = TRUE)

grid.arrange(one_cmt_dv_pred, two_cmt_dv_pred, nrow = 1)
```

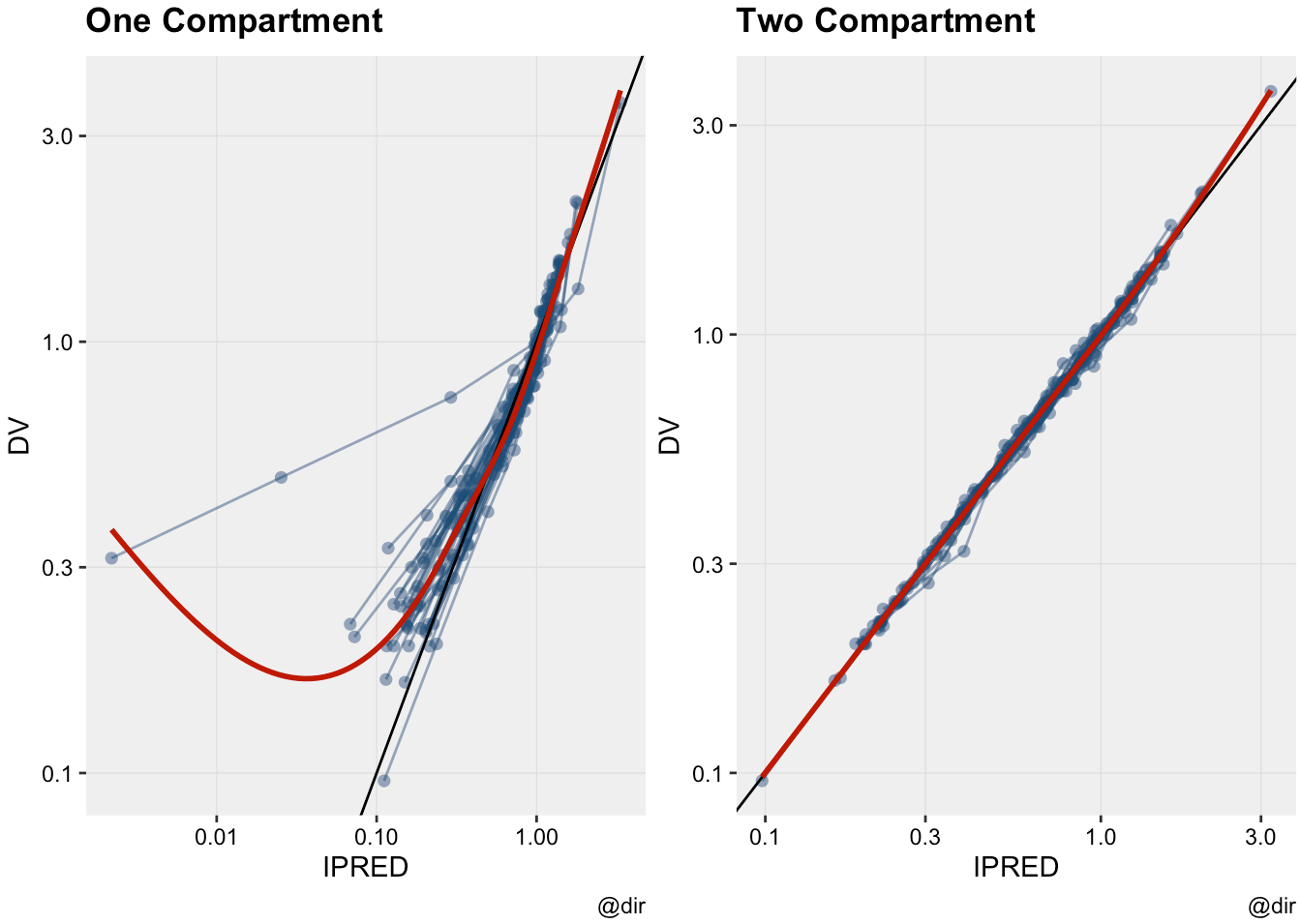
```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```




```
# observation vs individual prediction plot
one_cmt_dv_ipred <- dv_vs_ipred(one_cmt_xpdb_pk,
                                group="ID",
                                title = "One Compartment",
                                log   = 'xy',
                                subtitle = NULL,
                                guide = TRUE
                                )
two_cmt_dv_ipred <- dv_vs_ipred(two_cmt_xpdb_pk,
                                group="ID",
                                title = "Two Compartment",
                                log   = 'xy',
                                subtitle = NULL,
                                guide = TRUE
                                )

grid.arrange(one_cmt_dv_ipred, two_cmt_dv_ipred, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```

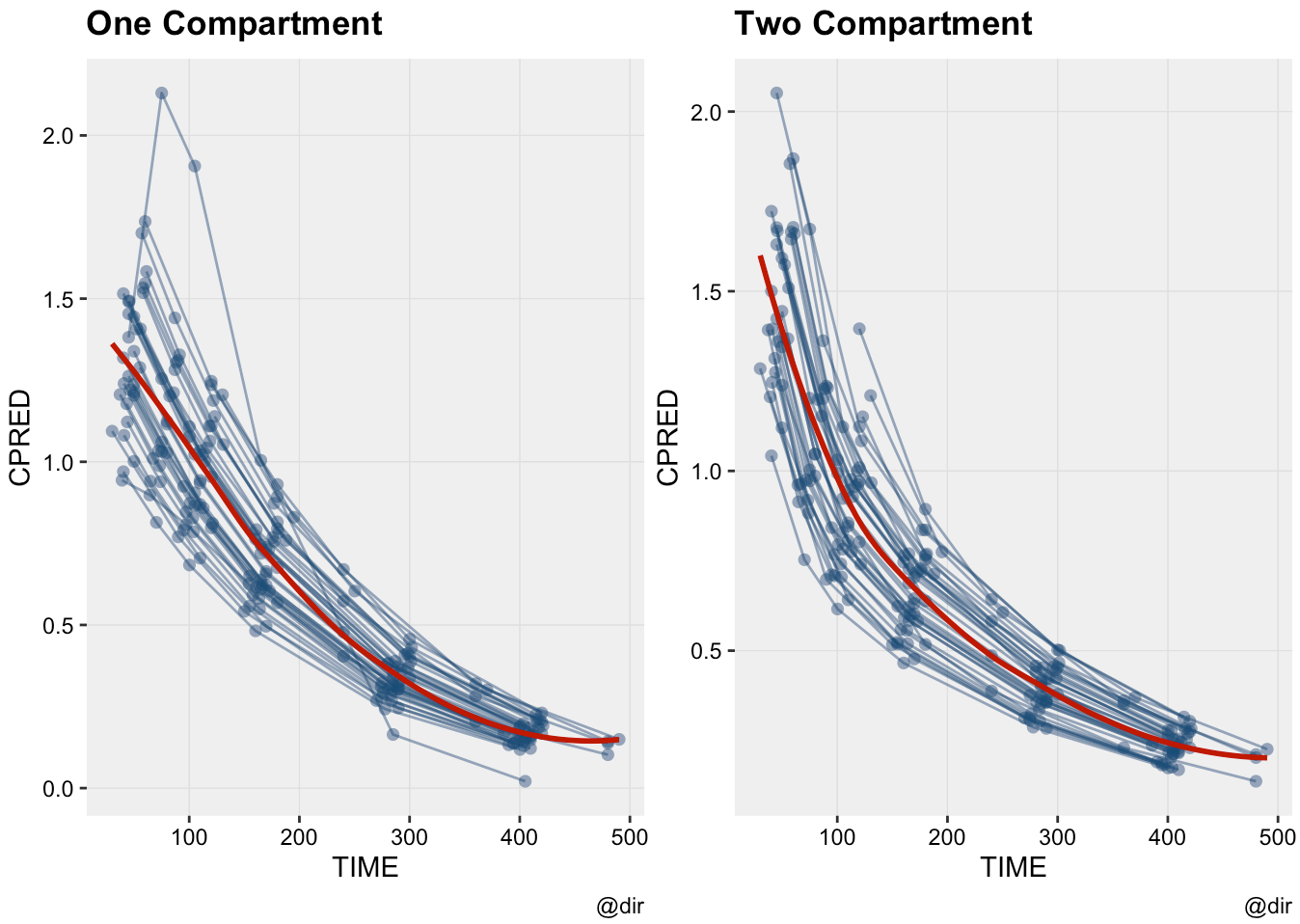



```
# IPRED vs TIME
one_cmt_ipred_time <- pred_vs_idv(one_cmt_xpdb_pk,
                                  group="ID",
                                  title = "One Compartment",
                                  subtitle = NULL,
                                  guide = TRUE
                                  )

two_cmt_ipred_time <- pred_vs_idv(two_cmt_xpdb_pk,
                                  group="ID",
                                  title = "Two Compartment",
                                  subtitle = NULL,
                                  guide = TRUE
                                  )

grid.arrange(one_cmt_ipred_time, two_cmt_ipred_time, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```




```
# residual error vs population prediction plot
one_cmt_cwres_pred <- res_vs_pred(one_cmt_xpdb_pk,
                                  res="CWRES",
                                  type="ps",
                                  title = "One Compartment",
                                  subtitle = NULL,
                                  guide = TRUE
                                  )

two_cmt_cwres_pred <- res_vs_pred(two_cmt_xpdb_pk,
                                  res="CWRES",
                                  type="ps",
                                  title = "Two Compartment",
                                  subtitle = NULL,
                                  guide = TRUE
                                  )

grid.arrange(one_cmt_cwres_pred, two_cmt_cwres_pred, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```

3.4 Two-cmt model parameters

```
# Parameter estimates - Fixed + RUV
two_cmt_pk_fit$parFixedDf %>% select(`Back-transformed`, `%RSE`, `Shrink(SD)%`) %>% rena
me(Parameters = `Back-transformed`)
```

```
.           Parameters      %RSE Shrink(SD)%
. tvcl      0.17748053  2.193853   -1.245711
. tvv1     24.92234149  2.249408  -23.089747
. tvq       0.34392708 15.701199          NA
. tvv2     14.79209350  2.535389   19.804161
. prop.err  0.05221194        NA          NA
```

```
# IIV
two_cmt_pk_fit$omega
```

```
.            eta_cl    eta_v1     eta_v2
. eta_cl 0.04841429 0.0000000 0.00000000
. eta_v1 0.00000000 0.1109996 0.00000000
. eta_v2 0.00000000 0.0000000 0.04513207
```

4 Showcase 2. Error model (Additive vs Proporational vs Combined)

4.1 Fitting with proportional vs combined vs

additive error

```
# Two compartment model with additive model
busulfan_2cmt_add_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(0.187)
    tvv1  <- log(29)
    tvq   <- log(0.41)
    tvv2  <- log(17.3)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0222
    eta_v1  ~ 0.0222
    eta_v2  ~ 0.0241

    # Residual variability
    add.err <-  0.0955
  })

  model({
    # Individual parameters
    cl <- exp(tvcl + eta_cl)
    v1 <- exp(tvv1 + eta_v1)
    q  <- exp(tvq)
    v2 <- exp(tvv2 + eta_v2)

    # Conversion
    k10 <- cl / v1
    k12 <- q / v1
    k21 <- q / v2

    # ODEs
    d / dt(central) = -k10 * central - k12 * central + k21 * peripheral
    d / dt(peripheral) = -k21 * peripheral + k12 * central

    # Concentration
    cp = central / v1

    # Error model (on log scale)
    IPRED = cp
    IPRED ~ add(add.err)
  })
}

# additive model fitting
two_cmt_add_pk_fit <- nlmixr2(
  busulfan_2cmt_add_model,
  busulfan_dataset,
  "focei",
```

```
  table = list(cwres = TRUE)
)
```

```
. ℹ parameter labels from comments are typically ignored in non-interactive mode
```

```
. ℹ Need to run with the source intact to parse comments
```

```
. → loading into symengine environment...
```

```
. → pruning branches (`if`/`else`) of full model...
```

```
. ✔ done
```

```
. → calculate jacobian
```

```
. → calculate sensitivities
```

```
. → calculate ∂(f)/∂(η)
```

```
. → calculate ∂(R²)/∂(η)
```

```
. → finding duplicate expressions in inner model...
```

```
. → optimizing duplicate expressions in inner model...
```

```
. → finding duplicate expressions in EBE model...
```

```
. → optimizing duplicate expressions in EBE model...
```

```
. → compiling inner model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. → finding duplicate expressions in FD model...
```

```
. → optimizing duplicate expressions in FD model...
```

```
. → compiling EBE model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. → compiling events FD model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. Key: U: Unscaled Parameters; X: Back-transformed parameters; G: Gill difference gradie
nt approximation
. F: Forward difference gradient approximation
. C: Central difference gradient approximation
. M: Mixed forward and central difference gradient approximation
. Unscaled parameters for Omegas=chol(solve(omega));
. Diagonals are transformed, as specified by foceiControl(diagXform=)
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    #| Objective Fun |      tvcl |      tvv1 |       tvq |      tvv2 |
. |.....................|   add.err |        o1 |        o2 |        o3 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    1|    -475.80082 |    -1.000 |     1.000 |   -0.6887 |    0.7952 |
. |.....................|   -0.2973 |    0.6921 |    0.6921 |    0.6712 |
. |    U|    -475.80082 |    -1.677 |     3.367 |   -0.8916 |     2.851 |
. |.....................|   0.09550 |     2.591 |     2.591 |     2.538 |
. |    X|    -475.80082 |    0.1870 |     29.00 |    0.4100 |     17.30 |
. |.....................|   0.09550 |     2.591 |     2.591 |     2.538 |
. |    G|    Gill Diff. |     175.5 |     416.4 |     178.7 |     143.4 |
. |.....................|     5.698 |     15.42 |     91.59 |     6.949 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    2|     75.865863 |    -1.341 |    0.1917 |    -1.036 |    0.5168 |
. |.....................|   -0.3084 |    0.6621 |    0.5143 |    0.6577 |
. |    U|     75.865863 |    -2.017 |     2.559 |    -1.238 |     2.572 |
. |.....................|   0.09497 |     2.579 |     2.522 |     2.533 |
. |    X|     75.865863 |    0.1330 |     12.92 |    0.2898 |     13.10 |
. |.....................|   0.09497 |     2.579 |     2.522 |     2.533 |
. |    3|    -536.90131 |    -1.082 |    0.8048 |   -0.7725 |    0.7280 |
. |.....................|   -0.3000 |    0.6848 |    0.6491 |    0.6679 |
. |    U|    -536.90131 |    -1.759 |     3.172 |   -0.9753 |     2.783 |
. |.....................|   0.09537 |     2.588 |     2.574 |     2.537 |
. |    X|    -536.90131 |    0.1722 |     23.86 |    0.3771 |     16.18 |
. |.....................|   0.09537 |     2.588 |     2.574 |     2.537 |
. |    F| Forward Diff. |    -45.75 |    -48.27 |     86.16 |     7.008 |
. |.....................|     36.08 |     13.39 |     76.91 |     3.473 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    4|    -558.10516 |    -1.003 |    0.8887 |   -0.9222 |    0.7158 |
. |.....................|   -0.3627 |    0.6616 |    0.5155 |    0.6619 |
. |    U|    -558.10516 |    -1.679 |     3.256 |    -1.125 |     2.771 |
. |.....................|   0.09238 |     2.579 |     2.523 |     2.534 |
. |    X|    -558.10516 |    0.1865 |     25.95 |    0.3246 |     15.98 |
. |.....................|   0.09238 |     2.579 |     2.523 |     2.534 |
. |    F| Forward Diff. |     142.1 |     66.29 |     77.31 |     60.22 |
. |.....................|     48.83 |     16.03 |     74.49 |     3.375 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    5|    -581.58287 |    -1.138 |    0.8933 |    -1.040 |    0.6559 |
. |.....................|   -0.4447 |    0.6360 |    0.3924 |    0.6568 |
. |    U|    -581.58287 |    -1.815 |     3.261 |    -1.243 |     2.711 |
. |.....................|   0.08846 |     2.569 |     2.475 |     2.532 |
. |    X|    -581.58287 |    0.1629 |     26.07 |    0.2886 |     15.05 |
. |.....................|   0.08846 |     2.569 |     2.475 |     2.532 |
. |    F| Forward Diff. |    -142.0 |    -10.63 |     58.08 |    -26.35 |
. |.....................|     60.27 |     15.07 |     73.96 |     2.735 |
```

```
. |-----+---------------+----------+----------+----------+----------|
. |    6|    -605.44703 |   -1.033 |   0.9339 |   -1.125 |   0.6781 |
. |.....................|  -0.5775 |   0.6048 |   0.2542 |   0.6523 |
. |    U|    -605.44703 |   -1.709 |    3.301 |   -1.328 |    2.734 |
. |.....................|  0.08212 |    2.557 |    2.422 |    2.531 |
. |    X|    -605.44703 |   0.1810 |    27.15 |   0.2650 |    15.39 |
. |.....................|  0.08212 |    2.557 |    2.422 |    2.531 |
. |    F| Forward Diff. |    99.68 |    58.91 |    33.35 |    40.44 |
. |.....................|    65.58 |    15.96 |    71.93 |    3.040 |
. |-----+---------------+----------+----------+----------+----------|
. |    7|    -652.70943 |   -1.132 |   0.9216 |   -1.189 |   0.6490 |
. |.....................|  -0.9211 |   0.5326 | -0.05378 |   0.6421 |
. |    U|    -652.70943 |   -1.808 |    3.289 |   -1.392 |    2.705 |
. |.....................|  0.06572 |    2.529 |    2.303 |    2.527 |
. |    X|    -652.70943 |   0.1639 |    26.81 |   0.2485 |    14.95 |
. |.....................|  0.06572 |    2.529 |    2.303 |    2.527 |
. |    8|    -677.18138 |   -1.151 |   0.9918 |   -1.251 |   0.6608 |
. |.....................|   -1.424 |   0.4302 |  -0.4842 |   0.6288 |
. |    U|    -677.18138 |   -1.828 |    3.359 |   -1.454 |    2.716 |
. |.....................|  0.04170 |    2.490 |    2.137 |    2.521 |
. |    X|    -677.18138 |   0.1608 |    28.76 |   0.2337 |    15.12 |
. |.....................|  0.04170 |    2.490 |    2.137 |    2.521 |
. |    F| Forward Diff. |   -171.1 |    96.76 |   -195.0 |    22.83 |
. |.....................|   -108.0 |    22.00 |    60.24 |    7.566 |
. |-----+---------------+----------+----------+----------+----------|
. |    9|    -651.46935 |  -0.8300 |   0.6212 |  -0.6732 |   0.5112 |
. |.....................|   -1.700 |   0.2184 |   -1.263 |   0.5840 |
. |    U|    -651.46935 |   -1.507 |    2.988 |  -0.8761 |    2.567 |
. |.....................|  0.02852 |    2.408 |    1.836 |    2.504 |
. |    X|    -651.46935 |   0.2216 |    19.86 |   0.4164 |    13.02 |
. |.....................|  0.02852 |    2.408 |    1.836 |    2.504 |
. |   10|    -684.43250 |  -0.8758 |   0.8162 |  -0.9147 |   0.6129 |
. |.....................|   -1.300 |   0.3769 |  -0.6510 |   0.6135 |
. |    U|     -684.4325 |   -1.552 |    3.184 |   -1.118 |    2.668 |
. |.....................|  0.04761 |    2.469 |    2.072 |    2.515 |
. |    X|     -684.4325 |   0.2117 |    24.13 |   0.3271 |    14.42 |
. |.....................|  0.04761 |    2.469 |    2.072 |    2.515 |
. |    F| Forward Diff. |    418.2 |   -35.82 |    21.61 |    17.73 |
. |.....................|    54.14 |    37.88 |    65.74 |    5.660 |
. |-----+---------------+----------+----------+----------+----------|
. |   11|    -721.62965 |   -1.127 |   0.8377 |  -0.9277 |   0.6022 |
. |.....................|   -1.333 |   0.3542 |  -0.6905 |   0.6101 |
. |    U|    -721.62965 |   -1.804 |    3.205 |   -1.131 |    2.658 |
. |.....................|  0.04605 |    2.460 |    2.057 |    2.514 |
. |    X|    -721.62965 |   0.1647 |    24.66 |   0.3228 |    14.26 |
. |.....................|  0.04605 |    2.460 |    2.057 |    2.514 |
. |    F| Forward Diff. |   -165.4 |   -18.89 |    47.33 |   -72.92 |
. |.....................|    55.38 |    19.40 |    64.21 |    6.641 |
. |-----+---------------+----------+----------+----------+----------|
. |   12|    -744.24630 |   -1.030 |   0.8114 |  -0.9027 |   0.6593 |
. |.....................|   -1.446 |   0.2940 |  -0.8811 |   0.5942 |
. |    U|     -744.2463 |   -1.707 |    3.179 |   -1.106 |    2.715 |
```

