2025 National Taiwan University - Population Pharmacokinetics workshop

1 Load Packages

Here we will import our installed packages into our R environment

```
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
to 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)
library(mrgsolve)
```

```
##
## Attaching package: 'mrgsolve'
##
## The following object is masked from 'package:renv':
##
##     init
##
## The following object is masked from 'package:stats':
##
##     filter
```

```
library(vpc)
```

```
##
## Attaching package: 'vpc'
##
## The following object is masked from 'package:xpose':
##
##     vpc
```

```
library(patchwork)
```

2 Dataset

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

busulfan_TDM_dataset <- busulfan_First_Dose_dataset %>%
  group_by(ID) %>%
  filter(row_number() == 1 | row_number() == 2 | row_number() == n())
```

3 Showcase 4

3.1 Overlay First Dose data with the built model - Individual fits

```
model_code <- 'model/busulfan_test_dose_model.mod'
mod <- mread('busulfan_test_dose', file = model_code)
```

```
## Building busulfan_test_dose ... done.
```

```
sim <- function(rep, data, model,
                recover = c('AMT', 'DV', 'Sex', 'BSA')) {
  mrgsim(
    model,
    data = data,
    recover = recover,
    Req = c('CP_no_RUV', 'CP', 'no_obs_AUC'),
    output = 'df',
  ) %>% mutate(irep = rep)
}

isim <- seq(1000)

set.seed(86486)

sims <- lapply(
  isim, sim,
  data = busulfan_First_Dose_dataset,
  mod = mod
) %>% bind_rows()

indv_fits <- sims %>% filter(irep == 1)

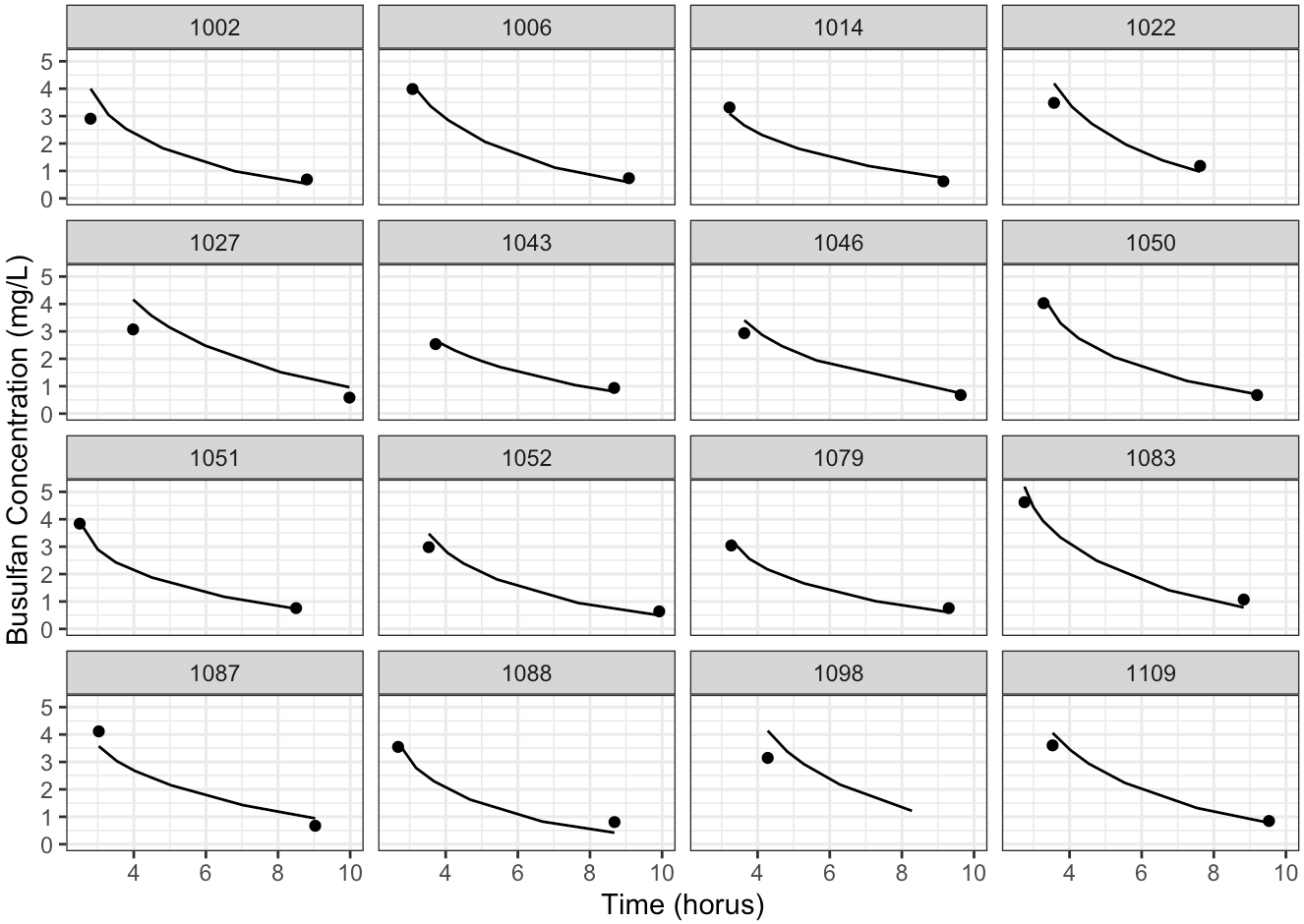
p1 <- ggplot() +
  geom_line(data = indv_fits, aes(TIME/60, CP_no_RUV, group = ID)) +
  geom_point(data = busulfan_TDM_dataset, aes(TIME/60, DV, group = ID)) +
  facet_wrap_paginate(~ID, nrow = 4, ncol = 4, page = 1) +
  xlim(2.5, 10) +
  labs(x = 'Time (horus)',  y = "Busulfan Concentration (mg/L)") +
  theme_bw()

p2 <- ggplot() +
  geom_line(data = indv_fits, aes(TIME/60, CP_no_RUV, group = ID)) +
  geom_point(data = busulfan_TDM_dataset, aes(TIME/60, DV, group = ID)) +
  facet_wrap_paginate(~ID, nrow = 4, ncol = 4, page = 2) +
  xlim(2.5, 10) +
  labs(x = 'Time (horus)',  y = "Busulfan Concentration (mg/L)") +
  theme_bw()