```
. |.....................|   0.04065 |     2.437 |     1.983 |     2.508 |
. |    X|     -744.2463 |    0.1815 |     24.02 |    0.3310 |     15.10 |
. |.....................|   0.04065 |     2.437 |     1.983 |     2.508 |
. |    F| Forward Diff. |     73.17 |    -26.45 |     11.55 |     9.823 |
. |.....................|     25.78 |     16.69 |     59.24 |     7.177 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   13|    -754.33047 |    -1.107 |    0.8353 |   -0.8690 |    0.6183 |
. |.....................|    -1.537 |    0.2398 |    -1.096 |    0.5730 |
. |    U|    -754.33047 |    -1.784 |     3.203 |    -1.072 |     2.674 |
. |.....................|   0.03631 |     2.416 |     1.901 |     2.499 |
. |    X|    -754.33047 |    0.1680 |     24.60 |    0.3424 |     14.50 |
. |.....................|   0.03631 |     2.416 |     1.901 |     2.499 |
. |    F| Forward Diff. |    -115.8 |     7.988 |     37.11 |    -68.72 |
. |.....................|    -17.27 |     16.97 |     52.54 |     9.180 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   14|    -768.73876 |    -1.042 |    0.8393 |   -0.8618 |    0.6985 |
. |.....................|    -1.491 |    0.1775 |    -1.317 |    0.5400 |
. |    U|    -768.73876 |    -1.718 |     3.207 |    -1.065 |     2.754 |
. |.....................|   0.03851 |     2.392 |     1.815 |     2.486 |
. |    X|    -768.73876 |    0.1794 |     24.70 |    0.3448 |     15.71 |
. |.....................|   0.03851 |     2.392 |     1.815 |     2.486 |
. |    F| Forward Diff. |     51.47 |     16.28 |     6.291 |     46.07 |
. |.....................|     15.57 |     14.07 |     42.12 |     7.524 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   15|    -777.36125 |    -1.056 |    0.7896 |   -0.8355 |    0.6137 |
. |.....................|    -1.543 |    0.1008 |    -1.531 |    0.5017 |
. |    U|    -777.36125 |    -1.733 |     3.157 |    -1.038 |     2.669 |
. |.....................|   0.03600 |     2.362 |     1.732 |     2.471 |
. |    X|    -777.36125 |    0.1767 |     23.50 |    0.3540 |     14.43 |
. |.....................|   0.03600 |     2.362 |     1.732 |     2.471 |
. |    F| Forward Diff. |    -4.779 |    -16.27 |     17.36 |    -71.46 |
. |.....................|    -7.757 |     12.70 |     34.60 |     8.757 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   16|    -772.43747 |    -1.141 |    0.7398 |   -0.8758 |    0.7389 |
. |.....................|    -1.523 |  -0.06703 |    -1.531 |    0.3942 |
. |    U|    -772.43747 |    -1.817 |     3.107 |    -1.079 |     2.794 |
. |.....................|   0.03698 |     2.298 |     1.732 |     2.429 |
. |    X|    -772.43747 |    0.1625 |     22.36 |    0.3401 |     16.35 |
. |.....................|   0.03698 |     2.298 |     1.732 |     2.429 |
. |   17|    -779.77788 |    -1.063 |    0.7973 |   -0.8558 |    0.6920 |
. |.....................|    -1.534 |   0.06800 |    -1.531 |    0.4802 |
. |    U|    -779.77788 |    -1.740 |     3.165 |    -1.059 |     2.748 |
. |.....................|   0.03645 |     2.350 |     1.732 |     2.463 |
. |    X|    -779.77788 |    0.1756 |     23.68 |    0.3469 |     15.60 |
. |.....................|   0.03645 |     2.350 |     1.732 |     2.463 |
. |    F| Forward Diff. |     2.371 |    -10.84 |    -16.16 |     28.33 |
. |.....................|    -5.019 |     11.84 |     33.37 |     7.728 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   18|    -780.60913 |    -1.065 |    0.8377 |   -0.8400 |    0.6575 |
. |.....................|    -1.506 |   0.01238 |    -1.531 |    0.4434 |
. |    U|    -780.60913 |    -1.742 |     3.205 |    -1.043 |     2.713 |
. |.....................|   0.03777 |     2.328 |     1.732 |     2.448 |
```

```
. |    X|    -780.60913 |    0.1752 |     24.65 |    0.3524 |     15.07 |
. |.....................|   0.03777 |     2.328 |     1.732 |     2.448 |
. |    F| Forward Diff. |    -12.00 |     16.86 |     16.94 |    -15.79 |
. |.....................|     16.76 |     10.80 |     33.85 |     6.930 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   19|    -782.01794 |    -1.052 |    0.8053 |   -0.8432 |    0.6698 |
. |.....................|    -1.541 |  -0.04961 |    -1.531 |    0.3998 |
. |    U|    -782.01794 |    -1.729 |     3.173 |    -1.046 |     2.725 |
. |.....................|   0.03614 |     2.304 |     1.732 |     2.431 |
. |    X|    -782.01794 |    0.1775 |     23.87 |    0.3513 |     15.26 |
. |.....................|   0.03614 |     2.304 |     1.732 |     2.431 |
. |    F| Forward Diff. |     17.14 |    -4.476 |    -1.449 |     1.812 |
. |.....................|    -4.125 |     9.675 |     34.08 |     7.265 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   20|    -781.51544 |    -1.100 |    0.7976 |   -0.8428 |    0.6682 |
. |.....................|    -1.534 |   -0.1108 |    -1.531 |    0.3531 |
. |    U|    -781.51544 |    -1.776 |     3.165 |    -1.046 |     2.724 |
. |.....................|   0.03647 |     2.281 |     1.732 |     2.413 |
. |    X|    -781.51544 |    0.1693 |     23.69 |    0.3515 |     15.24 |
. |.....................|   0.03647 |     2.281 |     1.732 |     2.413 |
. |   21|    -781.97314 |    -1.080 |    0.8125 |   -0.8409 |    0.6669 |
. |.....................|    -1.534 |  -0.06517 |    -1.531 |    0.3881 |
. |    U|    -781.97314 |    -1.756 |     3.180 |    -1.044 |     2.722 |
. |.....................|   0.03645 |     2.298 |     1.732 |     2.427 |
. |    X|    -781.97314 |    0.1727 |     24.04 |    0.3521 |     15.22 |
. |.....................|   0.03645 |     2.298 |     1.732 |     2.427 |
. |   22|    -782.19175 |    -1.065 |    0.8087 |   -0.8421 |    0.6684 |
. |.....................|    -1.537 |  -0.05696 |    -1.531 |    0.3943 |
. |    U|    -782.19175 |    -1.742 |     3.176 |    -1.045 |     2.724 |
. |.....................|   0.03629 |     2.302 |     1.732 |     2.429 |
. |    X|    -782.19175 |    0.1752 |     23.95 |    0.3517 |     15.24 |
. |.....................|   0.03629 |     2.302 |     1.732 |     2.429 |
. |    F| Forward Diff. |    -7.822 |    -2.198 |     2.258 |    -2.073 |
. |.....................|    -1.709 |     9.550 |     34.08 |     7.175 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   23|    -782.36695 |    -1.056 |    0.8112 |   -0.8446 |    0.6708 |
. |.....................|    -1.535 |  -0.06769 |    -1.531 |    0.3862 |
. |    U|    -782.36695 |    -1.733 |     3.178 |    -1.048 |     2.726 |
. |.....................|   0.03638 |     2.297 |     1.732 |     2.426 |
. |    X|    -782.36695 |    0.1767 |     24.01 |    0.3508 |     15.28 |
. |.....................|   0.03638 |     2.297 |     1.732 |     2.426 |
. |    F| Forward Diff. |     9.341 |   -0.9803 |   -0.1245 |     3.234 |
. |.....................|   -0.6742 |     9.289 |     33.89 |     7.088 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   24|    -782.64928 |    -1.069 |    0.8096 |   -0.8445 |    0.6664 |
. |.....................|    -1.535 |  -0.09123 |    -1.531 |    0.3669 |
. |    U|    -782.64928 |    -1.746 |     3.177 |    -1.047 |     2.722 |
. |.....................|   0.03640 |     2.288 |     1.732 |     2.418 |
. |    X|    -782.64928 |    0.1745 |     23.97 |    0.3509 |     15.21 |
. |.....................|   0.03640 |     2.288 |     1.732 |     2.418 |
. |    F| Forward Diff. |    -15.38 |    -2.336 |     2.207 |    -4.720 |
. |.....................|   0.07007 |     8.872 |     33.89 |     6.982 |
```

```
. |-----+---------------+----------+----------+----------+----------|
. |   25|    -783.33583 |   -1.056 |   0.7989 |  -0.8419 |   0.6706 |
. |.....................|   -1.542 |  -0.1379 |   -1.531 |   0.3231 |
. |    U|    -783.33583 |   -1.732 |    3.166 |   -1.045 |    2.726 |
. |.....................|  0.03608 |    2.270 |    1.732 |    2.401 |
. |    X|    -783.33583 |   0.1769 |    23.72 |   0.3518 |    15.27 |
. |.....................|  0.03608 |    2.270 |    1.732 |    2.401 |
. |    F| Forward Diff. |    10.15 |   -8.247 |   -1.260 |    3.155 |
. |.....................|   -2.964 |    7.978 |    34.25 |    6.810 |
. |-----+---------------+----------+----------+----------+----------|
. |   26|    -784.19535 |   -1.062 |   0.8403 |  -0.8308 |   0.6703 |
. |.....................|   -1.533 |  -0.2072 |   -1.531 |   0.2178 |
. |    U|    -784.19535 |   -1.739 |    3.208 |   -1.034 |    2.726 |
. |.....................|  0.03650 |    2.244 |    1.732 |    2.359 |
. |    X|    -784.19535 |   0.1757 |    24.72 |   0.3557 |    15.27 |
. |.....................|  0.03650 |    2.244 |    1.732 |    2.359 |
. |    F| Forward Diff. |   -2.581 |    21.46 |    17.64 |  -0.1228 |
. |.....................|    6.094 |    6.628 |    34.94 |    6.058 |
. |-----+---------------+----------+----------+----------+----------|
. |   27|    -785.21415 |   -1.072 |   0.8086 |  -0.8743 |   0.6694 |
. |.....................|   -1.526 |  -0.2690 |   -1.531 |   0.1130 |
. |    U|    -785.21415 |   -1.749 |    3.176 |   -1.077 |    2.725 |
. |.....................|  0.03683 |    2.220 |    1.732 |    2.318 |
. |    X|    -785.21415 |   0.1740 |    23.95 |   0.3406 |    15.26 |
. |.....................|  0.03683 |    2.220 |    1.732 |    2.318 |
. |    F| Forward Diff. |   -16.62 |   -8.672 |   -16.90 |    5.936 |
. |.....................|    5.265 |    5.503 |    31.78 |    5.501 |
. |-----+---------------+----------+----------+----------+----------|
. |   28|    -785.69037 |   -1.051 |   0.7951 |  -0.8234 |   0.6470 |
. |.....................|   -1.565 |  -0.3152 |   -1.531 |  0.01080 |
. |    U|    -785.69037 |   -1.728 |    3.162 |   -1.026 |    2.703 |
. |.....................|  0.03495 |    2.202 |    1.732 |    2.278 |
. |    X|    -785.69037 |   0.1777 |    23.63 |   0.3583 |    14.92 |
. |.....................|  0.03495 |    2.202 |    1.732 |    2.278 |
. |    F| Forward Diff. |    9.679 |   -8.241 |    14.86 |   -24.73 |
. |.....................|   -11.25 |    4.621 |    35.75 |    5.355 |
. |-----+---------------+----------+----------+----------+----------|
. |   29|    -786.77796 |   -1.066 |   0.8228 |  -0.8357 |   0.6861 |
. |.....................|   -1.545 |  -0.3491 |   -1.531 |  -0.1058 |
. |    U|    -786.77796 |   -1.743 |    3.190 |   -1.039 |    2.742 |
. |.....................|  0.03594 |    2.189 |    1.732 |    2.232 |
. |    X|    -786.77796 |   0.1750 |    24.29 |   0.3539 |    15.51 |
. |.....................|  0.03594 |    2.189 |    1.732 |    2.232 |
. |    F| Forward Diff. |   -5.570 |    8.096 |    7.681 |    16.45 |
. |.....................|    2.527 |    3.770 |    34.58 |    4.160 |
. |-----+---------------+----------+----------+----------+----------|
. |   30|    -787.34572 |   -1.064 |   0.8180 |  -0.8589 |   0.6457 |
. |.....................|   -1.532 |  -0.3707 |   -1.531 |  -0.2283 |
. |    U|    -787.34572 |   -1.740 |    3.185 |   -1.062 |    2.701 |
. |.....................|  0.03656 |    2.180 |    1.732 |    2.184 |
. |    X|    -787.34572 |   0.1755 |    24.17 |   0.3458 |    14.90 |
. |.....................|  0.03656 |    2.180 |    1.732 |    2.184 |
```

```
. |    F| Forward Diff. |    -6.796 |    0.3948 |     1.474 |    -16.98 |
. |.....................|     9.936 |     3.433 |     32.64 |     3.322 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   31|    -787.65801 |    -1.063 |    0.7996 |   -0.8526 |    0.6710 |
. |.....................|    -1.573 |   -0.3921 |    -1.531 |   -0.3494 |
. |    U|    -787.65801 |    -1.740 |     3.167 |    -1.055 |     2.727 |
. |.....................|   0.03458 |     2.172 |     1.732 |     2.136 |
. |    X|    -787.65801 |    0.1755 |     23.73 |    0.3480 |     15.28 |
. |.....................|   0.03458 |     2.172 |     1.732 |     2.136 |
. |    F| Forward Diff. |    -3.536 |    -9.816 |    -10.08 |     6.225 |
. |.....................|    -18.40 |     2.841 |     33.71 |     2.669 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   32|    -787.90653 |    -1.052 |    0.8280 |   -0.8253 |    0.6736 |
. |.....................|    -1.549 |   -0.4397 |    -1.531 |   -0.4648 |
. |    U|    -787.90653 |    -1.728 |     3.195 |    -1.028 |     2.729 |
. |.....................|   0.03571 |     2.154 |     1.732 |     2.090 |
. |    X|    -787.90653 |    0.1776 |     24.42 |    0.3577 |     15.32 |
. |.....................|   0.03571 |     2.154 |     1.732 |     2.090 |
. |    F| Forward Diff. |     13.24 |     14.79 |     19.50 |     4.521 |
. |.....................|     5.610 |     1.778 |     35.34 |     1.159 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   33|    -787.39259 |    -1.094 |    0.8008 |   -0.8269 |    0.6627 |
. |.....................|    -1.548 |   -0.5291 |    -1.531 |   -0.5495 |
. |    U|    -787.39259 |    -1.771 |     3.168 |    -1.030 |     2.718 |
. |.....................|   0.03580 |     2.119 |     1.732 |     2.057 |
. |    X|    -787.39259 |    0.1702 |     23.76 |    0.3571 |     15.15 |
. |.....................|   0.03580 |     2.119 |     1.732 |     2.057 |
. |   34|    -788.22651 |    -1.074 |    0.8080 |   -0.8434 |    0.6668 |
. |.....................|    -1.554 |   -0.4628 |    -1.531 |   -0.4862 |
. |    U|    -788.22651 |    -1.750 |     3.175 |    -1.046 |     2.722 |
. |.....................|   0.03549 |     2.145 |     1.732 |     2.082 |
. |    X|    -788.22651 |    0.1737 |     23.93 |    0.3512 |     15.22 |
. |.....................|   0.03549 |     2.145 |     1.732 |     2.082 |
. |    F| Forward Diff. |    -19.69 |     6.286 |     7.658 |     3.155 |
. |.....................|   -0.1743 |     1.517 |     34.05 |     1.140 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   35|    -787.62235 |    -1.035 |    0.7945 |   -0.8662 |    0.6602 |
. |.....................|    -1.555 |   -0.4582 |    -1.531 |   -0.4852 |
. |    U|    -787.62235 |    -1.712 |     3.162 |    -1.069 |     2.716 |
. |.....................|   0.03545 |     2.147 |     1.732 |     2.082 |
. |    X|    -787.62235 |    0.1806 |     23.61 |    0.3433 |     15.12 |
. |.....................|   0.03545 |     2.147 |     1.732 |     2.082 |
. |   36|    -788.35216 |    -1.061 |    0.8037 |   -0.8486 |    0.6647 |
. |.....................|    -1.554 |   -0.4638 |    -1.531 |   -0.4870 |
. |    U|    -788.35216 |    -1.737 |     3.171 |    -1.051 |     2.720 |
. |.....................|   0.03550 |     2.144 |     1.732 |     2.082 |
. |    X|    -788.35216 |    0.1760 |     23.83 |    0.3494 |     15.18 |
. |.....................|   0.03550 |     2.144 |     1.732 |     2.082 |
. |    F| Forward Diff. |   -0.3933 |    -6.867 |   -0.1403 |   -0.3102 |
. |.....................|   -0.8616 |     1.510 |     33.70 |     1.157 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   37|    -788.39626 |    -1.060 |    0.8181 |   -0.8483 |    0.6654 |
```

```
. |.....................|    -1.552 |   -0.4671 |    -1.531 |   -0.4898 |
. |    U|    -788.39626 |    -1.736 |     3.185 |    -1.051 |     2.721 |
. |.....................|   0.03558 |     2.143 |     1.732 |     2.081 |
. |    X|    -788.39626 |    0.1762 |     24.18 |    0.3495 |     15.19 |
. |.....................|   0.03558 |     2.143 |     1.732 |     2.081 |
. |    F| Forward Diff. |    0.6938 |     4.477 |     3.172 |    0.7853 |
. |.....................|    0.3197 |     1.407 |     33.59 |     1.117 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   38|    -788.42213 |    -1.060 |    0.8120 |   -0.8512 |    0.6643 |
. |.....................|    -1.553 |   -0.4759 |    -1.531 |   -0.5000 |
. |    U|    -788.42213 |    -1.737 |     3.179 |    -1.054 |     2.720 |
. |.....................|   0.03554 |     2.140 |     1.732 |     2.077 |
. |    X|    -788.42213 |    0.1761 |     24.03 |    0.3485 |     15.18 |
. |.....................|   0.03554 |     2.140 |     1.732 |     2.077 |
. |    F| Forward Diff. |    0.1269 |   -0.6612 |   0.04576 |   0.09751 |
. |.....................|   -0.6481 |     1.279 |     33.42 |     1.069 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   39|    -788.44389 |    -1.061 |    0.8172 |   -0.8516 |    0.6635 |
. |.....................|    -1.548 |   -0.4860 |    -1.531 |   -0.5084 |
. |    U|    -788.44389 |    -1.738 |     3.185 |    -1.054 |     2.719 |
. |.....................|   0.03579 |     2.136 |     1.732 |     2.073 |
. |    X|    -788.44389 |    0.1759 |     24.16 |    0.3484 |     15.17 |
. |.....................|   0.03579 |     2.136 |     1.732 |     2.073 |
. |   40|    -788.45989 |    -1.061 |    0.8152 |   -0.8485 |    0.6632 |
. |.....................|    -1.549 |   -0.4970 |    -1.531 |   -0.5212 |
. |    U|    -788.45989 |    -1.737 |     3.183 |    -1.051 |     2.719 |
. |.....................|   0.03575 |     2.132 |     1.732 |     2.068 |
. |    X|    -788.45989 |    0.1760 |     24.11 |    0.3494 |     15.16 |
. |.....................|   0.03575 |     2.132 |     1.732 |     2.068 |
. |    F| Forward Diff. |   -0.8097 |     1.439 |     3.932 |    -1.006 |
. |.....................|     3.202 |    0.8250 |     33.53 |    0.7426 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   41|    -788.48956 |    -1.059 |    0.8158 |   -0.8531 |    0.6644 |
. |.....................|    -1.554 |   -0.5016 |    -1.531 |   -0.5505 |
. |    U|    -788.48956 |    -1.736 |     3.183 |    -1.056 |     2.720 |
. |.....................|   0.03549 |     2.130 |     1.732 |     2.057 |
. |    X|    -788.48956 |    0.1763 |     24.12 |    0.3479 |     15.18 |
. |.....................|   0.03549 |     2.130 |     1.732 |     2.057 |
. |    F| Forward Diff. |     2.087 |     1.446 |   -0.2160 |     1.110 |
. |.....................|    -1.347 |    0.8108 |     33.30 |    0.6142 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   42|    -788.49408 |    -1.059 |    0.8114 |   -0.8494 |    0.6630 |
. |.....................|    -1.557 |   -0.5184 |    -1.531 |   -0.5750 |
. |    U|    -788.49408 |    -1.736 |     3.179 |    -1.052 |     2.718 |
. |.....................|   0.03533 |     2.123 |     1.732 |     2.047 |
. |    X|    -788.49408 |    0.1762 |     24.01 |    0.3491 |     15.16 |
. |.....................|   0.03533 |     2.123 |     1.732 |     2.047 |
. |    F| Forward Diff. |    0.9847 |   -0.8672 |     1.216 |   -0.8057 |
. |.....................|    -2.879 |    0.4294 |     33.59 |    0.3037 |
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   43|    -788.49407 |    -1.059 |    0.8114 |   -0.8494 |    0.6630 |
. |.....................|    -1.557 |   -0.5184 |    -1.531 |   -0.5750 |
```

```
. |    U|    -788.49407 |    -1.736 |     3.179 |    -1.052 |     2.718 |
. |.....................|   0.03533 |     2.123 |     1.732 |     2.047 |
. |    X|    -788.49407 |    0.1762 |     24.01 |    0.3491 |     15.16 |
. |.....................|   0.03533 |     2.123 |     1.732 |     2.047 |
. calculating covariance matrix
. done
```

```
. → Calculating residuals/tables
. ✔ done
```

```
. → compress origData in nlmixr2 object, save 13504
```

```
. → compress parHistData in nlmixr2 object, save 6384
```

```
# Two compartment model with combined
busulfan_2cmt_combined_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(0.187)
    tvv1  <- log(29)
    tvq   <- log(0.41)
    tvv2  <- log(17.3)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0222
    eta_v1  ~ 0.0222
    eta_v2  ~ 0.0241

    # Residual variability
    prop.err <-  0.0955
    add.err  <-  0.02
  })

  model({
    # Individual parameters
    cl <- exp(tvcl + eta_cl)
    v1 <- exp(tvv1 + eta_v1)
    q  <- exp(tvq)
    v2 <- exp(tvv2 + eta_v2)

    # Conversion
    k10 <- cl / v1
    k12 <- q / v1
    k21 <- q / v2

    # ODEs
    d / dt(central) = -k10 * central - k12 * central + k21 * peripheral
    d / dt(peripheral) = -k21 * peripheral + k12 * central

    # Concentration
    cp = central / v1

    # Error model (on log scale)
    IPRED = cp
    IPRED ~ prop(prop.err) + add(add.err)
  })
}

# combined model fitting
two_cmt_combined_pk_fit <- nlmixr2(
  busulfan_2cmt_combined_model,
  busulfan_dataset,
  "focei",
  table = list(cwres = TRUE)
  )
```

```
. ℹ parameter labels from comments are typically ignored in non-interactive mode
```

```
. ℹ Need to run with the source intact to parse comments
```

```
. → loading into symengine environment...
```

```
. → pruning branches (`if`/`else`) of full model...
```

```
. ✔ done
```

```
. → calculate jacobian
```

```
. → calculate sensitivities
```

```
. → calculate ∂(f)/∂(η)
```

```
. → calculate ∂(R²)/∂(η)
```

```
. → finding duplicate expressions in inner model...
```

```
. → optimizing duplicate expressions in inner model...
```

```
. → finding duplicate expressions in EBE model...
```

```
. → optimizing duplicate expressions in EBE model...
```

```
. → compiling inner model...
```

```
. using C compiler: 'Apple clang version 16.0.0 (clang-1600.0.26.6)'
. using SDK: 'MacOSX15.2.sdk'
```

```
. ✔ done
```

```
. → finding duplicate expressions in FD model...
```

```
. → optimizing duplicate expressions in FD model...
```

```
. → compiling EBE model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. → compiling events FD model...
```

```
. using C compiler: ‘Apple clang version 16.0.0 (clang-1600.0.26.6)’
. using SDK: ‘MacOSX15.2.sdk’
```

```
. ✔ done
```

```
. Key: U: Unscaled Parameters; X: Back-transformed parameters; G: Gill difference gradie
nt approximation
. F: Forward difference gradient approximation
. C: Central difference gradient approximation
. M: Mixed forward and central difference gradient approximation
. Unscaled parameters for Omegas=chol(solve(omega));
. Diagonals are transformed, as specified by foceiControl(diagXform=)
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    #| Objective Fun |      tvcl |      tvv1 |       tvq |      tvv2 |
. |.....................|  prop.err |   add.err |        o1 |        o2 |
. |.....................|        o3 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    1|    -673.68045 |    -1.000 |     1.000 |   -0.6887 |    0.7952 |
. |.....................|   -0.2973 |   -0.3273 |    0.6921 |    0.6921 |
. |.....................|    0.6712 |...........|...........|...........|
. |    U|    -673.68045 |    -1.677 |     3.367 |   -0.8916 |     2.851 |
. |.....................|  0.09550 |   0.02000 |     2.591 |     2.591 |
. |.....................|     2.538 |...........|...........|...........|
. |    X|    -673.68045 |    0.1870 |     29.00 |    0.4100 |     17.30 |
. |.....................|  0.09550 |   0.02000 |     2.591 |     2.591 |
. |.....................|     2.538 |...........|...........|...........|
. |    G|    Gill Diff. |     122.6 |     345.3 |     69.82 |     165.1 |
. |.....................|    -1.519 |     12.17 |     18.46 |     47.64 |
. |.....................|     7.785 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    2|    -145.10915 |    -1.298 |    0.1606 |   -0.8584 |    0.3938 |
. |.....................|   -0.2936 |   -0.3568 |    0.6472 |    0.5763 |
. |.....................|    0.6523 |...........|...........|...........|
. |    U|    -145.10915 |    -1.975 |     2.528 |    -1.061 |     2.449 |
. |.....................|  0.09568 |   0.01970 |     2.573 |     2.546 |
. |.....................|     2.531 |...........|...........|...........|
. |    X|    -145.10915 |    0.1388 |     12.53 |    0.3460 |     11.58 |
. |.....................|  0.09568 |   0.01970 |     2.573 |     2.546 |
. |.....................|     2.531 |...........|...........|...........|
. |    3|    -713.01446 |    -1.065 |    0.8163 |   -0.7259 |    0.7073 |
. |.....................|   -0.2965 |   -0.3337 |    0.6822 |    0.6667 |
. |.....................|    0.6670 |...........|...........|...........|
. |    U|    -713.01446 |    -1.742 |     3.184 |   -0.9287 |     2.763 |
. |.....................|  0.09554 |   0.01994 |     2.587 |     2.581 |
. |.....................|     2.536 |...........|...........|...........|
. |    X|    -713.01446 |    0.1752 |     24.13 |    0.3951 |     15.85 |
. |.....................|  0.09554 |   0.01994 |     2.587 |     2.581 |
. |.....................|     2.536 |...........|...........|...........|
. |    F| Forward Diff. |    -62.01 |    -35.33 |     21.89 |    -16.49 |
. |.....................|     14.02 |     12.88 |     16.52 |     34.31 |
. |.....................|     3.745 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    4|    -697.16966 |   -0.9165 |    0.8297 |   -0.8077 |    0.7126 |
. |.....................|   -0.3369 |   -0.3744 |    0.6294 |    0.5545 |
. |.....................|    0.6541 |...........|...........|...........|
. |    U|    -697.16966 |    -1.593 |     3.197 |    -1.011 |     2.768 |
. |.....................|  0.09361 |   0.01953 |     2.566 |     2.538 |
```

```
. |                  |     2.531 |           |           |           |
. |    X|    -697.16966 |    0.2033 |     24.46 |    0.3640 |     15.93 |
. |                  |   0.09361 |   0.01953 |     2.566 |     2.538 |
. |                  |     2.531 |           |           |           |
. |    5|    -714.98092 |    -1.025 |    0.8395 |   -0.7402 |    0.7181 |
. |                  |   -0.3057 |   -0.3422 |    0.6714 |    0.6443 |
. |                  |    0.6646 |           |           |           |
. |    U|    -714.98092 |    -1.701 |     3.207 |   -0.9431 |     2.774 |
. |                  |   0.09510 |   0.01985 |     2.583 |     2.572 |
. |                  |     2.535 |           |           |           |
. |    X|    -714.98092 |    0.1824 |     24.70 |    0.3894 |     16.02 |
. |                  |   0.09510 |   0.01985 |     2.583 |     2.572 |
. |                  |     2.535 |           |           |           |
. |    F| Forward Diff. |     55.18 |    0.5397 |     19.86 |     15.39 |
. |                  |     14.16 |     12.91 |     16.52 |     34.81 |
. |                  |     3.783 |           |           |           |
. |-----+--------------+-----------+-----------+-----------+-----------|
. |    6|    -717.14225 |    -1.064 |    0.8432 |   -0.7571 |    0.7079 |
. |                  |   -0.3179 |   -0.3532 |    0.6573 |    0.6145 |
. |                  |    0.6614 |           |           |           |
. |    U|    -717.14225 |    -1.740 |     3.210 |   -0.9600 |     2.763 |
. |                  |   0.09452 |   0.01974 |     2.577 |     2.561 |
. |                  |     2.534 |           |           |           |
. |    X|    -717.14225 |    0.1755 |     24.79 |    0.3829 |     15.85 |
. |                  |   0.09452 |   0.01974 |     2.577 |     2.561 |
. |                  |     2.534 |           |           |           |
. |    F| Forward Diff. |    -53.74 |   -0.9194 |     24.01 |     3.502 |
. |                  |     16.13 |     12.99 |     16.40 |     35.22 |
. |                  |     3.590 |           |           |           |
. |-----+--------------+-----------+-----------+-----------+-----------|
. |    7|    -722.73963 |    -1.030 |    0.8603 |   -0.8024 |    0.6940 |
. |                  |   -0.3554 |   -0.3820 |    0.6212 |    0.5378 |
. |                  |    0.6539 |           |           |           |
. |    U|    -722.73963 |    -1.706 |     3.228 |    -1.005 |     2.750 |
. |                  |   0.09273 |   0.01945 |     2.563 |     2.531 |
. |                  |     2.531 |           |           |           |
. |    X|    -722.73963 |    0.1815 |     25.22 |    0.3659 |     15.64 |
. |                  |   0.09273 |   0.01945 |     2.563 |     2.531 |
. |                  |     2.531 |           |           |           |
. |    8|    -729.53733 |    -1.032 |    0.8898 |   -0.8554 |    0.6734 |
. |                  |   -0.4036 |   -0.4184 |    0.5759 |    0.4419 |
. |                  |    0.6447 |           |           |           |
. |    U|    -729.53733 |    -1.708 |     3.257 |    -1.058 |     2.729 |
. |                  |   0.09042 |   0.01909 |     2.546 |     2.494 |
. |                  |     2.528 |           |           |           |
. |    X|    -729.53733 |    0.1812 |     25.97 |    0.3470 |     15.32 |
. |                  |   0.09042 |   0.01909 |     2.546 |     2.494 |
. |                  |     2.528 |           |           |           |
. |    9|    -756.80483 |    -1.041 |     1.050 |    -1.144 |    0.5611 |
. |                  |   -0.6656 |   -0.6159 |    0.3299 |  -0.07941 |
. |                  |    0.5946 |           |           |           |
. |    U|    -756.80483 |    -1.718 |     3.417 |    -1.346 |     2.617 |
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. |.....................|   0.07791 |   0.01711 |     2.451 |     2.293 |
. |.....................|     2.508 |...........|...........|...........|
. |    X|    -756.80483 |    0.1794 |     30.49 |    0.2602 |     13.69 |
. |.....................|   0.07791 |   0.01711 |     2.451 |     2.293 |
. |.....................|     2.508 |...........|...........|...........|
. |   10|    -704.73882 |    -1.060 |     1.343 |    -1.671 |    0.3557 |
. |.....................|    -1.145 |   -0.9772 |   -0.1203 |    -1.033 |
. |.....................|    0.5030 |...........|...........|...........|
. |    U|    -704.73882 |    -1.736 |     3.710 |    -1.873 |     2.411 |
. |.....................|   0.05503 |   0.01350 |     2.277 |     1.925 |
. |.....................|     2.472 |...........|...........|...........|
. |    X|    -704.73882 |    0.1762 |     40.87 |    0.1536 |     11.15 |
. |.....................|   0.05503 |   0.01350 |     2.277 |     1.925 |
. |.....................|     2.472 |...........|...........|...........|
. |    F| Forward Diff. |     18.92 |     164.5 |     13.20 |     27.04 |
. |.....................|     24.35 |     13.60 |     14.15 |     41.08 |
. |.....................|     3.178 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   11|    -391.76190 |    -1.090 |    0.6891 |    -1.975 |    0.1769 |
. |.....................|    -1.549 |    -1.239 |   -0.4264 |    -1.531 |
. |.....................|    0.4423 |...........|...........|...........|
. |    U|     -391.7619 |    -1.767 |     3.056 |    -2.178 |     2.232 |
. |.....................|   0.03572 |   0.01088 |     2.159 |     1.732 |
. |.....................|     2.448 |...........|...........|...........|
. |    X|     -391.7619 |    0.1709 |     21.25 |    0.1133 |     9.323 |
. |.....................|   0.03572 |   0.01088 |     2.159 |     1.732 |
. |.....................|     2.448 |...........|...........|...........|
. |   12|    -771.07245 |    -1.055 |    0.8829 |    -1.255 |    0.4948 |
. |.....................|   -0.7926 |   -0.7023 |    0.2269 |   -0.3140 |
. |.....................|    0.5737 |...........|...........|...........|
. |    U|    -771.07245 |    -1.732 |     3.250 |    -1.458 |     2.550 |
. |.....................|   0.07185 |   0.01625 |     2.411 |     2.202 |
. |.....................|     2.500 |...........|...........|...........|
. |    X|    -771.07245 |    0.1770 |     25.80 |    0.2328 |     12.81 |
. |.....................|   0.07185 |   0.01625 |     2.411 |     2.202 |
. |.....................|     2.500 |...........|...........|...........|
. |    F| Forward Diff. |    -4.499 |    -124.6 |    -51.01 |    -46.60 |
. |.....................|     23.48 |     13.40 |     12.99 |     38.40 |
. |.....................|     3.474 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   13|    -787.51796 |    -1.042 |     1.006 |    -1.302 |    0.5040 |
. |.....................|   -0.9394 |   -0.8014 |    0.1107 |   -0.5812 |
. |.....................|    0.5494 |...........|...........|...........|
. |    U|    -787.51796 |    -1.719 |     3.373 |    -1.505 |     2.560 |
. |.....................|   0.06484 |   0.01526 |     2.366 |     2.099 |
. |.....................|     2.490 |...........|...........|...........|
. |    X|    -787.51796 |    0.1792 |     29.18 |    0.2221 |     12.93 |
. |.....................|   0.06484 |   0.01526 |     2.366 |     2.099 |
. |.....................|     2.490 |...........|...........|...........|
. |    F| Forward Diff. |     28.15 |     42.07 |    -54.02 |    -4.939 |
. |.....................|     6.011 |     12.36 |     11.68 |     30.81 |
. |.....................|     4.250 |...........|...........|...........|
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. |-----+---------------+-----------+-----------+-----------+-----------|
. |   14|    -801.86351 |    -1.117 |    0.8811 |    -1.077 |    0.5314 |
. |.....................|    -1.001 |   -0.8835 |   0.02591 |   -0.7901 |
. |.....................|    0.5233 |...........|...........|...........|
. |    U|    -801.86351 |    -1.794 |     3.248 |    -1.280 |     2.587 |
. |.....................|   0.06192 |   0.01444 |     2.334 |     2.019 |
. |.....................|     2.480 |...........|...........|...........|
. |    X|    -801.86351 |    0.1663 |     25.75 |    0.2781 |     13.29 |
. |.....................|   0.06192 |   0.01444 |     2.334 |     2.019 |
. |.....................|     2.480 |...........|...........|...........|
. |    F| Forward Diff. |    -135.9 |    -45.53 |    -17.43 |    -64.55 |
. |.....................|     25.83 |     12.98 |     12.77 |     31.97 |
. |.....................|     4.805 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   15|    -819.52489 |    -1.023 |    0.8748 |    -1.076 |    0.6035 |
. |.....................|    -1.133 |   -0.9929 |  -0.09991 |    -1.062 |
. |.....................|    0.4886 |...........|...........|...........|
. |    U|    -819.52489 |    -1.700 |     3.242 |    -1.279 |     2.659 |
. |.....................|   0.05558 |   0.01334 |     2.285 |     1.914 |
. |.....................|     2.466 |...........|...........|...........|
. |    X|    -819.52489 |    0.1828 |     25.59 |    0.2782 |     14.28 |
. |.....................|   0.05558 |   0.01334 |     2.285 |     1.914 |
. |.....................|     2.466 |...........|...........|...........|
. |    F| Forward Diff. |     64.28 |    -29.47 |    -59.62 |     22.16 |
. |.....................|     8.352 |     10.72 |     8.678 |     26.67 |
. |.....................|     4.880 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   16|    -827.77516 |    -1.067 |    0.9031 |   -0.9869 |    0.5078 |
. |.....................|    -1.257 |    -1.103 |   -0.2177 |    -1.329 |
. |.....................|    0.4478 |...........|...........|...........|
. |    U|    -827.77516 |    -1.744 |     3.270 |    -1.190 |     2.563 |
. |.....................|   0.04967 |   0.01225 |     2.240 |     1.810 |
. |.....................|     2.450 |...........|...........|...........|
. |    X|    -827.77516 |    0.1749 |     26.32 |    0.3043 |     12.98 |
. |.....................|   0.04967 |   0.01225 |     2.240 |     1.810 |
. |.....................|     2.450 |...........|...........|...........|
. |    F| Forward Diff. |    -31.83 |     3.752 |     3.766 |    -112.6 |
. |.....................|    -8.935 |     8.103 |     6.145 |     21.53 |
. |.....................|     8.514 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   17|    -831.49767 |    -1.117 |    0.8663 |   -0.8727 |    0.7488 |
. |.....................|    -1.264 |    -1.187 |   -0.2922 |    -1.531 |
. |.....................|    0.3895 |...........|...........|...........|
. |    U|    -831.49767 |    -1.794 |     3.234 |    -1.076 |     2.804 |
. |.....................|   0.04935 |   0.01141 |     2.211 |     1.732 |
. |.....................|     2.427 |...........|...........|...........|
. |    X|    -831.49767 |    0.1663 |     25.37 |    0.3411 |     16.52 |
. |.....................|   0.04935 |   0.01141 |     2.211 |     1.732 |
. |.....................|     2.427 |...........|...........|...........|
. |    F| Forward Diff. |    -97.46 |     22.01 |    -40.96 |     129.7 |
. |.....................|    -8.677 |     5.497 |     6.294 |     19.10 |
. |.....................|     6.420 |...........|...........|...........|
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. |-----+---------------+-----------+-----------+-----------+-----------|
. |   18|    -818.07709 |   -0.9098 |    0.8985 |   -0.7157 |    0.6754 |
. |.....................|    -1.060 |    -1.248 |   -0.3413 |    -1.531 |
. |.....................|    0.2773 |...........|...........|...........|
. |    U|    -818.07709 |    -1.586 |     3.266 |   -0.9186 |     2.731 |
. |.....................|   0.05909 |   0.01079 |     2.192 |     1.732 |
. |.....................|     2.383 |...........|...........|...........|
. |    X|    -818.07709 |    0.2047 |     26.20 |    0.3991 |     15.35 |
. |.....................|   0.05909 |   0.01079 |     2.192 |     1.732 |
. |.....................|     2.383 |...........|...........|...........|
. |   19|    -841.42226 |    -1.039 |    0.8486 |   -0.8398 |    0.6446 |
. |.....................|    -1.257 |    -1.191 |   -0.2972 |    -1.531 |
. |.....................|    0.3843 |...........|...........|...........|
. |    U|    -841.42226 |    -1.716 |     3.216 |    -1.043 |     2.700 |
. |.....................|   0.04969 |   0.01136 |     2.209 |     1.732 |
. |.....................|     2.425 |...........|...........|...........|
. |    X|    -841.42226 |    0.1799 |     24.92 |    0.3525 |     14.88 |
. |.....................|   0.04969 |   0.01136 |     2.209 |     1.732 |
. |.....................|     2.425 |...........|...........|...........|
. |    F| Forward Diff. |     22.52 |     4.522 |     7.689 |    -11.51 |
. |.....................|     2.230 |     7.568 |     4.415 |     19.19 |
. |.....................|     4.860 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   20|    -841.94207 |    -1.069 |    0.8278 |   -0.8800 |    0.6358 |
. |.....................|    -1.299 |    -1.276 |   -0.3621 |    -1.531 |
. |.....................|    0.3360 |...........|...........|...........|
. |    U|    -841.94207 |    -1.746 |     3.195 |    -1.083 |     2.691 |
. |.....................|   0.04769 |   0.01052 |     2.184 |     1.732 |
. |.....................|     2.406 |...........|...........|...........|
. |    X|    -841.94207 |    0.1745 |     24.41 |    0.3386 |     14.75 |
. |.....................|   0.04769 |   0.01052 |     2.184 |     1.732 |
. |.....................|     2.406 |...........|...........|...........|
. |    F| Forward Diff. |    -25.08 |    -14.06 |    -11.42 |    -8.565 |
. |.....................|    -12.02 |     5.141 |     3.284 |     19.16 |
. |.....................|     5.269 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   21|    -843.47986 |    -1.048 |    0.8496 |   -0.8637 |    0.6593 |
. |.....................|    -1.243 |    -1.357 |   -0.4150 |    -1.531 |
. |.....................|    0.2708 |...........|...........|...........|
. |    U|    -843.47986 |    -1.724 |     3.217 |    -1.067 |     2.715 |
. |.....................|   0.05036 |  0.009705 |     2.163 |     1.732 |
. |.....................|     2.380 |...........|...........|...........|
. |    X|    -843.47986 |    0.1783 |     24.95 |    0.3442 |     15.10 |
. |.....................|   0.05036 |  0.009705 |     2.163 |     1.732 |
. |.....................|     2.380 |...........|...........|...........|
. |    F| Forward Diff. |     9.495 |     3.018 |    -7.917 |     16.26 |
. |.....................|     1.510 |     5.879 |     2.100 |     18.47 |
. |.....................|     4.169 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   22|    -842.61570 |    -1.086 |    0.8462 |   -0.8159 |    0.6316 |
. |.....................|    -1.215 |    -1.443 |   -0.4415 |    -1.531 |
. |.....................|    0.1993 |...........|...........|...........|
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. |    U|     -842.6157 |    -1.762 |     3.214 |    -1.019 |     2.687 |
. |.....................|   0.05167 |  0.008843 |     2.153 |     1.732 |
. |.....................|     2.352 |...........|...........|...........|
. |    X|     -842.6157 |    0.1717 |     24.87 |    0.3610 |     14.69 |
. |.....................|   0.05167 |  0.008843 |     2.153 |     1.732 |
. |.....................|     2.352 |...........|...........|...........|
. |   23|    -843.19023 |    -1.068 |    0.8436 |   -0.8459 |    0.6265 |
. |.....................|    -1.244 |    -1.373 |   -0.4205 |    -1.531 |
. |.....................|    0.2589 |...........|...........|...........|
. |    U|    -843.19023 |    -1.745 |     3.211 |    -1.049 |     2.682 |
. |.....................|   0.05030 |  0.009545 |     2.161 |     1.732 |
. |.....................|     2.376 |...........|...........|...........|
. |    X|    -843.19023 |    0.1747 |     24.80 |    0.3504 |     14.61 |
. |.....................|   0.05030 |  0.009545 |     2.161 |     1.732 |
. |.....................|     2.376 |...........|...........|...........|
. |   24|    -843.67024 |    -1.056 |    0.8471 |   -0.8570 |    0.6455 |
. |.....................|    -1.244 |    -1.362 |   -0.4168 |    -1.531 |
. |.....................|    0.2673 |...........|...........|...........|
. |    U|    -843.67024 |    -1.732 |     3.214 |    -1.060 |     2.701 |
. |.....................|   0.05030 |  0.009655 |     2.163 |     1.732 |
. |.....................|     2.379 |...........|...........|...........|
. |    X|    -843.67024 |    0.1769 |     24.89 |    0.3465 |     14.90 |
. |.....................|   0.05030 |  0.009655 |     2.163 |     1.732 |
. |.....................|     2.379 |...........|...........|...........|
. |    F| Forward Diff. |    -4.368 |    0.6934 |    0.1401 |    -3.482 |
. |.....................|     1.997 |     5.877 |     2.059 |     18.65 |
. |.....................|     4.252 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   25|    -843.75538 |    -1.047 |    0.8457 |   -0.8573 |    0.6522 |
. |.....................|    -1.248 |    -1.373 |   -0.4208 |    -1.531 |
. |.....................|    0.2590 |...........|...........|...........|
. |    U|    -843.75538 |    -1.724 |     3.213 |    -1.060 |     2.708 |
. |.....................|   0.05012 |  0.009541 |     2.161 |     1.732 |
. |.....................|     2.376 |...........|...........|...........|
. |    X|    -843.75538 |    0.1784 |     24.85 |    0.3464 |     15.00 |
. |.....................|   0.05012 |  0.009541 |     2.161 |     1.732 |
. |.....................|     2.376 |...........|...........|...........|
. |    F| Forward Diff. |     9.385 |    0.9616 |   -3.358  |     5.488 |
. |.....................|    0.4175 |     5.609 |     1.980 |     18.72 |
. |.....................|     4.184 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   26|    -844.02531 |    -1.058 |    0.8444 |   -0.8522 |    0.6503 |
. |.....................|    -1.244 |    -1.400 |   -0.4286 |    -1.531 |
. |.....................|    0.2374 |...........|...........|...........|
. |    U|    -844.02531 |    -1.735 |     3.212 |    -1.055 |     2.706 |
. |.....................|   0.05028 |  0.009276 |     2.158 |     1.732 |
. |.....................|     2.367 |...........|...........|...........|
. |    X|    -844.02531 |    0.1765 |     24.82 |    0.3482 |     14.97 |
. |.....................|   0.05028 |  0.009276 |     2.158 |     1.732 |
. |.....................|     2.367 |...........|...........|...........|
. |    F| Forward Diff. |    -7.571 |    0.7492 |    0.1563 |    0.4811 |
. |.....................|     1.205 |     5.411 |     1.816 |     18.82 |
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. |.....................|     4.032 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   27|    -844.25654 |    -1.047 |    0.8428 |   -0.8544 |    0.6500 |
. |.....................|    -1.244 |    -1.427 |   -0.4348 |    -1.531 |
. |.....................|    0.2159 |...........|...........|...........|
. |    U|    -844.25654 |    -1.724 |     3.210 |    -1.057 |     2.706 |
. |.....................|   0.05030 |  0.009000 |     2.156 |     1.732 |
. |.....................|     2.359 |...........|...........|...........|
. |    X|    -844.25654 |    0.1784 |     24.78 |    0.3474 |     14.96 |
. |.....................|   0.05030 |  0.009000 |     2.156 |     1.732 |
. |.....................|     2.359 |...........|...........|...........|
. |    F| Forward Diff. |     9.147 |    -1.127 |    -1.457 |     1.927 |
. |.....................|    0.6238 |     5.129 |     1.673 |     18.75 |
. |.....................|     3.934 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   28|    -844.68221 |    -1.058 |    0.8439 |   -0.8580 |    0.6536 |
. |.....................|    -1.231 |    -1.481 |   -0.4445 |    -1.531 |
. |.....................|    0.1688 |...........|...........|...........|
. |    U|    -844.68221 |    -1.734 |     3.211 |    -1.061 |     2.709 |
. |.....................|   0.05093 |  0.008459 |     2.152 |     1.732 |
. |.....................|     2.340 |...........|...........|...........|
. |    X|    -844.68221 |    0.1765 |     24.81 |    0.3462 |     15.02 |
. |.....................|   0.05093 |  0.008459 |     2.152 |     1.732 |
. |.....................|     2.340 |...........|...........|...........|
. |   29|    -844.95513 |    -1.059 |    0.8438 |   -0.8643 |    0.6605 |
. |.....................|    -1.213 |    -1.542 |   -0.4542 |    -1.531 |
. |.....................|    0.1153 |...........|...........|...........|
. |    U|    -844.95513 |    -1.735 |     3.211 |    -1.067 |     2.716 |
. |.....................|   0.05176 |  0.007852 |     2.148 |     1.732 |
. |.....................|     2.319 |...........|...........|...........|
. |    X|    -844.95513 |    0.1763 |     24.81 |    0.3440 |     15.12 |
. |.....................|   0.05176 |  0.007852 |     2.148 |     1.732 |
. |.....................|     2.319 |...........|...........|...........|
. |    F| Forward Diff. |    -7.880 |    -1.821 |    -8.205 |     17.37 |
. |.....................|     6.009 |     4.643 |     1.321 |     18.09 |
. |.....................|     3.091 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   30|    -845.58324 |    -1.059 |    0.8418 |   -0.8529 |    0.6259 |
. |.....................|    -1.247 |    -1.654 |   -0.4506 |    -1.531 |
. |.....................|   0.01607 |...........|...........|...........|
. |    U|    -845.58324 |    -1.735 |     3.209 |    -1.056 |     2.681 |
. |.....................|   0.05014 |  0.006729 |     2.150 |     1.732 |
. |.....................|     2.280 |...........|...........|...........|
. |    X|    -845.58324 |    0.1764 |     24.76 |    0.3479 |     14.61 |
. |.....................|   0.05014 |  0.006729 |     2.150 |     1.732 |
. |.....................|     2.280 |...........|...........|...........|
. |    F| Forward Diff. |    -10.43 |    -3.542 |     8.752 |    -23.52 |
. |.....................|    -4.169 |     2.822 |     1.317 |     18.85 |
. |.....................|     3.196 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   31|    -845.93574 |    -1.058 |    0.8451 |   -0.8287 |    0.6675 |
. |.....................|    -1.262 |    -1.741 |   -0.4324 |    -1.531 |
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. |.....................|   -0.1043 |...........|...........|...........|
. |    U|    -845.93574 |    -1.734 |     3.212 |    -1.032 |     2.723 |
. |.....................|   0.04942 |  0.005859 |     2.157 |     1.732 |
. |.....................|     2.232 |...........|...........|...........|
. |    X|    -845.93574 |    0.1765 |     24.84 |    0.3565 |     15.23 |
. |.....................|   0.04942 |  0.005859 |     2.157 |     1.732 |
. |.....................|     2.232 |...........|...........|...........|
. |    F| Forward Diff. |    -7.892 |     5.843 |     4.782 |     15.04 |
. |.....................|    -11.39 |     1.595 |     1.573 |     19.74 |
. |.....................|     1.923 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   32|    -846.53426 |    -1.048 |    0.8403 |   -0.8914 |    0.6389 |
. |.....................|    -1.217 |    -1.831 |   -0.4339 |    -1.531 |
. |.....................|   -0.2041 |...........|...........|...........|
. |    U|    -846.53426 |    -1.724 |     3.208 |    -1.094 |     2.694 |
. |.....................|   0.05158 |  0.004961 |     2.156 |     1.732 |
. |.....................|     2.193 |...........|...........|...........|
. |    X|    -846.53426 |    0.1783 |     24.72 |    0.3348 |     14.80 |
. |.....................|   0.05158 |  0.004961 |     2.156 |     1.732 |
. |.....................|     2.193 |...........|...........|...........|
. |    F| Forward Diff. |     8.317 |    -9.879 |    -13.10 |     6.784 |
. |.....................|    0.4509 |     2.166 |     1.588 |     17.48 |
. |.....................|     1.242 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   33|    -845.62404 |    -1.051 |    0.8694 |   -0.8298 |    0.6208 |
. |.....................|    -1.153 |    -1.930 |   -0.4820 |    -1.531 |
. |.....................|   -0.2649 |...........|...........|...........|
. |    U|    -845.62404 |    -1.728 |     3.237 |    -1.033 |     2.676 |
. |.....................|   0.05465 |  0.003969 |     2.137 |     1.732 |
. |.....................|     2.169 |...........|...........|...........|
. |    X|    -845.62404 |    0.1777 |     25.45 |    0.3560 |     14.53 |
. |.....................|   0.05465 |  0.003969 |     2.137 |     1.732 |
. |.....................|     2.169 |...........|...........|...........|
. |   34|    -846.42669 |    -1.066 |    0.8636 |   -0.8585 |    0.6231 |
. |.....................|    -1.212 |    -1.844 |   -0.4414 |    -1.531 |
. |.....................|   -0.2121 |...........|...........|...........|
. |    U|    -846.42669 |    -1.742 |     3.231 |    -1.061 |     2.679 |
. |.....................|   0.05181 |  0.004828 |     2.153 |     1.732 |
. |.....................|     2.190 |...........|...........|...........|
. |    X|    -846.42669 |    0.1751 |     25.30 |    0.3460 |     14.56 |
. |.....................|   0.05181 |  0.004828 |     2.153 |     1.732 |
. |.....................|     2.190 |...........|...........|...........|
. |   35|    -846.73115 |    -1.057 |    0.8515 |   -0.8765 |    0.6312 |
. |.....................|    -1.218 |    -1.834 |   -0.4357 |    -1.531 |
. |.....................|   -0.2055 |...........|...........|...........|
. |    U|    -846.73115 |    -1.734 |     3.219 |    -1.079 |     2.687 |
. |.....................|   0.05156 |  0.004936 |     2.155 |     1.732 |
. |.....................|     2.193 |...........|...........|...........|
. |    X|    -846.73115 |    0.1766 |     25.00 |    0.3398 |     14.68 |
. |.....................|   0.05156 |  0.004936 |     2.155 |     1.732 |
. |.....................|     2.193 |...........|...........|...........|
. |    F| Forward Diff. |    -7.228 |    -1.174 |    -1.906 |    -5.441 |
```