p1
```

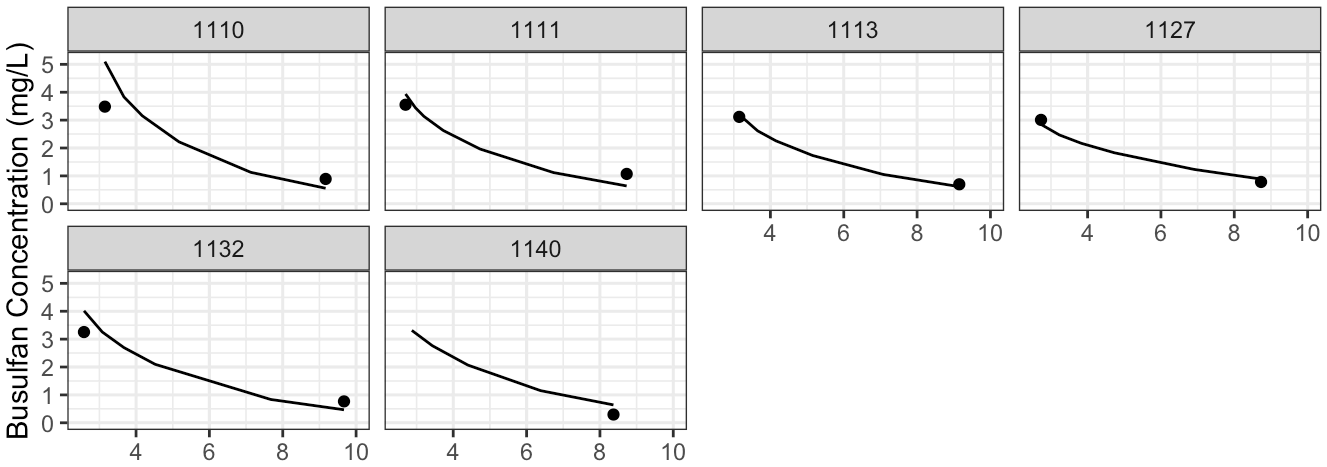
```
## Warning: Removed 24 rows containing missing values or values outside the scale range
## (`geom_line()`).
```

```
## Warning: Removed 24 rows containing missing values or values outside the scale range
## (`geom_point()`).
```




```
p2
```

```
## Warning: Removed 24 rows containing missing values or values outside the scale range
## (`geom_line()`).
## Removed 24 rows containing missing values or values outside the scale range
## (`geom_point()`).
```



Time (horus)

3.2 Overlay First Dose data with the built model -

pcVPC

```
mrg_vpc_theme = new_vpc_theme(list(
  sim_pi_fill = "steelblue3", sim_pi_alpha = 0.5,
  sim_median_fill = "grey60", sim_median_alpha = 0.5
))

vpc_plot <- vpc(obs = busulfan_TDM_dataset,
          obs_cols = list(dv = 'DV',
                          idv = 'TIME',
                          id = 'ID'
                          ),
          sim = sims,
          bins = "pretty",
          n_bins = 10,
          sim_cols = list(dv = 'CP',
                          idv = 'TIME',
                          id = 'ID',
                          sim = 'irep'
                          ),
          #log_y = TRUE,
          #stratify = 'DOSCOV',
          pi = c(0.025, 0.975),
          ci = c(0.025, 0.975),
          show = list(obs_dv = TRUE
                      #obs_ci = FALSE
                      #obs_median = FALSE
                      ),
          vpc_theme = mrg_vpc_theme,
          ylab  = 'Busuflan Concentration (mg/L)',
          xlab  = 'Time (hours)',
          title = "Prediction-Corrected Visual Predictive Check - pcVPC"
          ) +
  theme_bw() +
  scale_x_continuous(limits = c(150, 600),
                     breaks = seq(0, 650, by = 30),
                     labels = function(x) x / 60)

vpc_plot +
  # Add dummy geoms to create legend entries
  geom_rect(aes(xmin = 0, xmax = 0, ymin = 0, ymax = 0, fill = "PI (95%)"), alpha = 0.5)
+
  geom_rect(aes(xmin = 0, xmax = 0, ymin = 0, ymax = 0, fill = "Median"), alpha = 0.5) +

  # Define manual fill scale
  scale_fill_manual(name = "Simulated Data",
                    values = c("PI (95%)" = "steelblue3", "Median" = "grey60")) +

  # Customize the legend position inside plot
  theme(
    legend.position = c(0.90, 0.80),   # x and y coordinates (0~1 scale)
    legend.background = element_rect(fill = "white", color = "black"),
```

```
    legend.title = element_text(size = 10),
    legend.text = element_text(size = 9)
  ) +

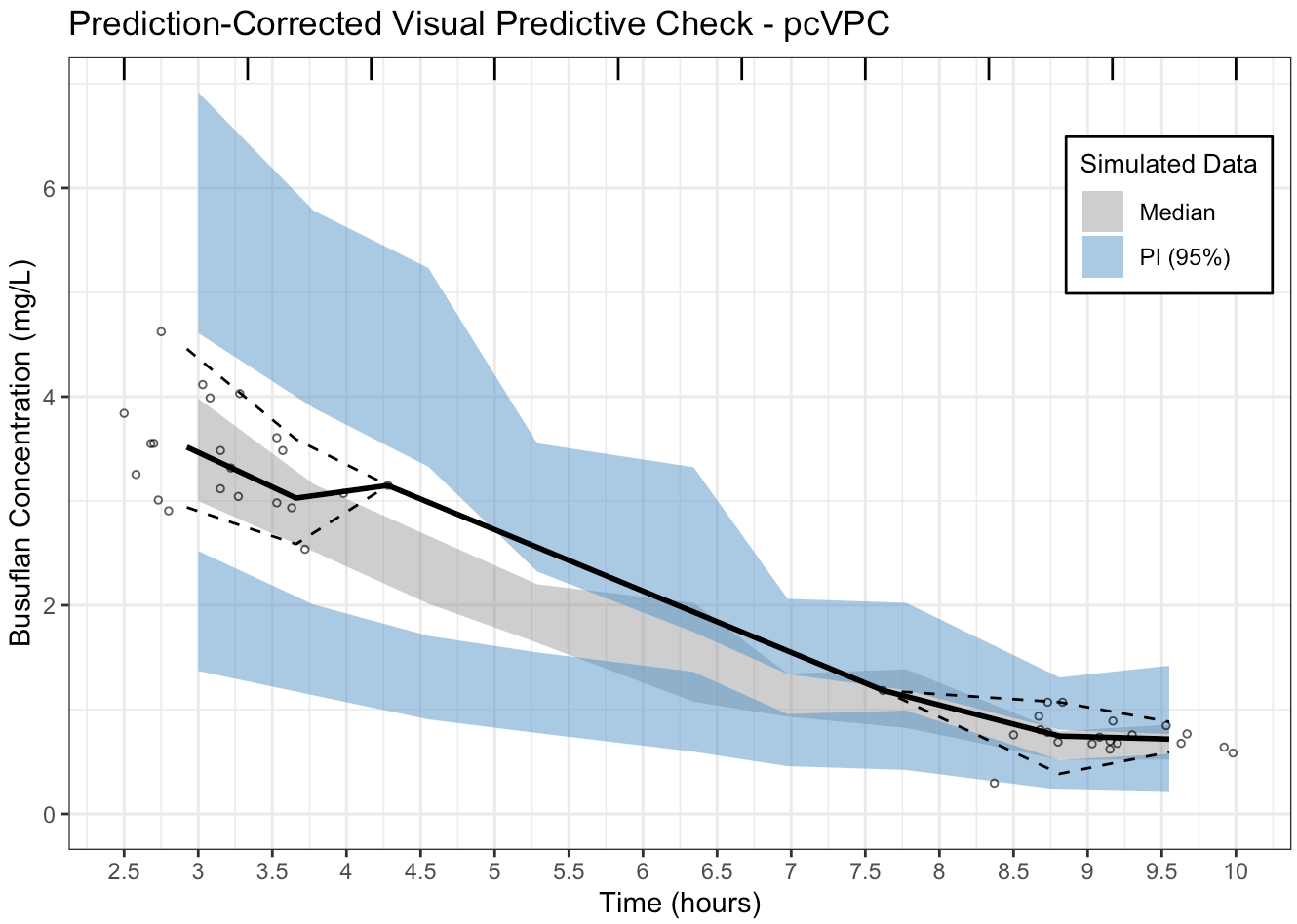
  guides(fill = guide_legend(override.aes = list(alpha = 0.5)))
```