```
. |.....................|     1.046 |     2.184 |     1.551 |     17.71 |
. |.....................|     1.276 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   36|    -846.76912 |    -1.045 |    0.8534 |   -0.8721 |    0.6401 |
. |.....................|    -1.216 |    -1.844 |   -0.4475 |    -1.531 |
. |.....................|   -0.2088 |...........|...........|...........|
. |    U|    -846.76912 |    -1.722 |     3.221 |    -1.075 |     2.696 |
. |.....................|   0.05162 |  0.004834 |     2.151 |     1.732 |
. |.....................|     2.191 |...........|...........|...........|
. |    X|    -846.76912 |    0.1788 |     25.05 |    0.3413 |     14.82 |
. |.....................|   0.05162 |  0.004834 |     2.151 |     1.732 |
. |.....................|     2.191 |...........|...........|...........|
. |    F| Forward Diff. |     11.90 |     1.512 |    -3.026 |     3.063 |
. |.....................|     1.016 |     2.132 |     1.297 |     17.76 |
. |.....................|     1.141 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   37|    -846.86869 |    -1.054 |    0.8513 |   -0.8714 |    0.6389 |
. |.....................|    -1.218 |    -1.858 |   -0.4614 |    -1.531 |
. |.....................|   -0.2136 |...........|...........|...........|
. |    U|    -846.86869 |    -1.731 |     3.219 |    -1.074 |     2.694 |
. |.....................|   0.05154 |  0.004692 |     2.145 |     1.732 |
. |.....................|     2.189 |...........|...........|...........|
. |    X|    -846.86869 |    0.1772 |     24.99 |    0.3415 |     14.80 |
. |.....................|   0.05154 |  0.004692 |     2.145 |     1.732 |
. |.....................|     2.189 |...........|...........|...........|
. |    F| Forward Diff. |    -2.437 |    0.1142 |    -2.388 |     1.609 |
. |.....................|    0.3814 |     2.015 |     1.005 |     17.85 |
. |.....................|     1.119 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   38|    -846.90597 |    -1.048 |    0.8503 |   -0.8666 |    0.6355 |
. |.....................|    -1.218 |    -1.876 |   -0.4697 |    -1.531 |
. |.....................|   -0.2204 |...........|...........|...........|
. |    U|    -846.90597 |    -1.725 |     3.218 |    -1.069 |     2.691 |
. |.....................|   0.05155 |  0.004512 |     2.142 |     1.732 |
. |.....................|     2.187 |...........|...........|...........|
. |    X|    -846.90597 |    0.1782 |     24.97 |    0.3432 |     14.75 |
. |.....................|   0.05155 |  0.004512 |     2.142 |     1.732 |
. |.....................|     2.187 |...........|...........|...........|
. |    F| Forward Diff. |     6.196 |   -0.4146 |    0.5649 |    -3.701 |
. |.....................|    0.3840 |     1.891 |    0.8738 |     17.97 |
. |.....................|     1.085 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   39|    -846.97153 |    -1.052 |    0.8502 |   -0.8684 |    0.6390 |
. |.....................|    -1.218 |    -1.896 |   -0.4742 |    -1.531 |
. |.....................|   -0.2277 |...........|...........|...........|
. |    U|    -846.97153 |    -1.729 |     3.218 |    -1.071 |     2.695 |
. |.....................|   0.05153 |  0.004311 |     2.141 |     1.732 |
. |.....................|     2.184 |...........|...........|...........|
. |    X|    -846.97153 |    0.1775 |     24.97 |    0.3426 |     14.80 |
. |.....................|   0.05153 |  0.004311 |     2.141 |     1.732 |
. |.....................|     2.184 |...........|...........|...........|
. |    F| Forward Diff. |    0.8313 |   -0.3494 |    -1.324 |    0.3443 |
```

```
. |.....................|   -0.2414 |     1.768 |    0.7819 |     17.94 |
. |.....................|    0.9900 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   40|    -846.94512 |    -1.059 |    0.8531 |   -0.8575 |    0.6362 |
. |.....................|    -1.216 |    -1.911 |   -0.4806 |    -1.531 |
. |.....................|   -0.2359 |...........|...........|...........|
. |    U|    -846.94512 |    -1.736 |     3.220 |    -1.060 |     2.692 |
. |.....................|   0.05162 |  0.004165 |     2.138 |     1.732 |
. |.....................|     2.181 |...........|...........|...........|
. |    X|    -846.94512 |    0.1763 |     25.04 |    0.3463 |     14.76 |
. |.....................|   0.05162 |  0.004165 |     2.138 |     1.732 |
. |.....................|     2.181 |...........|...........|...........|
. |   41|    -846.98236 |    -1.054 |    0.8512 |   -0.8646 |    0.6380 |
. |.....................|    -1.218 |    -1.901 |   -0.4764 |    -1.531 |
. |.....................|   -0.2306 |...........|...........|...........|
. |    U|    -846.98236 |    -1.731 |     3.219 |    -1.067 |     2.694 |
. |.....................|   0.05156 |  0.004260 |     2.140 |     1.732 |
. |.....................|     2.183 |...........|...........|...........|
. |    X|    -846.98236 |    0.1771 |     24.99 |    0.3439 |     14.78 |
. |.....................|   0.05156 |  0.004260 |     2.140 |     1.732 |
. |.....................|     2.183 |...........|...........|...........|
. |    F| Forward Diff. |    -3.009 |    0.6929 |    0.9629 |    -1.961 |
. |.....................|    0.2043 |     1.735 |    0.7407 |     18.03 |
. |.....................|    0.9806 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   42|    -847.00041 |    -1.051 |    0.8506 |   -0.8655 |    0.6400 |
. |.....................|    -1.218 |    -1.908 |   -0.4776 |    -1.531 |
. |.....................|   -0.2332 |...........|...........|...........|
. |    U|    -847.00041 |    -1.728 |     3.218 |    -1.068 |     2.696 |
. |.....................|   0.05155 |  0.004197 |     2.139 |     1.732 |
. |.....................|     2.182 |...........|...........|...........|
. |    X|    -847.00041 |    0.1776 |     24.97 |    0.3435 |     14.81 |
. |.....................|   0.05155 |  0.004197 |     2.139 |     1.732 |
. |.....................|     2.182 |...........|...........|...........|
. |    F| Forward Diff. |     1.995 |    0.5275 |   -0.4169 |    0.4903 |
. |.....................|   -0.1937 |     1.709 |    0.7492 |     18.01 |
. |.....................|    0.9431 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   43|    -847.02992 |    -1.054 |    0.8499 |   -0.8649 |    0.6393 |
. |.....................|    -1.217 |    -1.922 |   -0.4797 |    -1.531 |
. |.....................|   -0.2386 |...........|...........|...........|
. |    U|    -847.02992 |    -1.730 |     3.217 |    -1.068 |     2.695 |
. |.....................|   0.05157 |  0.004053 |     2.138 |     1.732 |
. |.....................|     2.180 |...........|...........|...........|
. |    X|    -847.02992 |    0.1772 |     24.96 |    0.3438 |     14.80 |
. |.....................|   0.05157 |  0.004053 |     2.138 |     1.732 |
. |.....................|     2.180 |...........|...........|...........|
. |   44|    -847.07080 |    -1.054 |    0.8500 |   -0.8648 |    0.6392 |
. |.....................|    -1.217 |    -1.944 |   -0.4816 |    -1.531 |
. |.....................|   -0.2461 |...........|...........|...........|
. |    U|     -847.0708 |    -1.730 |     3.217 |    -1.068 |     2.695 |
. |.....................|   0.05158 |  0.003837 |     2.138 |     1.732 |
```

```
. |.....................|     2.177 |...........|...........|...........|
. |    X|     -847.0708 |    0.1772 |     24.96 |    0.3438 |     14.80 |
. |.....................|   0.05158 |  0.003837 |     2.138 |     1.732 |
. |.....................|     2.177 |...........|...........|...........|
. |   45|    -847.21080 |    -1.052 |    0.8505 |   -0.8643 |    0.6388 |
. |.....................|    -1.216 |    -2.035 |   -0.4897 |    -1.531 |
. |.....................|   -0.2780 |...........|...........|...........|
. |    U|     -847.2108 |    -1.729 |     3.218 |    -1.067 |     2.694 |
. |.....................|   0.05161 |  0.002919 |     2.135 |     1.732 |
. |.....................|     2.164 |...........|...........|...........|
. |    X|     -847.2108 |    0.1775 |     24.97 |    0.3440 |     14.80 |
. |.....................|   0.05161 |  0.002919 |     2.135 |     1.732 |
. |.....................|     2.164 |...........|...........|...........|
. |   46|    -847.34004 |    -1.051 |    0.8509 |   -0.8634 |    0.6379 |
. |.....................|    -1.215 |    -2.186 |   -0.5033 |    -1.531 |
. |.....................|   -0.3306 |...........|...........|...........|
. |    U|    -847.34004 |    -1.728 |     3.218 |    -1.066 |     2.693 |
. |.....................|   0.05167 |  0.001409 |     2.129 |     1.732 |
. |.....................|     2.143 |...........|...........|...........|
. |    X|    -847.34004 |    0.1776 |     24.98 |    0.3443 |     14.78 |
. |.....................|   0.05167 |  0.001409 |     2.129 |     1.732 |
. |.....................|     2.143 |...........|...........|...........|
. |    F| Forward Diff. |     2.836 |     2.932 |     1.979 |    0.8592 |
. |.....................|    -2.478 |    0.4759 |    0.2124 |     18.04 |
. |.....................|    0.1612 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   47|    -846.12063 |    -1.051 |    0.8416 |   -0.8805 |    0.6388 |
. |.....................|    -1.116 |    -2.325 |   -0.5551 |    -1.531 |
. |.....................|   -0.4278 |...........|...........|...........|
. |    U|    -846.12063 |    -1.728 |     3.209 |    -1.083 |     2.694 |
. |.....................|   0.05640 | 2.060e-05 |     2.109 |     1.732 |
. |.....................|     2.105 |...........|...........|...........|
. |    X|    -846.12063 |    0.1777 |     24.75 |    0.3384 |     14.80 |
. |.....................|   0.05640 | 2.060e-05 |     2.109 |     1.732 |
. |.....................|     2.105 |...........|...........|...........|
. |   48|    -847.34801 |    -1.056 |    0.8462 |   -0.8673 |    0.6367 |
. |.....................|    -1.205 |    -2.208 |   -0.4998 |    -1.531 |
. |.....................|   -0.3287 |...........|...........|...........|
. |    U|    -847.34801 |    -1.732 |     3.213 |    -1.070 |     2.692 |
. |.....................|   0.05215 |  0.001195 |     2.131 |     1.732 |
. |.....................|     2.144 |...........|...........|...........|
. |    X|    -847.34801 |    0.1769 |     24.86 |    0.3429 |     14.77 |
. |.....................|   0.05215 |  0.001195 |     2.131 |     1.732 |
. |.....................|     2.144 |...........|...........|...........|
. |    F| Forward Diff. |    -4.548 |    -3.267 |   -0.1230 |    -1.321 |
. |.....................|    0.6245 |    0.4773 |    0.3694 |     17.87 |
. |.....................|    0.1148 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   49|    -847.36856 |    -1.052 |    0.8497 |   -0.8672 |    0.6383 |
. |.....................|    -1.201 |    -2.230 |   -0.5026 |    -1.531 |
. |.....................|   -0.3216 |...........|...........|...........|
. |    U|    -847.36856 |    -1.728 |     3.217 |    -1.070 |     2.694 |
```

```
. |.....................|   0.05237 | 0.0009680 |     2.130 |     1.732 |
. |.....................|     2.147 |...........|...........|...........|
. |    X|    -847.36856 |    0.1776 |     24.95 |    0.3430 |     14.79 |
. |.....................|   0.05237 | 0.0009680 |     2.130 |     1.732 |
. |.....................|     2.147 |...........|...........|...........|
. |    F| Forward Diff. |     1.650 |   -0.7881 |  -0.04979 |    0.4066 |
. |.....................|     1.681 |    0.3884 |    0.2197 |     17.72 |
. |.....................|    0.1584 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   50|    -847.37635 |    -1.052 |    0.8495 |   -0.8674 |    0.6375 |
. |.....................|    -1.207 |    -2.248 |   -0.5187 |    -1.531 |
. |.....................|   -0.3161 |...........|...........|...........|
. |    U|    -847.37635 |    -1.728 |     3.217 |    -1.070 |     2.693 |
. |.....................|   0.05209 | 0.0007932 |     2.123 |     1.732 |
. |.....................|     2.149 |...........|...........|...........|
. |    X|    -847.37635 |    0.1776 |     24.95 |    0.3429 |     14.78 |
. |.....................|   0.05209 | 0.0007932 |     2.123 |     1.732 |
. |.....................|     2.149 |...........|...........|...........|
. |    F| Forward Diff. |    -2.906 |    -5.486 |    -1.016 |    -2.863 |
. |.....................|   -0.2623 |    0.2782 |  -0.05806 |     17.84 |
. |.....................|    0.2619 |...........|...........|...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   51|    -847.37685 |    -1.052 |    0.8495 |   -0.8674 |    0.6375 |
. |.....................|    -1.207 |    -2.248 |   -0.5187 |    -1.531 |
. |.....................|   -0.3161 |...........|...........|...........|
. |    U|    -847.37685 |    -1.728 |     3.217 |    -1.070 |     2.693 |
. |.....................|   0.05209 | 0.0007932 |     2.123 |     1.732 |
. |.....................|     2.149 |...........|...........|...........|
. |    X|    -847.37685 |    0.1776 |     24.95 |    0.3429 |     14.78 |
. |.....................|   0.05209 | 0.0007932 |     2.123 |     1.732 |
. |.....................|     2.149 |...........|...........|...........|
. calculating covariance matrix
. done
```

```
. → Calculating residuals/tables
. ✔ done
```

```
. → compress origData in nlmixr2 object, save 13504
```

```
. → compress parHistData in nlmixr2 object, save 7224
```

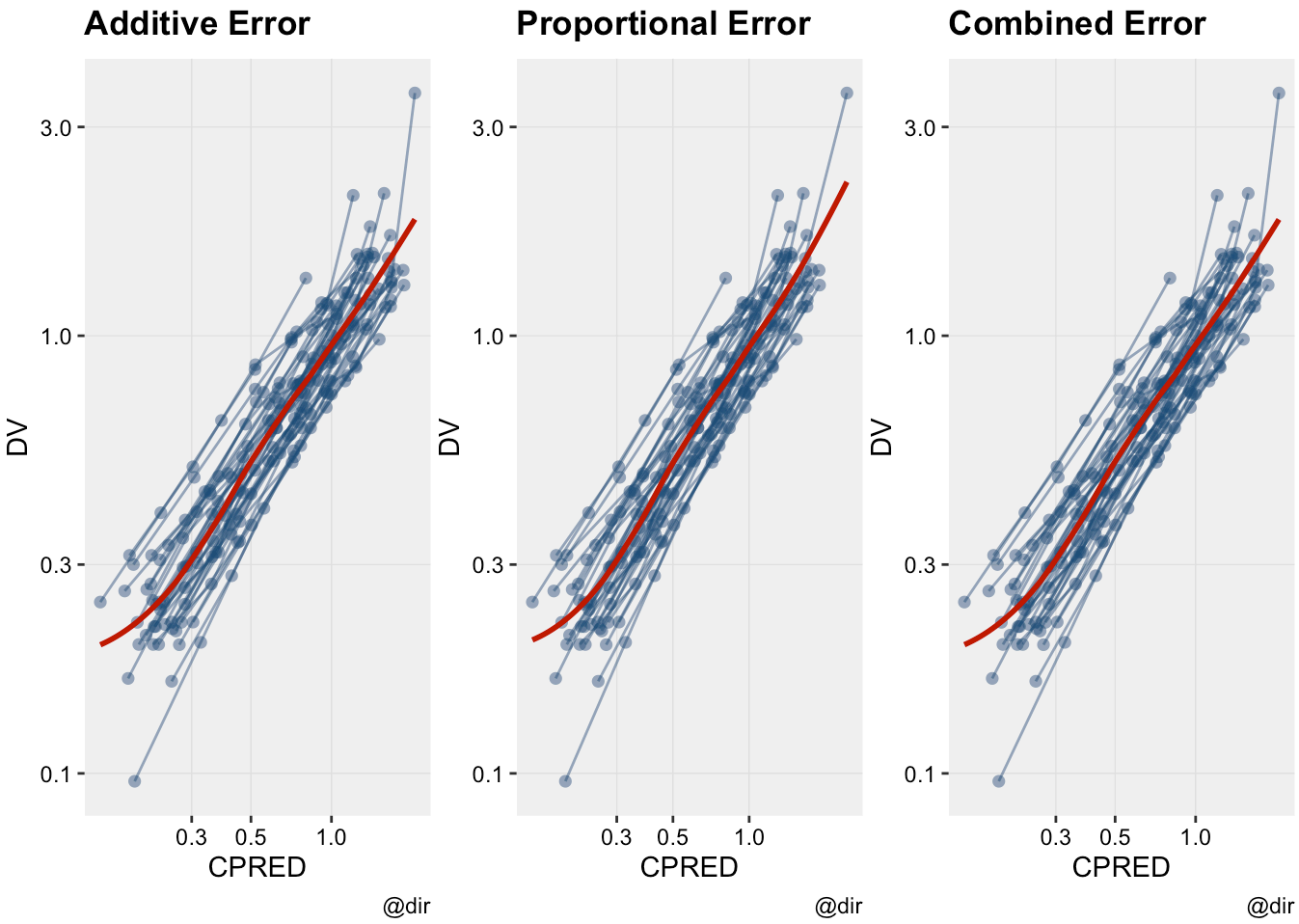
4.2 Model diagnostics - Objective Function Values

```
# Extract Objective Functions
two_cmt_add_objDf <- two_cmt_add_pk_fit$objDf
two_cmt_prop_objDf  <- two_cmt_pk_fit$objDf
two_cmt_comb_objDf <- two_cmt_combined_pk_fit$objDf

error_compare_obj <- rbind(two_cmt_add_objDf, two_cmt_prop_objDf, two_cmt_comb_objDf)
rownames(error_compare_obj) <- c("Additive", "Proportional", "Combined")
error_compare_obj
```

```
.                   OBJF       AIC       BIC Log-likelihood Condition#(Cov)
. Additive     -788.4941 -403.0808 -376.6544       209.5404       109.30042
. Proportional -847.3623 -461.9490 -435.5226       238.9745        76.94475
. Combined     -847.3769 -459.9636 -430.2338       238.9818        75.97811
.              Condition#(Cor)
. Additive            13.84881
. Proportional        13.50468
. Combined            13.24762
```

```
# Convert to XPOSE for goodness of fit

two_cmt_add_xpdb_pk <- xpose_data_nlmixr2(two_cmt_add_pk_fit,
                                    xp_theme = theme_xp_nlmixr2()
                                    )

two_cmt_combined_xpdb_pk <- xpose_data_nlmixr2(two_cmt_combined_pk_fit,
                                    xp_theme = theme_xp_nlmixr2()
                                    )

# observation vs individual prediction plot
add_error_dv_pred <- dv_vs_pred(two_cmt_xpdb_pk,
                                group="ID",
                                title = "Additive Error",
                                log = "xy",
                                subtitle = NULL,
                                guide = FALSE
                                )

prop_error_dv_pred <- dv_vs_pred(two_cmt_add_xpdb_pk,
                                group="ID",
                                title = "Proportional Error",
                                log = "xy",
                                subtitle = NULL,
                                guide = FALSE
                                )
comb_error_dv_pred <- dv_vs_pred(two_cmt_combined_xpdb_pk,
                                group="ID",
                                title = "Combined Error",
                                log = "xy",
                                subtitle = NULL,
                                guide = FALSE
                                )

grid.arrange(add_error_dv_pred, prop_error_dv_pred, comb_error_dv_pred, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```


Additive Error
Proportional Error
Combined Error
3.0
1.0
0.3
0.1
DV
0.3
0.5
1.0
CPRED
@dir

```
# residual error vs population prediction plot
add_error_cwres <- res_vs_pred(two_cmt_add_xpdb_pk,
                                    res="CWRES",
                                    type="ps",
                                    title = "Additive error",
                                    subtitle = NULL,
                                    guide = TRUE
                                    )

prop_error_cwres <- res_vs_pred(two_cmt_xpdb_pk,
                                    res="CWRES",
                                    type="ps",
                                    title = "Proportioanl error",
                                    subtitle = NULL,
                                    guide = TRUE
                                    )


comb_error_cwres <- res_vs_pred(two_cmt_combined_xpdb_pk,
                                    res="CWRES",
                                    type="ps",
                                    title = "Combined error",
                                    subtitle = NULL,
                                    guide = TRUE
                                    )

grid.arrange(add_error_cwres, prop_error_cwres, comb_error_cwres, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```

4.3 Two-cmt model parameters

```
# Parameter estimates - Fixed + RUV
two_cmt_pk_fit$parFixedDf %>% select(`Back-transformed`, `%RSE`, `Shrink(SD)%`) %>% rena
me(Parameters = `Back-transformed`)
```

```
.           Parameters      %RSE Shrink(SD)%
. tvcl      0.17748053  2.193853   -1.245711
. tvv1     24.92234149  2.249408  -23.089747
. tvq       0.34392708 15.701199          NA
. tvv2     14.79209350  2.535389   19.804161
. prop.err  0.05221194        NA          NA
```

```
# Parameter estimates - Fixed + RUV
two_cmt_combined_pk_fit$parFixedDf %>% select(`Back-transformed`, `%RSE`, `Shrink(SD)%`)
%>% rename(Parameters = `Back-transformed`)
```

```
.            Parameters      %RSE Shrink(SD)%
. tvcl     1.775744e-01  2.200118  -0.4427955
. tvv1     2.494689e+01  2.231199 -23.0478550
. tvq      3.429018e-01 15.495001          NA
. tvv2     1.477695e+01  2.495986  20.3316795
. prop.err 5.208566e-02        NA          NA
. add.err  7.931689e-04        NA          NA
```

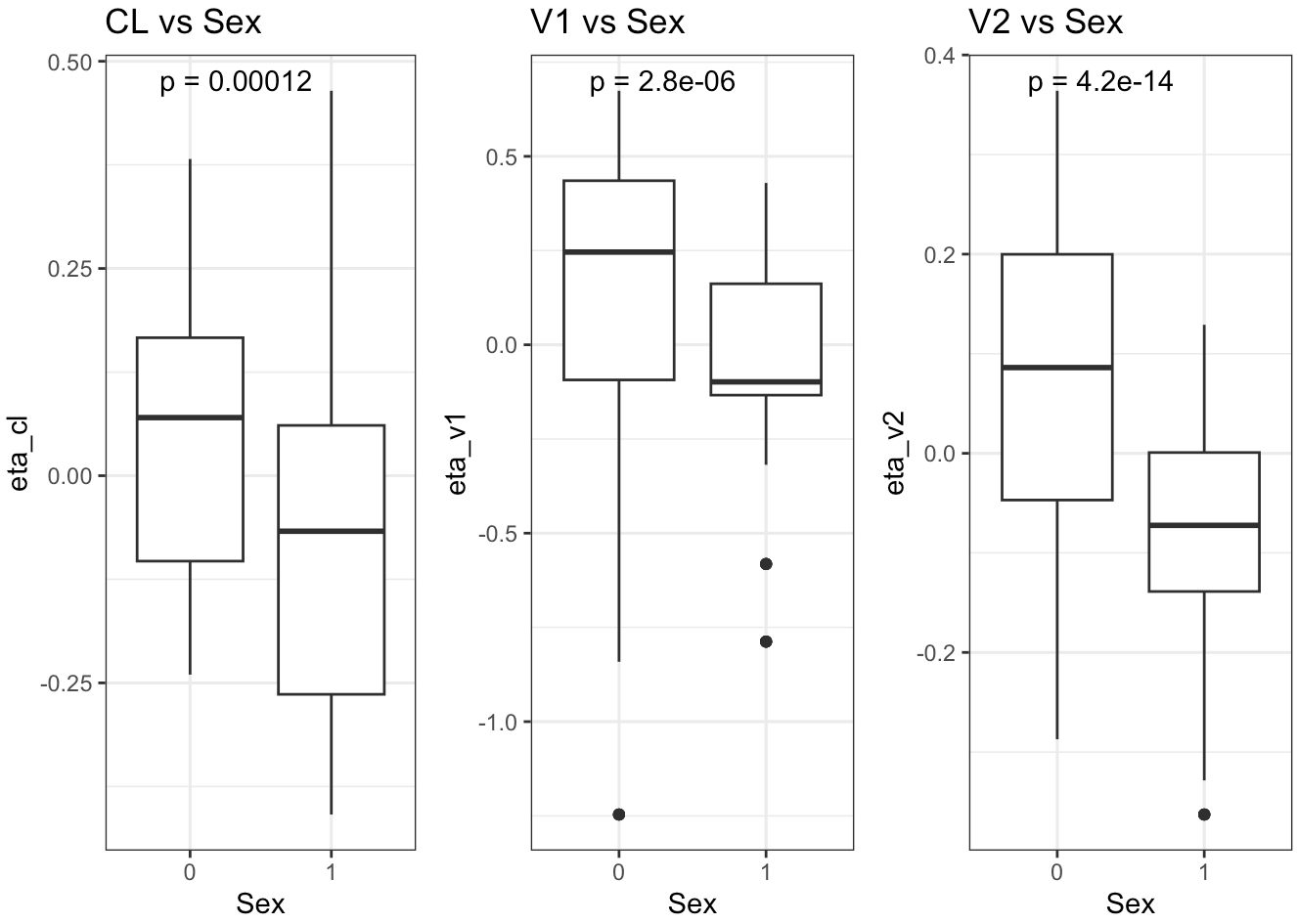
5 Showcase 3. Covariates to explain Inter-Individual Variability

5.1 Omegas and Etas - Distribution of individual parameters

```
# Parameter estimates - Fixed + RUV
two_cmt_pk_fit$parFixedDf %>% select(`Back-transformed`, `%RSE`, `Shrink(SD)%`) %>% rena
me(Parameters = `Back-transformed`)
```

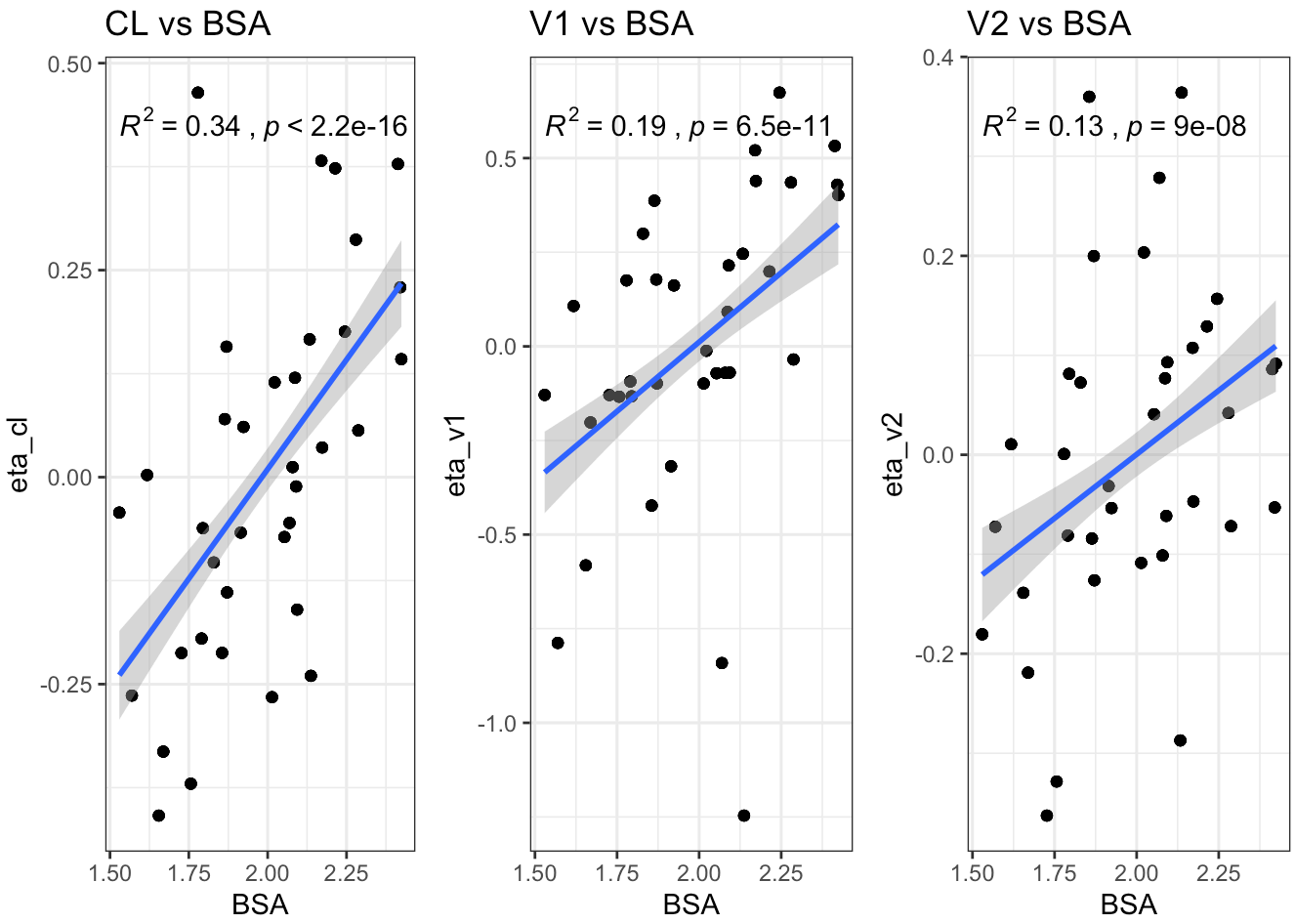
```
.           Parameters      %RSE Shrink(SD)%
. tvcl      0.17748053  2.193853   -1.245711
. tvv1     24.92234149  2.249408  -23.089747
. tvq       0.34392708 15.701199          NA
. tvv2     14.79209350  2.535389   19.804161
. prop.err  0.05221194        NA          NA
```

```
base_combined_dataset <- merge(two_cmt_pk_fit, busulfan_dataset, by = c("ID", "TIME", "D
V"))

# Sex as covariates
cov_sex_cl <- ggplot(base_combined_dataset, aes(as.factor(Sex), eta_cl)) +
  geom_boxplot() +
  stat_compare_means(method = "wilcox.test", label = "p.format") +
  theme_bw() +
  labs(title = "CL vs Sex", x = "Sex")

cov_sex_v1 <- ggplot(base_combined_dataset, aes(as.factor(Sex), eta_v1)) +
  geom_boxplot() +
  stat_compare_means(method = "wilcox.test", label = "p.format") +
  theme_bw() +
  labs(title = "V1 vs Sex", x = "Sex")

cov_sex_v2 <- ggplot(base_combined_dataset, aes(as.factor(Sex), eta_v2)) +
  geom_boxplot() +
  stat_compare_means(method = "wilcox.test", label = "p.format") +
  theme_bw() +
  labs(title = "V2 vs Sex", x = "Sex")

grid.arrange(cov_sex_cl, cov_sex_v1, cov_sex_v2, nrow = 1)
```



```
# BSA as covariates
cov_bsa_cl <- ggplot(base_combined_dataset, aes(BSA, eta_cl)) +
  geom_point() +
  geom_smooth(method = "lm", se = TRUE) +
  stat_cor(method = "pearson",
           aes(label = paste(..rr.label.., ..p.label.., sep = "~`,`~"))) +
  theme_bw() +
  labs(title = "CL vs BSA", x = "BSA")

cov_bsa_v1 <- ggplot(base_combined_dataset, aes(BSA, eta_v1)) +
  geom_point() +
  geom_smooth(method = "lm", se = TRUE) +
  stat_cor(method = "pearson",
           aes(label = paste(..rr.label.., ..p.label.., sep = "~`,`~"))) +
  theme_bw() +
  labs(title = "V1 vs BSA", x = "BSA")

cov_bsa_v2 <- ggplot(base_combined_dataset, aes(BSA, eta_v2)) +
  geom_point() +
  geom_smooth(method = "lm", se = TRUE) +
  stat_cor(method = "pearson",
           aes(label = paste(..rr.label.., ..p.label.., sep = "~`,`~"))) +
  theme_bw() +
  labs(title = "V2 vs BSA", x = "BSA")

grid.arrange(cov_bsa_cl, cov_bsa_v1, cov_bsa_v2, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```