```
## Warning: A numeric `legend.position` argument in `theme()` was deprecated in ggplot2
## 3.5.0.
## ℹ Please use the `legend.position.inside` argument of `theme()` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```

```
## Warning: Removed 2 rows containing missing values or values outside the scale range
## (`geom_line()`).
## Removed 2 rows containing missing values or values outside the scale range
## (`geom_line()`).
## Removed 2 rows containing missing values or values outside the scale range
## (`geom_line()`).
```

```
## Warning: Removed 2 rows containing missing values or values outside the scale range
## (`geom_point()`).
```

```
## Warning: Removed 12 rows containing missing values or values outside the scale range
## (`geom_rect()`).
## Removed 12 rows containing missing values or values outside the scale range
## (`geom_rect()`).
```

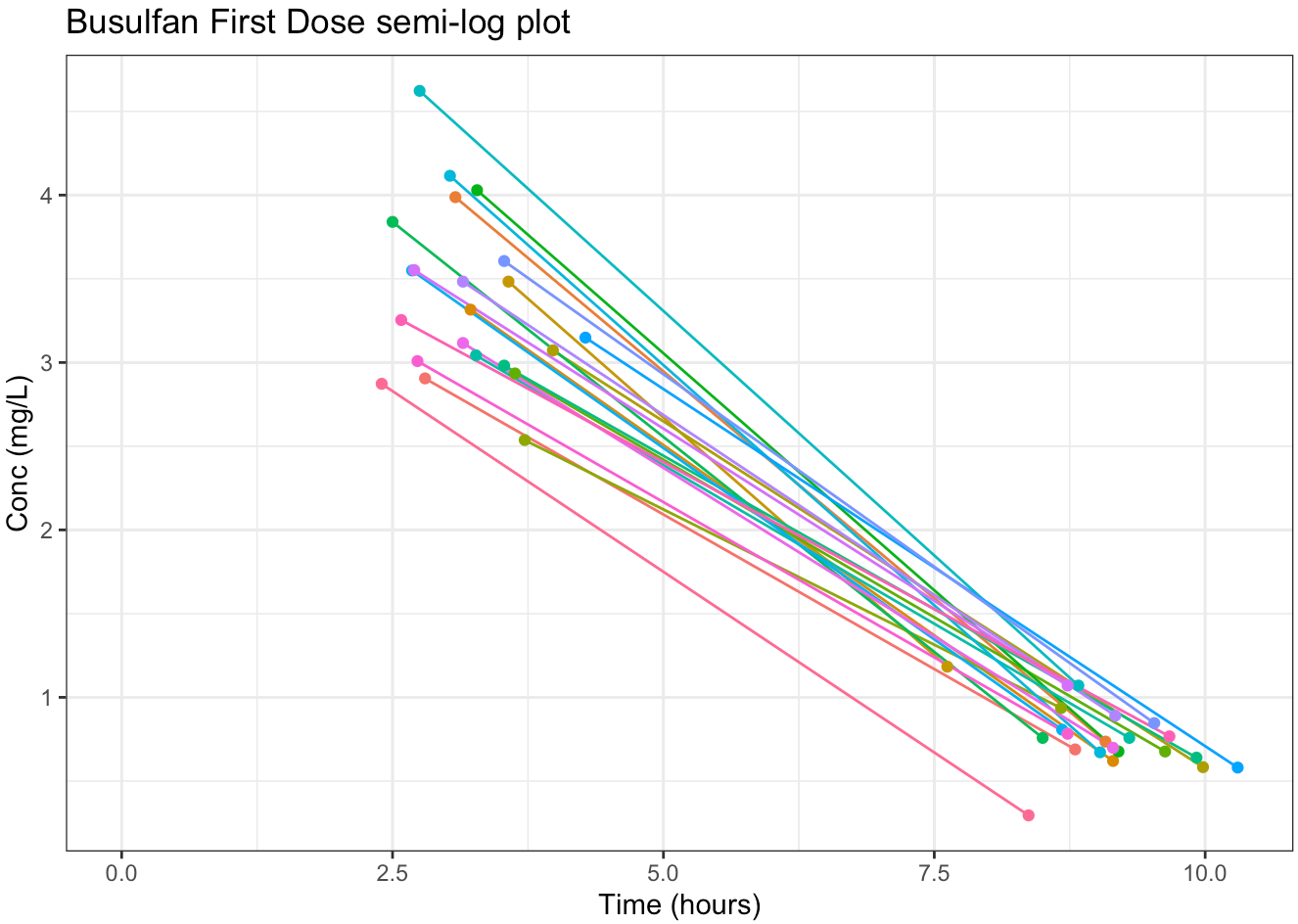


3.3 Estimating Individual exposure with TDM

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

```
## Warning: Removed 22 rows containing missing values or values outside the scale range
## (`geom_line()`).
```

```
## Warning: Removed 22 rows containing missing values or values outside the scale range
## (`geom_point()`).
```


Busulfan First Dose semi-log plot
Conc (mg/L)
4
3
2
1
0.0
2.5
5.0
7.5
10.0
Time (hours)

3.4 model fit

```
busulfan_final_2cmt_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(0.181)
    tvv1  <- log(25.34)
    tvq   <- log(0.355)
    tvv2  <- log(17.52)

    covbsav1 <- log(1.49)
    covbsacl <- log(1.03)
    covsexv2 <- log(0.757)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0327
    eta_v1  ~ 0.0111
    eta_v2  ~ 0.0237

    # Residual variability
    prop.err <-  0.05313
  })

  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 - Need MaxEval zero
two_cmt_TDM_pk_fit <- nlmixr2(
  busulfan_final_2cmt_model,
  busulfan_TDM_dataset,
  "posthoc",
  control = foceiControl(maxOuterIterations=0),
  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
```

```
## → 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
```

```
## → 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
```

```
## → Calculating residuals/tables
```