CL vs BSA
R^2 = 0.34 , p < 2.2e-16
eta_cl
BSA
V1 vs BSA
R^2 = 0.19 , p = 6.5e-11
eta_v1
BSA
V2 vs BSA
R^2 = 0.13 , p = 9e-08
eta_v2
BSA

5.2 Run covariate model

```
busulfan_final_2cmt_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(0.187)
    tvv1  <- log(29)
    tvq   <- log(0.41)
    tvv2  <- log(17.3)

    covbsav1 <- log(2.32)
    covbsacl <- log(1.30)
    covsexv2 <- log(0.8)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0222
    eta_v1  ~ 0.0222
    eta_v2  ~ 0.0241

    # Residual variability
    prop.err <-  0.0955
  })

  model({
    # Individual value
    cl <- exp(tvcl + eta_cl) * (BSA/2.01)^covbsacl
    v1 <- exp(tvv1 + eta_v1) * (BSA/2.01)^covbsav1
    q  <- exp(tvq)
    v2 <- exp(tvv2 + eta_v2)

    # Sex effect
    if (Sex == 1) {
      v2 <- v2 * covsexv2
    } else {
      v2 <- v2 * 1
    }

    # Conversion
    k10 <- cl / v1
    k12 <- q / v1
    k21 <- q / v2

    # ODEs
    d / dt(central) = -k10 * central - k12 * central + k21 * peripheral
    d / dt(peripheral) = -k21 * peripheral + k12 * central

    # Concentration
    cp = central / v1

    # Error model (on log scale)
    IPRED = cp
    IPRED ~ prop(prop.err)
```

```
  })
}

# Model Fitting
two_cmt_final_pk_fit <- nlmixr2(
  busulfan_final_2cmt_model,
  busulfan_dataset,
  "focei",
  table = list(cwres = TRUE, npde = TRUE)
)
```

```
. ℹ parameter labels from comments are typically ignored in non-interactive mode
```

```
. ℹ Need to run with the source intact to parse comments
```

```
. Key: U: Unscaled Parameters; X: Back-transformed parameters; G: Gill difference gradie
nt approximation
. F: Forward difference gradient approximation
. C: Central difference gradient approximation
. M: Mixed forward and central difference gradient approximation
. Unscaled parameters for Omegas=chol(solve(omega));
. Diagonals are transformed, as specified by foceiControl(diagXform=)
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    #| Objective Fun |      tvcl |      tvv1 |       tvq |      tvv2 |
. |.....................|  covbsav1 |  covbsacl |  covsexv2 |  prop.err |
. |.....................|        o1 |        o2 |        o3 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    1|     14127.970 |    -1.000 |     1.000 |   -0.6887 |    0.7952 |
. |.....................| -0.001490 |   -0.2312 |   -0.4237 |   -0.2973 |
. |.....................|    0.6921 |    0.6921 |    0.6712 |...........|
. |    U|      14127.97 |    -1.677 |     3.367 |   -0.8916 |     2.851 |
. |.....................|    0.8416 |    0.2624 |   -0.2231 |   0.09550 |
. |.....................|     2.591 |     2.591 |     2.538 |...........|
. |    X|      14127.97 |    0.1870 |     29.00 |    0.4100 |     17.30 |
. |.....................|    0.8416 |    0.2624 |   -0.2231 |   0.09550 |
. |.....................|     2.591 |     2.591 |     2.538 |...........|
. |    G|    Gill Diff. |     180.1 |     1391. |    -624.1 |    -178.0 |
. |.....................|    -106.7 |    -107.0 |     3622. |-1.164e+04 |
. |.....................|     7.575 |     357.4 |     19.64 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    2|     7763.8225 |    -1.015 |    0.8868 |   -0.6380 |    0.8096 |
. |.....................|  0.007187 |   -0.2225 |   -0.7183 |    0.6494 |
. |.....................|    0.6914 |    0.6630 |    0.6696 |...........|
. |    U|     7763.8225 |    -1.691 |     3.254 |   -0.8408 |     2.865 |
. |.....................|    0.8519 |    0.2955 |    -1.544 |    0.1407 |
. |.....................|     2.590 |     2.579 |     2.537 |...........|
. |    X|     7763.8225 |    0.1843 |     25.90 |    0.4314 |     17.55 |
. |.....................|    0.8519 |    0.2955 |    -1.544 |    0.1407 |
. |.....................|     2.590 |     2.579 |     2.537 |...........|
. |    M|   Mixed Diff. |     1325. |     62.48 | 1.393e+04 |     281.7 |
. |.....................|   0.02503 |    -488.0 |    -889.8 |    -7693. |
. |.....................|     482.2 |     28.62 |     71.46 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    3|     5140.7751 |    -1.091 |    0.8577 |    -1.399 |    0.7973 |
. |.....................|  0.009152 |   -0.1934 |   -0.7358 |     1.291 |
. |.....................|    0.6645 |    0.6548 |    0.6653 |...........|
. |    U|     5140.7751 |    -1.768 |     3.225 |    -1.602 |     2.853 |
. |.....................|    0.8542 |    0.4062 |    -1.622 |    0.1713 |
. |.....................|     2.580 |     2.576 |     2.536 |...........|
. |    X|     5140.7751 |    0.1707 |     25.15 |    0.2014 |     17.34 |
. |.....................|    0.8542 |    0.4062 |    -1.622 |    0.1713 |
. |.....................|     2.580 |     2.576 |     2.536 |...........|
. |    F| Forward Diff. |     1247. |    -139.6 |     4181. |     583.0 |
. |.....................|    0.2621 |    -427.8 |    -1681. |    -2694. |
. |.....................|     341.3 |     12.97 |     67.22 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    4|    -484.86977 |    -1.486 |    0.9280 |    -1.882 |    0.5812 |
```

```
. |.....................|  0.008500 |  -0.06114 |   -0.1036 |     1.655 |
. |.....................|    0.5669 |    0.6538 |    0.6440 |...........|
. |    U|    -484.86977 |    -2.163 |     3.295 |    -2.085 |     2.637 |
. |.....................|    0.8534 |    0.9104 |     1.211 |    0.1887 |
. |.....................|     2.542 |     2.576 |     2.527 |...........|
. |    X|    -484.86977 |    0.1150 |     26.98 |    0.1243 |     13.97 |
. |.....................|    0.8534 |    0.9104 |     1.211 |    0.1887 |
. |.....................|     2.542 |     2.576 |     2.527 |...........|
. |    5|     152.87675 |    -2.935 |     1.239 |    -1.926 |   -0.2767 |
. |.....................|  0.004941 |    0.4176 |     2.421 |     1.988 |
. |.....................|    0.2302 |    0.6568 |    0.5662 |...........|
. |    U|     152.87675 |    -3.612 |     3.607 |    -2.129 |     1.779 |
. |.....................|    0.8492 |     2.735 |     12.53 |    0.2046 |
. |.....................|     2.412 |     2.577 |     2.497 |...........|
. |    X|     152.87675 |   0.02700 |     36.84 |    0.1189 |     5.923 |
. |.....................|    0.8492 |     2.735 |     12.53 |    0.2046 |
. |.....................|     2.412 |     2.577 |     2.497 |...........|
. |    F| Forward Diff. |    -832.5 |    -167.6 |     6.251 |    -160.1 |
. |.....................|    -3.240 |     20.25 |    -276.2 |     27.27 |
. |.....................|     71.98 |     3.835 |     2.231 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    6|     8228552.5 |     1.828 |     1.772 |    -2.426 |     1.090 |
. |.....................|   0.01850 |  -0.03713 |     1.783 |     1.493 |
. |.....................|    0.1644 |    0.6483 |    0.6162 |...........|
. |    U|     8228552.5 |     1.151 |     4.139 |    -2.629 |     3.146 |
. |.....................|    0.8653 |     1.002 |     9.665 |    0.1810 |
. |.....................|     2.387 |     2.574 |     2.516 |...........|
. |    X|     8228552.5 |     3.163 |     62.73 |   0.07218 |     23.24 |
. |.....................|    0.8653 |     1.002 |     9.665 |    0.1810 |
. |.....................|     2.387 |     2.574 |     2.516 |...........|
. |    7|    -660.45343 |    -1.121 |     1.002 |    -1.885 |    0.6515 |
. |.....................|  0.009923 |  -0.07003 |   0.01768 |     1.643 |
. |.....................|    0.5353 |    0.6522 |    0.6430 |...........|
. |    U|    -660.45343 |    -1.797 |     3.369 |    -2.087 |     2.707 |
. |.....................|    0.8551 |    0.8765 |     1.755 |    0.1882 |
. |.....................|     2.530 |     2.575 |     2.527 |...........|
. |    X|    -660.45343 |    0.1657 |     29.05 |    0.1240 |     14.98 |
. |.....................|    0.8551 |    0.8765 |     1.755 |    0.1882 |
. |.....................|     2.530 |     2.575 |     2.527 |...........|
. |    F| Forward Diff. |     23.27 |    -154.7 |    -27.11 |     25.89 |
. |.....................|    -5.024 |    -62.93 |     111.7 |     39.81 |
. |.....................|     5.211 |     4.136 |    0.5134 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |    8|    -645.97275 |    -1.165 |     1.297 |    -1.833 |    0.6021 |
. |.....................|   0.01951 |   0.05002 |   -0.1954 |     1.567 |
. |.....................|    0.5254 |    0.6443 |    0.6421 |...........|
. |    U|    -645.97275 |    -1.842 |     3.664 |    -2.036 |     2.658 |
. |.....................|    0.8665 |     1.334 |    0.7996 |    0.1845 |
. |.....................|     2.526 |     2.572 |     2.527 |...........|
. |    X|    -645.97275 |    0.1585 |     39.01 |    0.1306 |     14.26 |
. |.....................|    0.8665 |     1.334 |    0.7996 |    0.1845 |
. |.....................|     2.526 |     2.572 |     2.527 |...........|
```

```
. |    9|    -678.38179 |    -1.140 |     1.127 |    -1.863 |    0.6304 |
. |.....................|   0.01401 |  -0.01885 |  -0.07319 |     1.611 |
. |.....................|    0.5311 |    0.6488 |    0.6426 |...........|
. |    U|    -678.38179 |    -1.816 |     3.495 |    -2.065 |     2.686 |
. |.....................|    0.8600 |     1.072 |     1.347 |    0.1866 |
. |.....................|     2.529 |     2.574 |     2.527 |...........|
. |    X|    -678.38179 |    0.1626 |     32.94 |    0.1268 |     14.67 |
. |.....................|    0.8600 |     1.072 |     1.347 |    0.1866 |
. |.....................|     2.529 |     2.574 |     2.527 |...........|
. |    F| Forward Diff. |    -121.8 |     22.47 |     10.22 |    -9.892 |
. |.....................|    -11.69 |    -14.33 |     43.34 |     45.56 |
. |.....................|     4.209 |     3.578 |  -0.01589 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   10|    -682.77832 |   -0.9922 |     1.100 |    -1.875 |    0.6424 |
. |.....................|   0.02816 | -0.001509 |   -0.1256 |     1.556 |
. |.....................|    0.5260 |    0.6445 |    0.6426 |...........|
. |    U|    -682.77832 |    -1.669 |     3.467 |    -2.078 |     2.698 |
. |.....................|    0.8768 |     1.138 |     1.112 |    0.1840 |
. |.....................|     2.527 |     2.572 |     2.527 |...........|
. |    X|    -682.77832 |    0.1885 |     32.06 |    0.1252 |     14.85 |
. |.....................|    0.8768 |     1.138 |     1.112 |    0.1840 |
. |.....................|     2.527 |     2.572 |     2.527 |...........|
. |    F| Forward Diff. |     160.2 |    -31.12 |    -27.00 |     37.00 |
. |.....................|    -11.47 |    -12.50 |     133.0 |     42.88 |
. |.....................|     3.874 |     3.827 |    0.1085 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   11|    -693.68378 |    -1.060 |     1.097 |    -1.886 |    0.6034 |
. |.....................|   0.05197 |   0.02261 |   -0.2467 |     1.474 |
. |.....................|    0.5095 |    0.6376 |    0.6412 |...........|
. |    U|    -693.68378 |    -1.737 |     3.465 |    -2.088 |     2.659 |
. |.....................|    0.9051 |     1.230 |    0.5697 |    0.1801 |
. |.....................|     2.520 |     2.570 |     2.526 |...........|
. |    X|    -693.68378 |    0.1761 |     31.96 |    0.1239 |     14.28 |
. |.....................|    0.9051 |     1.230 |    0.5697 |    0.1801 |
. |.....................|     2.520 |     2.570 |     2.526 |...........|
. |    F| Forward Diff. |    -89.64 |    -49.22 |    -22.11 |    -21.81 |
. |.....................|    -9.724 |     41.29 |    -100.9 |     50.63 |
. |.....................|     1.040 |     3.359 |   -0.3940 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   12|    -702.37449 |    -1.045 |     1.144 |    -1.921 |    0.6070 |
. |.....................|   0.07585 |  -0.03162 |   -0.1803 |     1.342 |
. |.....................|    0.5061 |    0.6319 |    0.6416 |...........|
. |    U|    -702.37449 |    -1.721 |     3.512 |    -2.124 |     2.662 |
. |.....................|    0.9335 |     1.023 |    0.8676 |    0.1738 |
. |.....................|     2.519 |     2.567 |     2.526 |...........|
. |    X|    -702.37449 |    0.1788 |     33.50 |    0.1195 |     14.33 |
. |.....................|    0.9335 |     1.023 |    0.8676 |    0.1738 |
. |.....................|     2.519 |     2.567 |     2.526 |...........|
. |    F| Forward Diff. |     1.029 |     27.12 |    -16.45 |     6.925 |
. |.....................|    -11.79 |    -5.123 |     61.43 |     46.65 |
. |.....................|     1.094 |     4.626 |   -0.2367 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
```

```
. |   13|    -710.57444 |    -1.037 |     1.116 |    -1.948 |    0.5903 |
. |.....................|    0.1112 |  -0.03931 |   -0.2386 |     1.193 |
. |.....................|    0.4956 |    0.6192 |    0.6414 |...........|
. |    U|    -710.57444 |    -1.714 |     3.483 |    -2.151 |     2.646 |
. |.....................|    0.9754 |    0.9936 |    0.6063 |    0.1667 |
. |.....................|     2.515 |     2.563 |     2.526 |...........|
. |    X|    -710.57444 |    0.1802 |     32.56 |    0.1164 |     14.09 |
. |.....................|    0.9754 |    0.9936 |    0.6063 |    0.1667 |
. |.....................|     2.515 |     2.563 |     2.526 |...........|
. |    F| Forward Diff. |    -12.68 |    -38.45 |    -29.01 |    -10.51 |
. |.....................|    -8.543 |     2.649 |    -44.28 |     49.59 |
. |.....................|    0.3335 |     4.500 |   -0.3845 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   14|    -717.60978 |    -1.046 |     1.145 |    -1.962 |    0.6036 |
. |.....................|    0.1374 |  -0.01669 |   -0.1919 |     1.037 |
. |.....................|    0.4939 |    0.6069 |    0.6423 |...........|
. |    U|    -717.60978 |    -1.723 |     3.513 |    -2.164 |     2.659 |
. |.....................|     1.007 |     1.080 |    0.8154 |    0.1592 |
. |.....................|     2.514 |     2.558 |     2.527 |...........|
. |    X|    -717.60978 |    0.1785 |     33.54 |    0.1148 |     14.28 |
. |.....................|     1.007 |     1.080 |    0.8154 |    0.1592 |
. |.....................|     2.514 |     2.558 |     2.527 |...........|
. |    F| Forward Diff. |   -0.2633 |     21.09 |    -22.57 |     6.064 |
. |.....................|    -10.38 |     3.637 |     54.07 |     47.41 |
. |.....................|     1.601 |     5.727 |   -0.2805 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   15|    -726.95515 |    -1.101 |     1.117 |    -2.033 |    0.6042 |
. |.....................|    0.1892 |  0.005576 |   -0.2321 |    0.7191 |
. |.....................|    0.4827 |    0.5705 |    0.6439 |...........|
. |    U|    -726.95515 |    -1.778 |     3.484 |    -2.236 |     2.660 |
. |.....................|     1.068 |     1.165 |    0.6355 |    0.1440 |
. |.....................|     2.510 |     2.544 |     2.527 |...........|
. |    X|    -726.95515 |    0.1690 |     32.60 |    0.1069 |     14.29 |
. |.....................|     1.068 |     1.165 |    0.6355 |    0.1440 |
. |.....................|     2.510 |     2.544 |     2.527 |...........|
. |    F| Forward Diff. |    -141.5 |    -46.45 |    -34.66 |    -18.81 |
. |.....................|    -7.046 |     33.80 |    -66.55 |     47.59 |
. |.....................|     4.251 |     6.797 |   -0.3726 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   16|    -739.82719 |   -0.9942 |     1.113 |    -2.076 |    0.5756 |
. |.....................|    0.2503 |  -0.05783 |   -0.2374 |    0.4226 |
. |.....................|    0.4380 |    0.5030 |    0.6434 |...........|
. |    U|    -739.82719 |    -1.671 |     3.480 |    -2.279 |     2.631 |
. |.....................|     1.141 |    0.9230 |    0.6115 |    0.1299 |
. |.....................|     2.493 |     2.518 |     2.527 |...........|
. |    X|    -739.82719 |    0.1881 |     32.46 |    0.1024 |     13.89 |
. |.....................|     1.141 |    0.9230 |    0.6115 |    0.1299 |
. |.....................|     2.493 |     2.518 |     2.527 |...........|
. |    F| Forward Diff. |     128.4 |    -85.66 |    -59.77 |     5.419 |
. |.....................|    -3.157 |    -20.29 |    -6.016 |     41.36 |
. |.....................|     3.690 |     8.767 |   -0.3749 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
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. |   17|    -743.84889 |    -1.101 |     1.206 |    -2.058 |    0.5373 |
. |.....................|    0.2943 |   -0.2005 |   -0.2236 |    0.2051 |
. |.....................|    0.3589 |    0.3672 |    0.6450 |...........|
. |    U|    -743.84889 |    -1.777 |     3.574 |    -2.261 |     2.593 |
. |.....................|     1.193 |    0.3791 |    0.6732 |    0.1195 |
. |.....................|     2.462 |     2.465 |     2.528 |...........|
. |    X|    -743.84889 |    0.1691 |     35.64 |    0.1043 |     13.37 |
. |.....................|     1.193 |    0.3791 |    0.6732 |    0.1195 |
. |.....................|     2.462 |     2.465 |     2.528 |...........|
. |    F| Forward Diff. |    -104.7 |     107.1 |    -28.32 |    -12.85 |
. |.....................|    -5.113 |    -76.94 |     9.653 |     36.34 |
. |.....................|     7.383 |     10.52 |   -0.3569 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   18|    -766.04796 |    -1.069 |     1.111 |    -1.992 |    0.5403 |
. |.....................|    0.3306 |  -0.03142 |   -0.1900 |   0.01341 |
. |.....................|    0.2577 |    0.2131 |    0.6476 |...........|
. |    U|    -766.04796 |    -1.746 |     3.478 |    -2.195 |     2.596 |
. |.....................|     1.236 |     1.024 |    0.8238 |    0.1103 |
. |.....................|     2.423 |     2.406 |     2.529 |...........|
. |    X|    -766.04796 |    0.1745 |     32.39 |    0.1114 |     13.41 |
. |.....................|     1.236 |     1.024 |    0.8238 |    0.1103 |
. |.....................|     2.423 |     2.406 |     2.529 |...........|
. |    F| Forward Diff. |    -31.40 |    -40.24 |    -56.68 |     2.315 |
. |.....................|    -1.900 |    -1.630 |     74.35 |     34.50 |
. |.....................|     1.658 |     10.21 |   -0.4460 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   19|     9505.7581 |   -0.9741 |     1.233 |    -1.820 |    0.5333 |
. |.....................|    0.3364 |  -0.02648 |   -0.4155 |  -0.09121 |
. |.....................|    0.2526 |    0.1821 |    0.6489 |...........|
. |    U|     9505.7581 |    -1.651 |     3.600 |    -2.023 |     2.589 |
. |.....................|     1.243 |     1.042 |   -0.1865 |    0.1053 |
. |.....................|     2.421 |     2.394 |     2.529 |...........|
. |    X|     9505.7581 |    0.1919 |     36.59 |    0.1323 |     13.31 |
. |.....................|     1.243 |     1.042 |   -0.1865 |    0.1053 |
. |.....................|     2.421 |     2.394 |     2.529 |...........|
. |   20|    -769.18889 |    -1.060 |     1.123 |    -1.975 |    0.5396 |
. |.....................|    0.3312 |  -0.03093 |   -0.2126 |  0.002949 |
. |.....................|    0.2572 |    0.2100 |    0.6477 |...........|
. |    U|    -769.18889 |    -1.736 |     3.490 |    -2.177 |     2.595 |
. |.....................|     1.237 |     1.026 |    0.7228 |    0.1098 |
. |.....................|     2.423 |     2.405 |     2.529 |...........|
. |    X|    -769.18889 |    0.1761 |     32.79 |    0.1133 |     13.40 |
. |.....................|     1.237 |     1.026 |    0.7228 |    0.1098 |
. |.....................|     2.423 |     2.405 |     2.529 |...........|
. |    F| Forward Diff. |    -28.30 |    -20.19 |    -53.84 |    -7.481 |
. |.....................|    -2.004 |     1.708 |     19.40 |     35.83 |
. |.....................|     1.285 |     10.02 |   -0.5813 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   21|    -771.51161 |    -1.047 |     1.132 |    -1.951 |    0.5429 |
. |.....................|    0.3321 |  -0.03168 |   -0.2212 |  -0.01292 |
. |.....................|    0.2566 |    0.2056 |    0.6480 |...........|
. |    U|    -771.51161 |    -1.724 |     3.499 |    -2.154 |     2.598 |
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. |.....................|     1.238 |     1.023 |    0.6842 |    0.1091 |
. |.....................|     2.423 |     2.403 |     2.529 |...........|
. |    X|    -771.51161 |    0.1784 |     33.08 |    0.1161 |     13.44 |
. |.....................|     1.238 |     1.023 |    0.6842 |    0.1091 |
. |.....................|     2.423 |     2.403 |     2.529 |...........|
. |   22|    -773.79921 |    -1.010 |     1.159 |    -1.879 |    0.5528 |
. |.....................|    0.3347 |  -0.03395 |   -0.2470 |  -0.06053 |
. |.....................|    0.2549 |    0.1922 |    0.6488 |...........|
. |    U|    -773.79921 |    -1.686 |     3.526 |    -2.082 |     2.608 |
. |.....................|     1.241 |     1.014 |    0.5687 |    0.1068 |
. |.....................|     2.422 |     2.398 |     2.529 |...........|
. |    X|    -773.79921 |    0.1852 |     33.98 |    0.1247 |     13.58 |
. |.....................|     1.241 |     1.014 |    0.5687 |    0.1068 |
. |.....................|     2.422 |     2.398 |     2.529 |...........|
. |    F| Forward Diff. |     56.38 |     48.97 |    -38.66 |    -20.11 |
. |.....................|    -2.236 |    -1.516 |    -122.9 |     34.96 |
. |.....................|     1.166 |     10.64 |   -0.6442 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   23|    -781.41867 |    -1.045 |     1.128 |    -1.814 |    0.5744 |
. |.....................|    0.3408 |  -0.03743 |   -0.1965 |   -0.1165 |
. |.....................|    0.2302 |    0.1192 |    0.6503 |...........|
. |    U|    -781.41867 |    -1.721 |     3.495 |    -2.016 |     2.630 |
. |.....................|     1.248 |     1.001 |    0.7949 |    0.1041 |
. |.....................|     2.412 |     2.370 |     2.530 |...........|
. |    X|    -781.41867 |    0.1788 |     32.95 |    0.1331 |     13.87 |
. |.....................|     1.248 |     1.001 |    0.7949 |    0.1041 |
. |.....................|     2.412 |     2.370 |     2.530 |...........|
. |    F| Forward Diff. |     6.592 |     42.19 |    -44.28 |     12.30 |
. |.....................|    -3.826 |    -5.711 |     124.9 |     36.27 |
. |.....................|     1.251 |     11.60 |   -0.6206 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   24|    -788.06206 |    -1.060 |     1.090 |    -1.756 |    0.5807 |
. |.....................|    0.3485 |  -0.05114 |   -0.2387 |   -0.1884 |
. |.....................|    0.2034 |   0.04369 |    0.6521 |...........|
. |    U|    -788.06206 |    -1.736 |     3.457 |    -1.959 |     2.636 |
. |.....................|     1.257 |    0.9485 |    0.6057 |    0.1007 |
. |.....................|     2.402 |     2.340 |     2.531 |...........|
. |    X|    -788.06206 |    0.1762 |     31.73 |    0.1410 |     13.96 |
. |.....................|     1.257 |    0.9485 |    0.6057 |    0.1007 |
. |.....................|     2.402 |     2.340 |     2.531 |...........|
. |    F| Forward Diff. |    -47.55 |    -25.87 |    -44.57 |    -35.27 |
. |.....................|   -0.4090 |    -3.092 |    -151.9 |     38.97 |
. |.....................|    0.6613 |     11.25 |   -0.7901 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   25|    -795.51055 |    -1.062 |     1.084 |    -1.705 |    0.6018 |