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

```
## ✔ done
```

```
## → compress origData in nlmixr2 object, save 4432
```

```
## → 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'
```

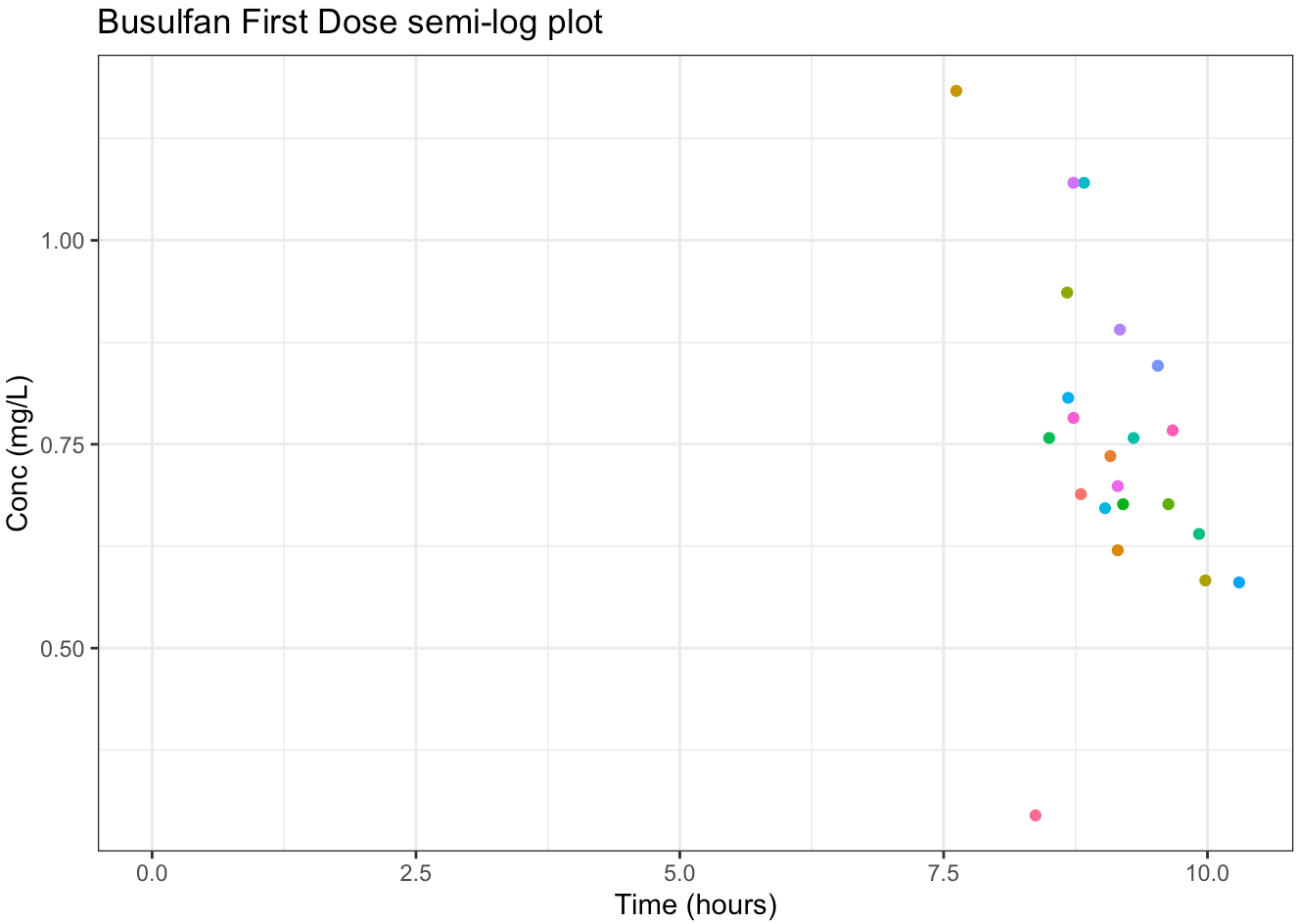
```
## ✔ done
```

3.5 Estimating individual exposures with last time point

```
last_time_point <- busulfan_TDM_dataset %>%
  group_by(ID) %>%
  filter(row_number() == 1 | row_number() == 3)

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

```
## Warning: Removed 22 rows containing missing values or values outside the scale range
## (`geom_point()`).
```


Busulfan First Dose semi-log plot
1.00
0.75
0.50
Conc (mg/L)
0.0
2.5
5.0
7.5
10.0
Time (hours)

3.6 model fit

```
busulfan_final_2cmt_model <- function() {
  ini({
    # Typical value (THETAs)
    tvcl   <- log(0.181)
    tvv1  <- log(25.34)
    tvq   <- log(0.355)
    tvv2  <- log(17.52)

    covbsav1 <- log(1.49)
    covbsacl <- log(1.03)
    covsexv2 <- log(0.757)

    # Interindividual variability (OMEGAs)
    eta_cl  ~ 0.0327
    eta_v1  ~ 0.0111
    eta_v2  ~ 0.0237

    # Residual variability
    prop.err <-  0.05313
  })

  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_last_tp_pk_fit <- nlmixr2(
  busulfan_final_2cmt_model,
  last_time_point,
  "posthoc",
  control = foceiControl(maxOuterIterations=0),
  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
```

```
## → Calculating residuals/tables
```

```
## ✔ done
```

```
## → compress origData in nlmixr2 object, save 3496
```

3.7 Estimating individual exposure with no observation

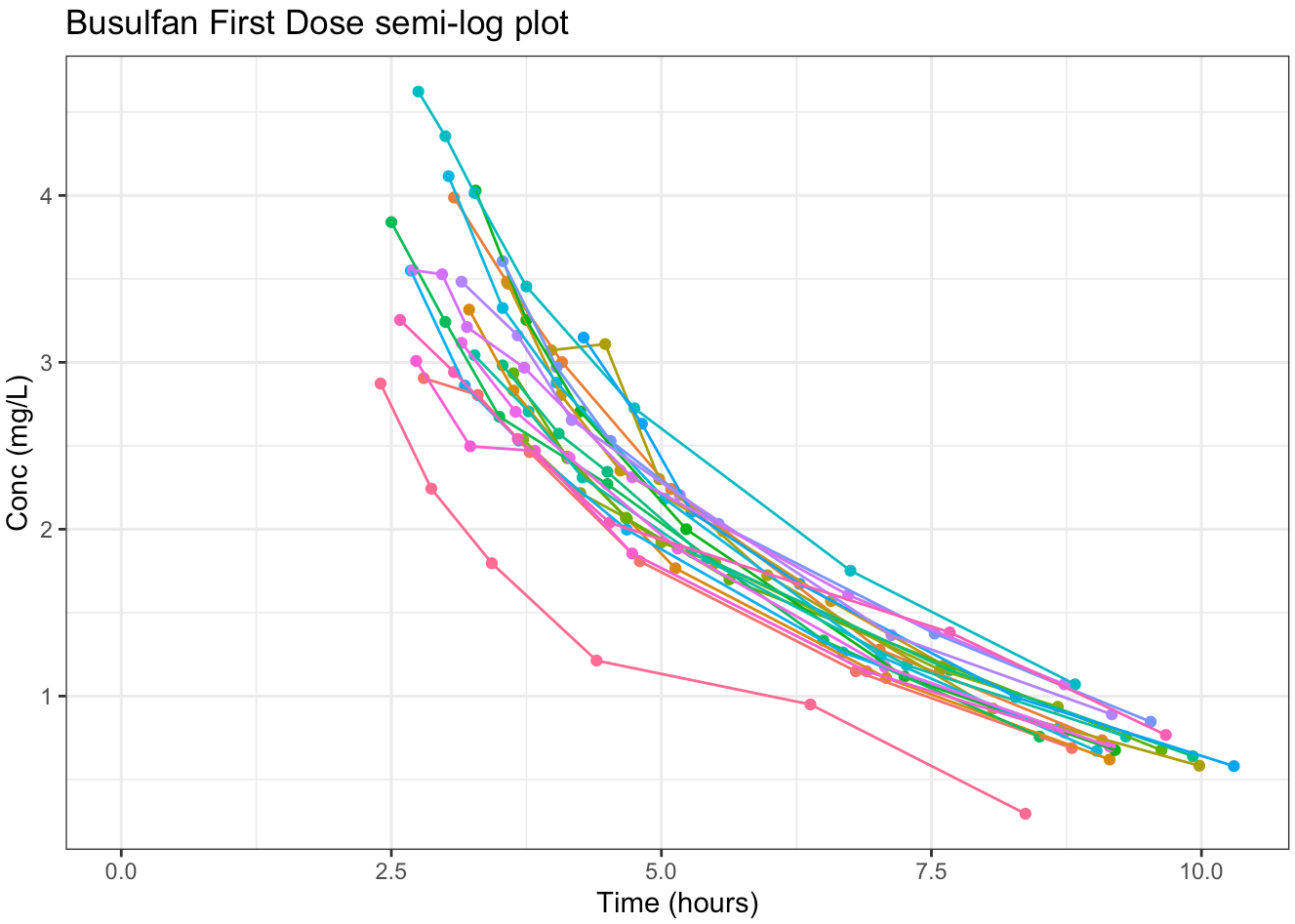
```
## No observation
no_tp_AUC <- indv_fits %>%
  group_by(ID) %>%
  summarize(no_tp_AUC = first(no_obs_AUC), .groups = "drop")
```

3.8 Full samples

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

```
## Warning: Removed 22 rows containing missing values or values outside the scale range
## (`geom_point()`).
```

```
## Warning: Removed 22 rows containing missing values or values outside the scale range
## (`geom_line()`).
```



3.9 model fit - full estimation

```
busulfan_first_dose_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
full_estimation_pk_fit <- nlmixr2(
  busulfan_first_dose_2cmt_model,
  busulfan_First_Dose_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 gradi
ent 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|     9562.9588 |    -1.000 |     1.000 |   -0.6887 |    0.7952 |
## |.....................| -0.001490 |   -0.2312 |   -0.4237 |   -0.2973 |
## |.....................|    0.6921 |    0.6921 |    0.6712 |...........|
## |    U|     9562.9588 |    -1.677 |     3.367 |   -0.8916 |     2.851 |
## |.....................|    0.8416 |    0.2624 |   -0.2231 |   0.09550 |
## |.....................|     2.591 |     2.591 |     2.538 |...........|
## |    X|     9562.9588 |    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. |     9.949 |     191.5 |     598.8 |    -850.7 |
## |.....................|    -16.01 |    -56.78 | 1.712e+04 |    -8155. |
## |.....................|   -0.7345 |     3.945 |     221.1 |...........|
## |-----+--------------+----------+----------+----------+----------|
## |    2|     71342.325 |    -1.001 |    0.9899 |   -0.7202 |    0.8400 |
## |.....................|-0.0006468 |   -0.2282 |    -1.325 |    0.1321 |
## |.....................|    0.6921 |    0.6918 |    0.6595 |...........|
## |    U|     71342.325 |    -1.677 |     3.357 |   -0.9231 |     2.895 |
## |.....................|    0.8426 |    0.2738 |    -4.262 |    0.1160 |
## |.....................|     2.591 |     2.591 |     2.533 |...........|
## |    X|     71342.325 |    0.1869 |     28.71 |    0.3973 |     18.09 |
## |.....................|    0.8426 |    0.2738 |    -4.262 |    0.1160 |
## |.....................|     2.591 |     2.591 |     2.533 |...........|
## |    3|     8748.2665 |    -1.000 |    0.9988 |   -0.6924 |    0.8004 |
## |.....................| -0.001391 |   -0.2308 |   -0.5296 |   -0.2468 |
## |.....................|    0.6921 |    0.6920 |    0.6698 |...........|
## |    U|     8748.2665 |    -1.677 |     3.366 |   -0.8953 |     2.856 |
## |.....................|    0.8417 |    0.2637 |   -0.6980 |   0.09791 |
## |.....................|     2.591 |     2.591 |     2.537 |...........|
## |    X|     8748.2665 |    0.1870 |     28.97 |    0.4085 |     17.39 |
## |.....................|    0.8417 |    0.2637 |   -0.6980 |   0.09791 |
## |.....................|     2.591 |     2.591 |     2.537 |...........|
## |    F| Forward Diff. |     26.10 |     188.6 |    -234.9 |     137.7 |
## |.....................|    -15.12 |    -59.44 |    -863.2 |    -7724. |
## |.....................|   -0.5593 |     3.985 |     1.696 |...........|
## |-----+--------------+----------+----------+----------+----------|
## |    4|     7909.0560 |    -1.000 |    0.9960 |   -0.6889 |    0.7983 |
## |.....................| -0.001162 |   -0.2299 |   -0.5166 |   -0.1301 |
## |.....................|    0.6921 |    0.6920 |    0.6698 |...........|
## |    U|      7909.056 |    -1.677 |     3.363 |   -0.8918 |     2.854 |
## |.....................|    0.8420 |    0.2671 |   -0.6395 |    0.1035 |
```