. |.....................|    0.3495 |  -0.05505 |   -0.2083 |   -0.2577 |
. |.....................|    0.1804 |  -0.05263 |    0.6546 |...........|
. |    U|    -795.51055 |    -1.739 |     3.452 |    -1.908 |     2.657 |
. |.....................|     1.259 |    0.9336 |    0.7421 |   0.09739 |
. |.....................|     2.393 |     2.303 |     2.531 |...........|
. |    X|    -795.51055 |    0.1757 |     31.56 |    0.1483 |     14.26 |
. |.....................|     1.259 |    0.9336 |    0.7421 |   0.09739 |
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. |.....................|     2.393 |     2.303 |     2.531 |.....|
. |    F| Forward Diff. |    -35.67 |     1.437 |    -51.00 |  -0.3824 |
. |.....................|    -2.351 |    -8.778 |     78.74 |     38.14 |
. |.....................|    0.8916 |     11.67 |   -0.9064 |.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   26|    -802.42911 |    -1.064 |     1.083 |    -1.644 |    0.6233 |
. |.....................|    0.3481 |  -0.04611 |   -0.2289 |   -0.3170 |
. |.....................|    0.1622 |   -0.1528 |    0.6587 |.....|
. |    U|    -802.42911 |    -1.740 |     3.451 |    -1.847 |     2.679 |
. |.....................|     1.257 |    0.9677 |    0.6496 |   0.09456 |
. |.....................|     2.386 |     2.265 |     2.533 |.....|
. |    X|    -802.42911 |    0.1755 |     31.52 |    0.1577 |     14.57 |
. |.....................|     1.257 |    0.9677 |    0.6496 |   0.09456 |
. |.....................|     2.386 |     2.265 |     2.533 |.....|
. |   27|    -813.40699 |    -1.089 |     1.082 |    -1.529 |    0.6745 |
. |.....................|    0.3435 |  -0.03010 |   -0.2303 |   -0.4354 |
. |.....................|    0.1194 |   -0.3850 |    0.6679 |.....|
. |    U|    -813.40699 |    -1.766 |     3.449 |    -1.732 |     2.730 |
. |.....................|     1.252 |     1.029 |    0.6436 |   0.08890 |
. |.....................|     2.370 |     2.175 |     2.537 |.....|
. |    X|    -813.40699 |    0.1711 |     31.47 |    0.1770 |     15.33 |
. |.....................|     1.252 |     1.029 |    0.6436 |   0.08890 |
. |.....................|     2.370 |     2.175 |     2.537 |.....|
. |   28|    -830.75318 |    -1.188 |     1.075 |    -1.081 |    0.8736 |
. |.....................|    0.3257 |   0.03220 |   -0.2355 |   -0.8964 |
. |.....................|  -0.04737 |    -1.288 |    0.7040 |.....|
. |    U|    -830.75318 |    -1.865 |     3.443 |    -1.284 |     2.929 |
. |.....................|     1.230 |     1.266 |    0.6200 |   0.06690 |
. |.....................|     2.305 |     1.826 |     2.551 |.....|
. |    X|    -830.75318 |    0.1549 |     31.27 |    0.2770 |     18.71 |
. |.....................|     1.230 |     1.266 |    0.6200 |   0.06690 |
. |.....................|     2.305 |     1.826 |     2.551 |.....|
. |    F| Forward Diff. |    -305.0 |     109.2 |    -12.49 |     47.69 |
. |.....................|    -4.421 |     53.43 |    -110.4 |     35.09 |
. |.....................|     14.57 |     11.71 |   -0.7567 |.....|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   29|    -76.750626 |    -1.129 |    0.9202 |   -0.2283 |    0.4076 |
. |.....................|    0.2356 |  -0.05071 |  -0.07669 |    -1.861 |
. |.....................|   -0.4678 |    -1.531 |    0.7842 |.....|
. |    U|    -76.750626 |    -1.806 |     3.287 |   -0.4312 |     2.463 |
. |.....................|     1.123 |    0.9501 |     1.332 |   0.02086 |
. |.....................|     2.143 |     1.732 |     2.583 |.....|
. |    X|    -76.750626 |    0.1643 |     26.78 |    0.6497 |     11.74 |
. |.....................|     1.123 |    0.9501 |     1.332 |   0.02086 |
. |.....................|     2.143 |     1.732 |     2.583 |.....|
. |   30|    -845.09518 |    -1.060 |     1.030 |    -1.076 |    0.8536 |
. |.....................|    0.3276 |  0.009783 |   -0.1892 |   -0.9111 |
. |.....................|  -0.05349 |    -1.293 |    0.7043 |.....|
. |    U|    -845.09518 |    -1.737 |     3.397 |    -1.279 |     2.909 |
. |.....................|     1.233 |     1.181 |    0.8276 |   0.06619 |
. |.....................|     2.303 |     1.824 |     2.551 |.....|
. |    X|    -845.09518 |    0.1760 |     29.87 |    0.2784 |     18.34 |
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. |.....................|     1.233 |     1.181 |    0.8276 |   0.06619 |
. |.....................|     2.303 |     1.824 |     2.551 |...........|
. |    F| Forward Diff. |    -37.93 |     92.02 |    -69.95 |     197.1 |
. |.....................|    -5.379 |     19.74 |     732.0 |     22.81 |
. |.....................|   -0.9198 |     10.90 |     2.868 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   31|    -863.32562 |    -1.056 |     1.016 |    -1.019 |    0.8061 |
. |.....................|    0.3239 |  0.009740 |   -0.2391 |   -0.9670 |
. |.....................|  -0.07103 |    -1.394 |    0.7071 |...........|
. |    U|    -863.32562 |    -1.733 |     3.384 |    -1.222 |     2.862 |
. |.....................|     1.228 |     1.181 |    0.6041 |   0.06352 |
. |.....................|     2.296 |     1.785 |     2.552 |...........|
. |    X|    -863.32562 |    0.1767 |     29.47 |    0.2947 |     17.49 |
. |.....................|     1.228 |     1.181 |    0.6041 |   0.06352 |
. |.....................|     2.296 |     1.785 |     2.552 |...........|
. |    F| Forward Diff. |    -53.86 |     57.35 |     4.228 |    -39.40 |
. |.....................|    -2.754 |     23.30 |    -514.1 |     31.71 |
. |.....................|    -1.318 |     6.444 |    0.4761 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   32|    -873.30356 |    -1.054 |     1.006 |   -0.9645 |    0.7731 |
. |.....................|    0.3210 |  0.009851 |   -0.2032 |    -1.032 |
. |.....................|  -0.08752 |    -1.504 |    0.7101 |...........|
. |    U|    -873.30356 |    -1.730 |     3.373 |    -1.167 |     2.829 |
. |.....................|     1.225 |     1.181 |    0.7648 |   0.06043 |
. |.....................|     2.290 |     1.743 |     2.553 |...........|
. |    X|    -873.30356 |    0.1772 |     29.17 |    0.3112 |     16.92 |
. |.....................|     1.225 |     1.181 |    0.7648 |   0.06043 |
. |.....................|     2.290 |     1.743 |     2.553 |...........|
. |    F| Forward Diff. |    -44.44 |     66.77 |    -16.38 |     26.43 |
. |.....................|    -4.121 |     20.31 |     128.8 |     31.59 |
. |.....................|    -1.528 |     7.055 |   -0.4839 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   33|    -876.52890 |    -1.057 |    0.9851 |   -0.9173 |    0.7416 |
. |.....................|    0.3113 | -0.006634 |   -0.2107 |    -1.149 |
. |.....................|  -0.09946 |    -1.531 |    0.7136 |...........|
. |    U|     -876.5289 |    -1.734 |     3.352 |    -1.120 |     2.797 |
. |.....................|     1.213 |     1.118 |    0.7314 |   0.05483 |
. |.....................|     2.285 |     1.732 |     2.555 |...........|
. |    X|     -876.5289 |    0.1766 |     28.57 |    0.3262 |     16.40 |
. |.....................|     1.213 |     1.118 |    0.7314 |   0.05483 |
. |.....................|     2.285 |     1.732 |     2.555 |...........|
. |    F| Forward Diff. |    -54.10 |     54.39 |     17.85 |    -60.13 |
. |.....................|    -3.695 |     14.23 |    -228.1 |     8.472 |
. |.....................|    -1.695 |     7.476 |     1.163 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   34|    -867.49446 |    -1.086 |    0.8964 |   -0.9044 |    0.9110 |
. |.....................|    0.3196 |   -0.1280 |   -0.2174 |    -1.298 |
. |.....................|  -0.08938 |    -1.531 |    0.6910 |...........|
. |    U|    -867.49446 |    -1.762 |     3.264 |    -1.107 |     2.967 |
. |.....................|     1.223 |    0.6554 |    0.7011 |   0.04774 |
. |.....................|     2.289 |     1.732 |     2.546 |...........|
. |    X|    -867.49446 |    0.1717 |     26.15 |    0.3305 |     19.43 |
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. |.....................|     1.223 |    0.6554 |    0.7011 |   0.04774 |
. |.....................|     2.289 |     1.732 |     2.546 |...........|
. |   35|    -878.38151 |    -1.062 |    0.9559 |   -0.9145 |    0.7950 |
. |.....................|    0.3139 |  -0.04327 |   -0.1999 |    -1.193 |
. |.....................|  -0.09639 |    -1.531 |    0.7069 |...........|
. |    U|    -878.38151 |    -1.739 |     3.323 |    -1.117 |     2.851 |
. |.....................|     1.216 |    0.9785 |    0.7798 |   0.05271 |
. |.....................|     2.286 |     1.732 |     2.552 |...........|
. |    X|    -878.38151 |    0.1757 |     27.75 |    0.3271 |     17.30 |
. |.....................|     1.216 |    0.9785 |    0.7798 |   0.05271 |
. |.....................|     2.286 |     1.732 |     2.552 |...........|
. |    F| Forward Diff. |    -51.07 |     48.15 |    -25.95 |     53.24 |
. |.....................|    -3.918 |    -1.748 |     228.2 |    -6.332 |
. |.....................|    -1.593 |     8.225 |    0.5063 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   36|    -880.31148 |    -1.059 |    0.9320 |   -0.8640 |    0.8179 |
. |.....................|    0.3401 |  -0.05886 |   -0.2144 |    -1.154 |
. |.....................|  -0.06919 |    -1.531 |    0.6965 |...........|
. |    U|    -880.31148 |    -1.735 |     3.299 |    -1.067 |     2.873 |
. |.....................|     1.248 |    0.9191 |    0.7148 |   0.05461 |
. |.....................|     2.297 |     1.732 |     2.548 |...........|
. |    X|    -880.31148 |    0.1764 |     27.09 |    0.3441 |     17.70 |
. |.....................|     1.248 |    0.9191 |    0.7148 |   0.05461 |
. |.....................|     2.297 |     1.732 |     2.548 |...........|
. |    F| Forward Diff. |    -45.81 |     36.39 |     7.540 |    -2.325 |
. |.....................|    -3.092 |    -8.555 |    -117.3 |     8.315 |
. |.....................|    -1.416 |     7.805 |   -0.1243 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   37|    -880.65100 |    -1.049 |    0.9248 |   -0.8300 |    0.7989 |
. |.....................|    0.3742 |  -0.04390 |   -0.1991 |    -1.124 |
. |.....................|  -0.01415 |    -1.531 |    0.6905 |...........|
. |    U|      -880.651 |    -1.726 |     3.292 |    -1.033 |     2.854 |
. |.....................|     1.288 |    0.9761 |    0.7833 |   0.05602 |
. |.....................|     2.318 |     1.732 |     2.546 |...........|
. |    X|      -880.651 |    0.1781 |     26.90 |    0.3560 |     17.36 |
. |.....................|     1.288 |    0.9761 |    0.7833 |   0.05602 |
. |.....................|     2.318 |     1.732 |     2.546 |...........|
. |    F| Forward Diff. |    -31.20 |     39.33 |     8.152 |     15.94 |
. |.....................|    -3.279 |    -3.537 |     122.2 |     17.51 |
. |.....................|   -0.9172 |     8.346 |   -0.4413 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   38|    -881.87208 |    -1.045 |    0.9214 |   -0.8592 |    0.7849 |
. |.....................|    0.4018 |  -0.02840 |   -0.2064 |    -1.152 |
. |.....................|   0.05119 |    -1.531 |    0.6840 |...........|
. |    U|    -881.87208 |    -1.721 |     3.289 |    -1.062 |     2.840 |
. |.....................|     1.321 |     1.035 |    0.7506 |   0.05469 |
. |.....................|     2.343 |     1.732 |     2.543 |...........|
. |    X|    -881.87208 |    0.1789 |     26.81 |    0.3457 |     17.12 |
. |.....................|     1.321 |     1.035 |    0.7506 |   0.05469 |
. |.....................|     2.343 |     1.732 |     2.543 |...........|
. |    F| Forward Diff. |    -26.54 |     28.88 |     9.718 |    -17.93 |
. |.....................|    -2.328 |     2.539 |    -60.01 |     10.63 |
```

```
. |.....................|  0.004676 |     7.486 |  0.001093 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   39|    -882.11404 |    -1.044 |    0.9027 |   -0.8807 |    0.8083 |
. |.....................|    0.4407 |  -0.03302 |   -0.2031 |    -1.184 |
. |.....................|    0.1078 |    -1.531 |    0.6734 |.....|
. |    U|    -882.11404 |    -1.721 |     3.270 |    -1.084 |     2.864 |
. |.....................|     1.367 |     1.018 |    0.7652 |   0.05318 |
. |.....................|     2.365 |     1.732 |     2.539 |.....|
. |    X|    -882.11404 |    0.1789 |     26.31 |    0.3384 |     17.53 |
. |.....................|     1.367 |     1.018 |    0.7652 |   0.05318 |
. |.....................|     2.365 |     1.732 |     2.539 |.....|
. |    F| Forward Diff. |    -21.04 |     18.80 |    -20.06 |     37.43 |
. |.....................|    -1.653 |   -0.1692 |     135.8 |   -0.8371 |
. |.....................|    0.9424 |     7.390 |  -0.07322 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   40|    -882.23691 |    -1.050 |    0.8761 |   -0.8309 |    0.8358 |
. |.....................|    0.4908 |  -0.05098 |   -0.2146 |    -1.193 |
. |.....................|   0.09467 |    -1.531 |    0.6673 |.....|
. |    U|    -882.23691 |    -1.726 |     3.243 |    -1.034 |     2.891 |
. |.....................|     1.427 |    0.9491 |    0.7139 |   0.05275 |
. |.....................|     2.360 |     1.732 |     2.536 |.....|
. |    X|    -882.23691 |    0.1780 |     25.62 |    0.3557 |     18.02 |
. |.....................|     1.427 |    0.9491 |    0.7139 |   0.05275 |
. |.....................|     2.360 |     1.732 |     2.536 |.....|
. |    F| Forward Diff. |    -32.04 |     7.756 |     4.821 |     1.499 |
. |.....................|   -0.6320 |    -7.594 |    -131.7 |    -2.356 |
. |.....................|    0.7778 |     8.380 |   -0.1293 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   41|    -882.92933 |    -1.047 |    0.8760 |   -0.8211 |    0.8185 |
. |.....................|    0.5215 |  -0.03813 |   -0.2051 |    -1.206 |
. |.....................|    0.1004 |    -1.531 |    0.6638 |.....|
. |    U|    -882.92933 |    -1.724 |     3.243 |    -1.024 |     2.874 |
. |.....................|     1.463 |    0.9981 |    0.7565 |   0.05213 |
. |.....................|     2.362 |     1.732 |     2.535 |.....|
. |    X|    -882.92933 |    0.1784 |     25.62 |    0.3592 |     17.71 |
. |.....................|     1.463 |    0.9981 |    0.7565 |   0.05213 |
. |.....................|     2.362 |     1.732 |     2.535 |.....|
. |    F| Forward Diff. |    -28.35 |     10.68 |     2.110 |     13.25 |
. |.....................|   -0.6021 |    -2.343 |     29.39 |    -5.516 |
. |.....................|    0.8152 |     8.920 |   -0.1917 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   42|    -883.13926 |    -1.040 |    0.8783 |   -0.8340 |    0.8105 |
. |.....................|    0.5377 |  -0.02654 |   -0.2078 |    -1.188 |
. |.....................|    0.1289 |    -1.531 |    0.6630 |.....|
. |    U|    -883.13926 |    -1.716 |     3.246 |    -1.037 |     2.866 |
. |.....................|     1.482 |     1.042 |    0.7444 |   0.05295 |
. |.....................|     2.373 |     1.732 |     2.535 |.....|
. |    X|    -883.13926 |    0.1798 |     25.68 |    0.3546 |     17.57 |
. |.....................|     1.482 |     1.042 |    0.7444 |   0.05295 |
. |.....................|     2.373 |     1.732 |     2.535 |.....|
. |    F| Forward Diff. |    -15.03 |     7.443 |     3.778 |    -3.610 |
. |.....................|   -0.1849 |     2.375 |    -53.89 |   0.04720 |
```

```
. |.....................|     1.113 |     8.197 |   -0.1846 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   43|    -882.88691 |    -1.035 |    0.8739 |   -0.8410 |    0.8204 |
. |.....................|    0.5419 |  -0.02995 |   -0.2045 |    -1.153 |
. |.....................|    0.1210 |    -1.531 |    0.6804 |.....|
. |    U|    -882.88691 |    -1.712 |     3.241 |    -1.044 |     2.876 |
. |.....................|     1.487 |     1.029 |    0.7590 |   0.05462 |
. |.....................|     2.370 |     1.732 |     2.542 |.....|
. |    X|    -882.88691 |    0.1805 |     25.57 |    0.3521 |     17.74 |
. |.....................|     1.487 |     1.029 |    0.7590 |   0.05462 |
. |.....................|     2.370 |     1.732 |     2.542 |.....|
. |   44|    -883.13352 |    -1.037 |    0.8767 |   -0.8361 |    0.8133 |
. |.....................|    0.5388 |  -0.02760 |   -0.2038 |    -1.179 |
. |.....................|    0.1267 |    -1.531 |    0.6677 |.....|
. |    U|    -883.13352 |    -1.714 |     3.244 |    -1.039 |     2.869 |
. |.....................|     1.484 |     1.038 |    0.7622 |   0.05341 |
. |.....................|     2.372 |     1.732 |     2.537 |.....|
. |    X|    -883.13352 |    0.1801 |     25.64 |    0.3538 |     17.62 |
. |.....................|     1.484 |     1.038 |    0.7622 |   0.05341 |
. |.....................|     2.372 |     1.732 |     2.537 |.....|
. |   45|    -883.15405 |    -1.038 |    0.8773 |   -0.8349 |    0.8116 |
. |.....................|    0.5381 |  -0.02703 |   -0.2036 |    -1.185 |
. |.....................|    0.1281 |    -1.531 |    0.6646 |.....|
. |    U|    -883.15405 |    -1.715 |     3.245 |    -1.038 |     2.867 |
. |.....................|     1.483 |     1.040 |    0.7630 |   0.05311 |
. |.....................|     2.373 |     1.732 |     2.535 |.....|
. |    X|    -883.15405 |    0.1800 |     25.65 |    0.3542 |     17.59 |
. |.....................|     1.483 |     1.040 |    0.7630 |   0.05311 |
. |.....................|     2.373 |     1.732 |     2.535 |.....|
. |    F| Forward Diff. |    -10.46 |     8.643 |    -3.856 |     16.02 |
. |.....................|   -0.3305 |     1.604 |     57.88 |    0.9087 |
. |.....................|     1.107 |     8.243 |   -0.2895 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   46|    -883.23807 |    -1.038 |    0.8769 |   -0.8344 |    0.8103 |
. |.....................|    0.5373 |  -0.02739 |   -0.2058 |    -1.186 |
. |.....................|    0.1231 |    -1.531 |    0.6663 |.....|
. |    U|    -883.23807 |    -1.714 |     3.244 |    -1.037 |     2.866 |
. |.....................|     1.482 |     1.039 |    0.7534 |   0.05305 |
. |.....................|     2.371 |     1.732 |     2.536 |.....|
. |    X|    -883.23807 |    0.1801 |     25.64 |    0.3544 |     17.56 |
. |.....................|     1.482 |     1.039 |    0.7534 |   0.05305 |
. |.....................|     2.371 |     1.732 |     2.536 |.....|
. |    F| Forward Diff. |    -10.36 |     7.283 |    0.2757 |     4.585 |
. |.....................|   -0.2444 |     1.466 |   -0.4464 |    0.5378 |
. |.....................|     1.010 |     8.210 |   -0.2502 |.....|
. |-----+---------------+-----------+-----------+-----------+-----|
. |   47|    -883.29021 |    -1.028 |    0.8703 |   -0.8346 |    0.8062 |
. |.....................|    0.5375 |  -0.02870 |   -0.2054 |    -1.187 |
. |.....................|    0.1222 |    -1.531 |    0.6665 |.....|
. |    U|    -883.29021 |    -1.705 |     3.238 |    -1.038 |     2.862 |
. |.....................|     1.482 |     1.034 |    0.7552 |   0.05303 |
. |.....................|     2.371 |     1.732 |     2.536 |.....|
```

```
. |    X|    -883.29021 |    0.1818 |     25.47 |    0.3543 |     17.49 |
. |.....................|     1.482 |     1.034 |    0.7552 |   0.05303 |
. |.....................|     2.371 |     1.732 |     2.536 |...........|
. |    F| Forward Diff. |     10.27 |     2.756 |  -0.02825 |    0.6403 |
. |.....................|   -0.1347 |   -0.7622 |    -8.418 |     1.000 |
. |.....................|    0.9924 |     8.207 |   -0.1819 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   48|    -883.31781 |    -1.030 |    0.8691 |   -0.8346 |    0.8047 |
. |.....................|    0.5407 |  -0.02786 |   -0.2042 |    -1.188 |
. |.....................|    0.1112 |    -1.531 |    0.6695 |...........|
. |    U|    -883.31781 |    -1.706 |     3.236 |    -1.038 |     2.860 |
. |.....................|     1.486 |     1.037 |    0.7603 |   0.05295 |
. |.....................|     2.366 |     1.732 |     2.537 |...........|
. |    X|    -883.31781 |    0.1815 |     25.44 |    0.3543 |     17.47 |
. |.....................|     1.486 |     1.037 |    0.7603 |   0.05295 |
. |.....................|     2.366 |     1.732 |     2.537 |...........|
. |    F| Forward Diff. |     6.791 |     2.322 |    -1.189 |     2.900 |
. |.....................|   -0.1162 |   -0.2299 |     12.32 |    0.4692 |
. |.....................|    0.8352 |     8.265 |   -0.1632 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   49|    -883.33504 |    -1.030 |    0.8668 |   -0.8337 |    0.8048 |
. |.....................|    0.5481 |  -0.02668 |   -0.2051 |    -1.187 |
. |.....................|   0.08943 |    -1.531 |    0.6768 |...........|
. |    U|    -883.33504 |    -1.707 |     3.234 |    -1.037 |     2.860 |
. |.....................|     1.495 |     1.042 |    0.7562 |   0.05300 |
. |.....................|     2.358 |     1.732 |     2.540 |...........|
. |    X|    -883.33504 |    0.1814 |     25.38 |    0.3547 |     17.47 |
. |.....................|     1.495 |     1.042 |    0.7562 |   0.05300 |
. |.....................|     2.358 |     1.732 |     2.540 |...........|
. |    F| Forward Diff. |     5.451 |    0.7262 |    0.3682 |    -1.721 |
. |.....................|   0.04049 |    0.5504 |    -11.58 |    0.5724 |
. |.....................|    0.4881 |     8.271 |   -0.1329 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   50|    -883.34441 |    -1.031 |    0.8652 |   -0.8311 |    0.8079 |
. |.....................|    0.5453 |  -0.02887 |   -0.2049 |    -1.185 |
. |.....................|   0.07158 |    -1.531 |    0.6921 |...........|
. |    U|    -883.34441 |    -1.708 |     3.233 |    -1.034 |     2.863 |
. |.....................|     1.491 |     1.033 |    0.7573 |   0.05313 |
. |.....................|     2.351 |     1.732 |     2.546 |...........|
. |    X|    -883.34441 |    0.1813 |     25.34 |    0.3556 |     17.52 |
. |.....................|     1.491 |     1.033 |    0.7573 |   0.05313 |
. |.....................|     2.351 |     1.732 |     2.546 |...........|
. |    F| Forward Diff. |     4.428 |    0.5501 |   -0.3180 |     1.888 |
. |.....................|  -0.02295 |   -0.4904 |  -0.05429 |     1.378 |
. |.....................|    0.2193 |     8.314 |   -0.1500 |...........|
. |-----+---------------+-----------+-----------+-----------+-----------|
. |   51|    -883.34442 |    -1.031 |    0.8652 |   -0.8311 |    0.8079 |
. |.....................|    0.5453 |  -0.02887 |   -0.2049 |    -1.185 |
. |.....................|   0.07158 |    -1.531 |    0.6921 |...........|
. |    U|    -883.34442 |    -1.708 |     3.233 |    -1.034 |     2.863 |
. |.....................|     1.491 |     1.033 |    0.7573 |   0.05313 |
. |.....................|     2.351 |     1.732 |     2.546 |...........|
```

```
. |    X|    -883.34442 |    0.1813 |     25.34 |    0.3556 |     17.52 |
. |.....................|     1.491 |     1.033 |    0.7573 |   0.05313 |
. |.....................|     2.351 |     1.732 |     2.546 |...........|
. calculating covariance matrix
. done
```

```
. → Calculating residuals/tables
```

```
. ✔ done
```

```
. → compress origData in nlmixr2 object, save 13504
```

```
. → compress parHistData in nlmixr2 object, save 7456
```