```
## |.....................|     2.591 |     2.591 |     2.537 |.....|
## |    X|      7909.056 |    0.1869 |     28.88 |    0.4099 |     17.36 |
## |.....................|    0.8420 |    0.2671 |   -0.6395 |    0.1035 |
## |.....................|     2.591 |     2.591 |     2.537 |.....|
## |    5|     6118.3784 |    -1.002 |    0.9874 |   -0.6782 |    0.7921 |
## |.....................|-0.0004765 |   -0.2272 |   -0.4774 |    0.2201 |
## |.....................|    0.6921 |    0.6918 |    0.6697 |.....|
## |    U|     6118.3784 |    -1.678 |     3.355 |   -0.8811 |     2.848 |
## |.....................|    0.8428 |    0.2774 |   -0.4642 |    0.1202 |
## |.....................|     2.591 |     2.591 |     2.537 |.....|
## |    X|     6118.3784 |    0.1867 |     28.64 |    0.4143 |     17.25 |
## |.....................|    0.8428 |    0.2774 |   -0.4642 |    0.1202 |
## |.....................|     2.591 |     2.591 |     2.537 |.....|
## |    F| Forward Diff. |     16.06 |     172.2 |     132.5 |    -305.0 |
## |.....................|    -14.64 |    -57.24 |     2894. |    -4157. |
## |.....................|   -0.8861 |     3.041 |     23.29 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |    6|     5909.7177 |    -1.003 |    0.9715 |   -0.6905 |    0.8203 |
## |.....................| 0.0008792 |   -0.2219 |   -0.7454 |    0.6049 |
## |.....................|    0.6922 |    0.6915 |    0.6676 |.....|
## |    U|     5909.7177 |    -1.680 |     3.339 |   -0.8934 |     2.876 |
## |.....................|    0.8444 |    0.2976 |    -1.665 |    0.1386 |
## |.....................|     2.591 |     2.590 |     2.537 |.....|
## |    X|     5909.7177 |    0.1864 |     28.18 |    0.4093 |     17.74 |
## |.....................|    0.8444 |    0.2976 |    -1.665 |    0.1386 |
## |.....................|     2.591 |     2.590 |     2.537 |.....|
## |    F| Forward Diff. |     167.1 |     249.1 |     737.7 |     636.4 |
## |.....................|    -21.91 |    -114.7 |    -1722. |    -3410. |
## |.....................|     48.69 |     21.99 |     184.4 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |    7|     4374.4716 |    -1.013 |    0.9567 |   -0.7343 |    0.7826 |
## |.....................|  0.002180 |   -0.2151 |   -0.6431 |    0.8074 |
## |.....................|    0.6893 |    0.6902 |    0.6566 |.....|
## |    U|     4374.4716 |    -1.690 |     3.324 |   -0.9372 |     2.838 |
## |.....................|    0.8459 |    0.3235 |    -1.207 |    0.1482 |
## |.....................|     2.590 |     2.590 |     2.532 |.....|
## |    X|     4374.4716 |    0.1846 |     27.77 |    0.3917 |     17.08 |
## |.....................|    0.8459 |    0.3235 |    -1.207 |    0.1482 |
## |.....................|     2.590 |     2.590 |     2.532 |.....|
## |    8|    -145.69986 |    -1.043 |    0.9123 |   -0.8657 |    0.6692 |
## |.....................|  0.006084 |   -0.1947 |   -0.3363 |     1.415 |
## |.....................|    0.6806 |    0.6863 |    0.6237 |.....|
## |    U|    -145.69986 |    -1.719 |     3.280 |    -1.069 |     2.725 |
## |.....................|    0.8506 |    0.4014 |    0.1683 |    0.1772 |
## |.....................|     2.586 |     2.588 |     2.519 |.....|
## |    X|    -145.69986 |    0.1792 |     26.57 |    0.3435 |     15.25 |
## |.....................|    0.8506 |    0.4014 |    0.1683 |    0.1772 |
## |.....................|     2.586 |     2.588 |     2.519 |.....|
## |    F| Forward Diff. |    -10.82 |    -260.8 |     4.307 |    -51.16 |
## |.....................|     10.31 |    -87.16 |    -580.0 |     36.81 |
## |.....................|  0.002161 |     10.84 |   -0.1617 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
```

```
## |    9|     6986.1965 |   -0.7128 |     3.663 |    0.1427 |     2.314 |
## |.....................|   -0.1112 |    0.5714 |    0.9840 |     1.993 |
## |.....................|    0.7528 |    0.6069 |    0.8785 |...........|
## |    U|     6986.1965 |    -1.389 |     6.031 |  -0.06019 |     4.369 |
## |.....................|    0.7112 |     3.321 |     6.085 |    0.2049 |
## |.....................|     2.614 |     2.558 |     2.620 |...........|
## |    X|     6986.1965 |    0.2492 |     415.9 |    0.9416 |     79.00 |
## |.....................|    0.7112 |     3.321 |     6.085 |    0.2049 |
## |.....................|     2.614 |     2.558 |     2.620 |...........|
## |   10|    -161.11558 |    -1.023 |     1.136 |   -0.8201 |    0.7649 |
## |.....................| -0.003165 |   -0.1270 |  -0.06297 |     1.428 |
## |.....................|    0.6840 |    0.6786 |    0.6357 |...........|
## |    U|    -161.11558 |    -1.700 |     3.504 |    -1.023 |     2.820 |
## |.....................|    0.8396 |    0.6593 |     1.393 |    0.1779 |
## |.....................|     2.588 |     2.585 |     2.524 |...........|
## |    X|    -161.11558 |    0.1827 |     33.23 |    0.3595 |     16.78 |
## |.....................|    0.8396 |    0.6593 |     1.393 |    0.1779 |
## |.....................|     2.588 |     2.585 |     2.524 |...........|
## |    F| Forward Diff. |     25.45 |     131.5 |     3.960 |     123.0 |
## |.....................|    -10.80 |    -75.59 |     373.5 |     27.64 |
## |.....................|     2.387 |     2.275 |     4.152 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   11|    -205.76948 |    -1.064 |     1.178 |   -0.8200 |    0.5694 |
## |.....................|  0.007749 |    0.1548 |   -0.2030 |     1.408 |
## |.....................|    0.6795 |    0.6598 |    0.6298 |...........|
## |    U|    -205.76948 |    -1.741 |     3.545 |    -1.023 |     2.625 |
## |.....................|    0.8525 |     1.733 |    0.7658 |    0.1769 |
## |.....................|     2.586 |     2.578 |     2.522 |...........|
## |    X|    -205.76948 |    0.1754 |     34.65 |    0.3595 |     13.80 |
## |.....................|    0.8525 |     1.733 |    0.7658 |    0.1769 |
## |.....................|     2.586 |     2.578 |     2.522 |...........|
## |    F| Forward Diff. |    -96.16 |     40.12 |     3.508 |     7.517 |
## |.....................|    -8.538 |     33.95 |     66.68 |     46.51 |
## |.....................|   -0.7104 |    -2.329 |   -0.6264 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   12|    -132.40469 |   -0.7635 |     1.085 |   -0.8362 |    0.5226 |
## |.....................|   0.03536 |   0.09631 |   -0.3634 |     1.307 |
## |.....................|    0.6809 |    0.6632 |    0.6298 |...........|
## |    U|    -132.40469 |    -1.440 |     3.452 |    -1.039 |     2.578 |
## |.....................|    0.8854 |     1.510 |   0.04688 |    0.1721 |
## |.....................|     2.586 |     2.580 |     2.522 |...........|
## |    X|    -132.40469 |    0.2369 |     31.57 |    0.3538 |     13.17 |
## |.....................|    0.8854 |     1.510 |   0.04688 |    0.1721 |
## |.....................|     2.586 |     2.580 |     2.522 |...........|
## |   13|    -211.88673 |    -1.010 |     1.156 |   -0.8220 |    0.5652 |
## |.....................|   0.01254 |    0.1357 |   -0.2404 |     1.382 |
## |.....................|    0.6799 |    0.6611 |    0.6302 |...........|
## |    U|    -211.88673 |    -1.687 |     3.523 |    -1.025 |     2.621 |
## |.....................|    0.8582 |     1.661 |    0.5982 |    0.1757 |
## |.....................|     2.586 |     2.579 |     2.522 |...........|
## |    X|    -211.88673 |    0.1851 |     33.88 |    0.3588 |     13.75 |
## |.....................|    0.8582 |     1.661 |    0.5982 |    0.1757 |
```

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## |.....................|     2.586 |     2.579 |     2.522 |.....|
## |    F| Forward Diff. |    -11.95 |    -12.01 |     1.855 |    -8.309 |
## |.....................|    -6.953 |     31.38 |    -23.11 |     47.93 |
## |.....................|    -2.705 |    -3.027 |   -0.5789 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   14|    -215.32986 |    -1.015 |     1.169 |   -0.8308 |    0.5628 |
## |.....................|   0.03086 |   0.07799 |   -0.2370 |     1.339 |
## |.....................|    0.6862 |    0.6679 |    0.6295 |.....|
## |    U|    -215.32986 |    -1.691 |     3.536 |    -1.034 |     2.618 |
## |.....................|    0.8800 |     1.441 |    0.6133 |    0.1736 |
## |.....................|     2.588 |     2.581 |     2.522 |.....|
## |    X|    -215.32986 |    0.1843 |     34.34 |    0.3557 |     13.71 |
## |.....................|    0.8800 |     1.441 |    0.6133 |    0.1736 |
## |.....................|     2.588 |     2.581 |     2.522 |.....|
## |   15|    -212.12418 |    -1.054 |     1.184 |   -0.8538 |    0.5381 |
## |.....................|   0.07202 |  -0.03186 |   -0.2753 |     1.309 |
## |.....................|    0.6995 |    0.6823 |    0.6262 |.....|
## |    U|    -212.12418 |    -1.730 |     3.552 |    -1.057 |     2.594 |
## |.....................|    0.9289 |     1.022 |    0.4419 |    0.1722 |
## |.....................|     2.594 |     2.587 |     2.520 |.....|
## |    X|    -212.12418 |    0.1772 |     34.87 |    0.3476 |     13.38 |
## |.....................|    0.9289 |     1.022 |    0.4419 |    0.1722 |
## |.....................|     2.594 |     2.587 |     2.520 |.....|
## |    F| Forward Diff. |    -21.66 |     2.344 |     1.929 |    -3.864 |
## |.....................|    -6.485 |     9.879 |    -1.474 |     48.02 |
## |.....................|    -3.105 |    -3.092 |   -0.5819 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   16|    -220.84166 |   -0.9353 |     1.156 |   -0.8428 |    0.5828 |
## |.....................|   0.06199 |   0.04420 |   -0.2274 |     1.155 |
## |.....................|    0.7024 |    0.6838 |    0.6315 |.....|
## |    U|    -220.84166 |    -1.612 |     3.523 |    -1.046 |     2.638 |
## |.....................|    0.9170 |     1.312 |    0.6565 |    0.1649 |
## |.....................|     2.595 |     2.587 |     2.522 |.....|
## |    X|    -220.84166 |    0.1995 |     33.89 |    0.3514 |     13.99 |
## |.....................|    0.9170 |     1.312 |    0.6565 |    0.1649 |
## |.....................|     2.595 |     2.587 |     2.522 |.....|
## |    F| Forward Diff. |     116.8 |   -0.4047 |    -1.713 |     2.944 |
## |.....................|    -7.083 |    -1.102 |     26.41 |     47.60 |
## |.....................|    -1.058 |    -2.963 |   -0.6483 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   17|    -229.82769 |    -1.019 |     1.090 |   -0.8527 |    0.6483 |
## |.....................|   0.09902 | 0.0004164 |   -0.2604 |     1.005 |
## |.....................|    0.7165 |    0.7064 |    0.6368 |.....|
## |    U|    -229.82769 |    -1.696 |     3.458 |    -1.056 |     2.704 |
## |.....................|    0.9610 |     1.145 |    0.5086 |    0.1577 |
## |.....................|     2.600 |     2.596 |     2.524 |.....|
## |    X|    -229.82769 |    0.1834 |     31.74 |    0.3480 |     14.94 |
## |.....................|    0.9610 |     1.145 |    0.5086 |    0.1577 |
## |.....................|     2.600 |     2.596 |     2.524 |.....|
## |    F| Forward Diff. |    -12.00 |    -53.91 |     2.195 |    -20.47 |
## |.....................|    -2.830 |    -18.41 |    -129.6 |     51.38 |
## |.....................|    -3.122 |    -2.684 |   -0.6386 |.....|
```