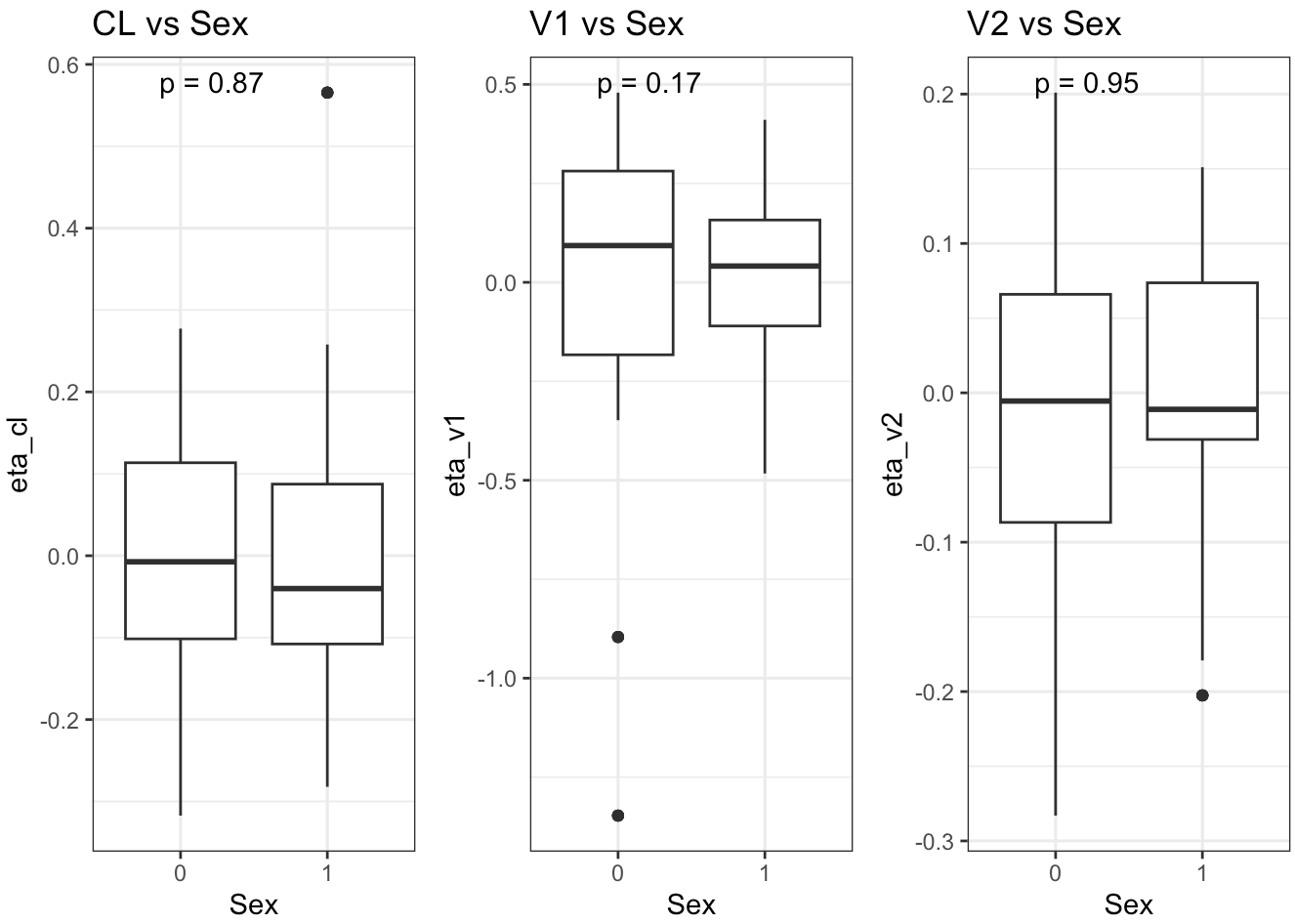
```
final_combined_dataset <- merge(two_cmt_final_pk_fit, busulfan_dataset, by = c("ID", "TI
ME", "DV", "BSA", "Sex"))

# Sex as covariates
cov_sex_cl <- ggplot(final_combined_dataset, aes(as.factor(Sex), eta_cl)) +
  geom_boxplot() +
  stat_compare_means(method = "wilcox.test", label = "p.format") +
  theme_bw() +
  labs(title = "CL vs Sex", x = "Sex")

cov_sex_v1 <- ggplot(final_combined_dataset, aes(as.factor(Sex), eta_v1)) +
  geom_boxplot() +
  stat_compare_means(method = "wilcox.test", label = "p.format") +
  theme_bw() +
  labs(title = "V1 vs Sex", x = "Sex")

cov_sex_v2 <- ggplot(final_combined_dataset, aes(as.factor(Sex), eta_v2)) +
  geom_boxplot() +
  stat_compare_means(method = "wilcox.test", label = "p.format") +
  theme_bw() +
  labs(title = "V2 vs Sex", x = "Sex")

grid.arrange(cov_sex_cl, cov_sex_v1, cov_sex_v2, nrow = 1)
```


CL vs Sex
p = 0.87
eta_cl
0.6
0.4
0.2
0.0
-0.2
0
1
Sex
V1 vs Sex
p = 0.17
eta_v1
0.5
0.0
-0.5
-1.0
0
1
Sex
V2 vs Sex
p = 0.95
eta_v2
0.2
0.1
0.0
-0.1
-0.2
-0.3
0
1
Sex

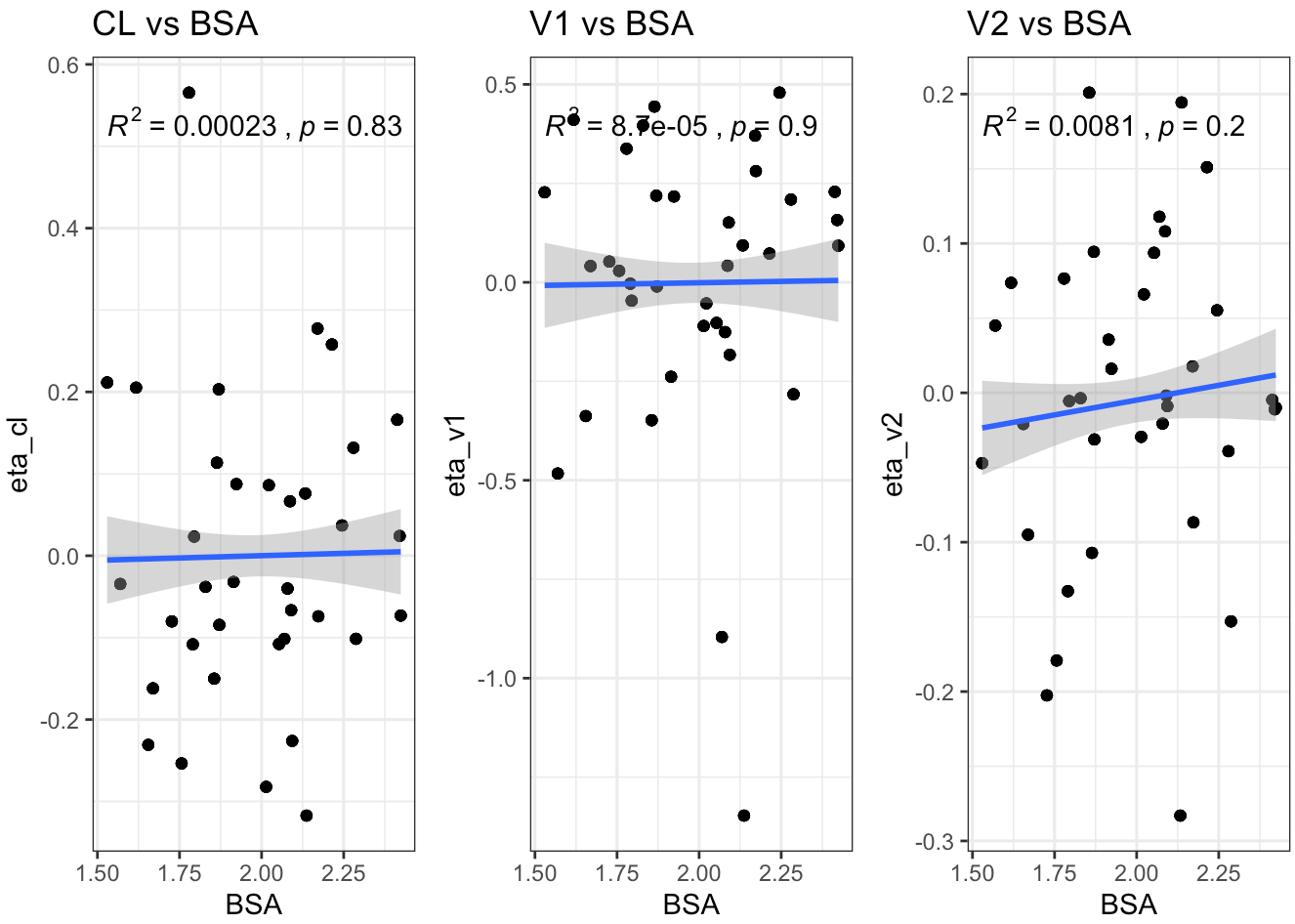
```
# BSA as covariates
cov_bsa_cl <- ggplot(final_combined_dataset, aes(BSA, eta_cl)) +
  geom_point() +
  geom_smooth(method = "lm", se = TRUE) +
  stat_cor(method = "pearson",
           aes(label = paste(..rr.label.., ..p.label.., sep = "~`,`~"))) +
  theme_bw() +
  labs(title = "CL vs BSA", x = "BSA")

cov_bsa_v1 <- ggplot(final_combined_dataset, aes(BSA, eta_v1)) +
  geom_point() +
  geom_smooth(method = "lm", se = TRUE) +
  stat_cor(method = "pearson",
           aes(label = paste(..rr.label.., ..p.label.., sep = "~`,`~"))) +
  theme_bw() +
  labs(title = "V1 vs BSA", x = "BSA")

cov_bsa_v2 <- ggplot(final_combined_dataset, aes(BSA, eta_v2)) +
  geom_point() +
  geom_smooth(method = "lm", se = TRUE) +
  stat_cor(method = "pearson",
           aes(label = paste(..rr.label.., ..p.label.., sep = "~`,`~"))) +
  theme_bw() +
  labs(title = "V2 vs BSA", x = "BSA")

grid.arrange(cov_bsa_cl, cov_bsa_v1, cov_bsa_v2, nrow = 1)
```

```
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
. `geom_smooth()` using formula = 'y ~ x'
```




```
## Two-cmt model parameters
# Parameter estimates - Fixed + RUV

# Compare etas between base vs final
print("Base Model etas")
```

```
. [1] "Base Model etas"
```

```
two_cmt_pk_fit$omega
```

```
.            eta_cl    eta_v1     eta_v2
. eta_cl 0.04841429 0.0000000 0.00000000
. eta_v1 0.00000000 0.1109996 0.00000000
. eta_v2 0.00000000 0.0000000 0.04513207
```

```
print("Final Model etas")
```

```
. [1] "Final Model etas"
```

```
two_cmt_final_pk_fit$omega
```

```
.            eta_cl    eta_v1     eta_v2
. eta_cl 0.03272423 0.0000000 0.00000000
. eta_v1 0.00000000 0.1109996 0.00000000
. eta_v2 0.00000000 0.0000000 0.02378925
```

```
# Final model parameters
two_cmt_final_pk_fit$parFixedDf %>% select(`Back-transformed`, `%RSE`, `Shrink(SD)%`) %
>% rename(Parameters = `Back-transformed`)
```

```
.          Parameters      %RSE Shrink(SD)%
. tvcl      0.1812724  1.820988  -0.3292268
. tvv1     25.3440942  1.878714 -10.0189771
. tvq       0.3556019 18.112391          NA
. tvv2     17.5216509  2.489762  31.0781841
. covbsav1  1.4912491 35.099656          NA
. covbsacl  1.0333656 23.876789          NA
. covsexv2  0.7573352  8.016240          NA
. prop.err  0.0531319        NA          NA
```

```
```