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## |-----+---------------+-----------+-----------+-----------+-----------|
## |   18|    -230.62315 |    -1.049 |     1.049 |   -0.8849 |    0.7337 |
## |.....................|    0.1633 |   0.02902 |   -0.1548 |    0.8822 |
## |.....................|    0.7332 |    0.7429 |    0.6420 |...........|
## |    U|    -230.62315 |    -1.725 |     3.417 |    -1.088 |     2.789 |
## |.....................|     1.037 |     1.254 |    0.9818 |    0.1518 |
## |.....................|     2.607 |     2.610 |     2.527 |...........|
## |    X|    -230.62315 |    0.1781 |     30.47 |    0.3369 |     16.27 |
## |.....................|     1.037 |     1.254 |    0.9818 |    0.1518 |
## |.....................|     2.607 |     2.610 |     2.527 |...........|
## |    F| Forward Diff. |    -28.69 |     54.58 |    -3.126 |     47.42 |
## |.....................|    -8.511 |    -13.22 |     227.9 |     46.43 |
## |.....................|    -2.017 |    -1.249 |   -0.2592 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   19|    -242.38899 |    -1.031 |     1.025 |   -0.9002 |    0.7454 |
## |.....................|    0.1887 |   0.02167 |   -0.2224 |    0.8185 |
## |.....................|    0.7398 |    0.7575 |    0.6431 |...........|
## |    U|    -242.38899 |    -1.708 |     3.392 |    -1.103 |     2.801 |
## |.....................|     1.068 |     1.226 |    0.6787 |    0.1488 |
## |.....................|     2.609 |     2.616 |     2.527 |...........|
## |    X|    -242.38899 |    0.1813 |     29.72 |    0.3318 |     16.46 |
## |.....................|     1.068 |     1.226 |    0.6787 |    0.1488 |
## |.....................|     2.609 |     2.616 |     2.527 |...........|
## |    F| Forward Diff. |    -7.981 |    -21.12 |    -1.645 |    -5.739 |
## |.....................|    -4.568 |    -11.52 |    -16.16 |     52.61 |
## |.....................|    -2.835 |    -2.522 |    -1.084 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   20|    -248.82504 |    -1.002 |     1.036 |   -0.9231 |    0.8135 |
## |.....................|    0.2350 |   0.02064 |   -0.2011 |    0.6350 |
## |.....................|    0.7553 |    0.7868 |    0.6473 |...........|
## |    U|    -248.82504 |    -1.678 |     3.403 |    -1.126 |     2.869 |
## |.....................|     1.123 |     1.222 |    0.7741 |    0.1400 |
## |.....................|     2.615 |     2.627 |     2.529 |...........|
## |    X|    -248.82504 |    0.1867 |     30.07 |    0.3243 |     17.62 |
## |.....................|     1.123 |     1.222 |    0.7741 |    0.1400 |
## |.....................|     2.615 |     2.627 |     2.529 |...........|
## |    F| Forward Diff. |     57.52 |     30.24 |    -8.877 |     40.27 |
## |.....................|    -5.949 |    -13.61 |     165.1 |     50.07 |
## |.....................|    -1.763 |    -2.084 |   -0.8204 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   21|    -266.51968 |    -1.029 |    0.9458 |   -0.9356 |    0.9233 |
## |.....................|    0.3768 |   0.01505 |   -0.2449 |    0.3039 |
## |.....................|    0.8126 |    0.9204 |    0.6663 |...........|
## |    U|    -266.51968 |    -1.706 |     3.313 |    -1.138 |     2.979 |
## |.....................|     1.291 |     1.201 |    0.5781 |    0.1242 |
## |.....................|     2.637 |     2.679 |     2.536 |...........|
## |    X|    -266.51968 |    0.1817 |     27.47 |    0.3203 |     19.66 |
## |.....................|     1.291 |     1.201 |    0.5781 |    0.1242 |
## |.....................|     2.637 |     2.679 |     2.536 |...........|
## |    F| Forward Diff. |     29.79 |    -49.91 |    -10.90 |     4.638 |
## |.....................|  -0.05793 |    -15.25 |    -143.5 |     53.18 |
## |.....................|    -2.175 |    -1.590 |    -1.165 |...........|
```

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## |-----+---------------+-----------+-----------+-----------+-----------|
## |   22|    -284.10395 |    -1.079 |    0.8818 |   -0.7706 |    0.8181 |
## |.....................|    0.4868 |   0.03905 |   -0.1840 |-0.0002456 |
## |.....................|    0.8692 |     1.046 |    0.7039 |...........|
## |    U|    -284.10395 |    -1.755 |     3.249 |   -0.9735 |     2.874 |
## |.....................|     1.422 |     1.292 |    0.8509 |    0.1097 |
## |.....................|     2.659 |     2.727 |     2.551 |...........|
## |    X|    -284.10395 |    0.1729 |     25.77 |    0.3777 |     17.70 |
## |.....................|     1.422 |     1.292 |    0.8509 |    0.1097 |
## |.....................|     2.659 |     2.727 |     2.551 |...........|
## |    F| Forward Diff. |    -61.35 |    -34.85 |    -11.41 |     2.500 |
## |.....................|    -4.762 |    -9.686 |     86.85 |     54.16 |
## |.....................|    -1.218 |    -1.578 |    -1.536 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   23|    -303.40249 |    -1.062 |     1.058 |   -0.5963 |    0.6796 |
## |.....................|    0.5876 |   0.09041 |   -0.2296 |   -0.2424 |
## |.....................|    0.8869 |     1.185 |    0.7173 |...........|
## |    U|    -303.40249 |    -1.739 |     3.425 |   -0.7992 |     2.735 |
## |.....................|     1.542 |     1.488 |    0.6463 |   0.09812 |
## |.....................|     2.666 |     2.781 |     2.556 |...........|
## |    X|    -303.40249 |    0.1757 |     30.74 |    0.4497 |     15.41 |
## |.....................|     1.542 |     1.488 |    0.6463 |   0.09812 |
## |.....................|     2.666 |     2.781 |     2.556 |...........|
## |    F| Forward Diff. |    -83.97 |    -32.35 |     2.966 |    -17.03 |
## |.....................|     2.113 |     12.39 |    -119.6 |     59.70 |
## |.....................|   -0.3117 |    -1.963 |   -0.9345 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   24|    -321.21982 |   -0.9760 |     1.060 |   -0.4117 |    0.6080 |
## |.....................|    0.5738 |   0.03081 |   -0.1788 |   -0.5688 |
## |.....................|    0.8610 |     1.300 |    0.7449 |...........|
## |    U|    -321.21982 |    -1.653 |     3.427 |   -0.6146 |     2.664 |
## |.....................|     1.525 |     1.261 |    0.8742 |   0.08254 |
## |.....................|     2.656 |     2.825 |     2.567 |...........|
## |    X|    -321.21982 |    0.1915 |     30.79 |    0.5409 |     14.35 |
## |.....................|     1.525 |     1.261 |    0.8742 |   0.08254 |
## |.....................|     2.656 |     2.825 |     2.567 |...........|
## |    F| Forward Diff. |     91.12 |     11.24 |    -2.340 |     12.26 |
## |.....................|    -4.800 |    -14.31 |     127.4 |     52.35 |
## |.....................|    0.2521 |    -1.254 |   -0.6026 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   25|    -328.28749 |   -0.9940 |     1.007 |   -0.3054 |    0.6000 |
## |.....................|    0.5495 |   0.01484 |   -0.2282 |   -0.9453 |
## |.....................|    0.8068 |     1.406 |    0.7662 |...........|
## |    U|    -328.28749 |    -1.671 |     3.374 |   -0.5083 |     2.656 |
## |.....................|     1.496 |     1.200 |    0.6528 |   0.06456 |
## |.....................|     2.635 |     2.866 |     2.575 |...........|
## |    X|    -328.28749 |    0.1881 |     29.21 |    0.6015 |     14.23 |
## |.....................|     1.496 |     1.200 |    0.6528 |   0.06456 |
## |.....................|     2.635 |     2.866 |     2.575 |...........|
## |    F| Forward Diff. |     52.69 |    -200.3 |     8.473 |    -90.86 |
## |.....................|     1.450 |    -20.73 |    -356.3 |     24.34 |
## |.....................|   -0.5948 |     3.123 |    0.6059 |...........|
```

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## |-----+---------------+-----------+-----------+-----------+-----------|
## |   26|    -329.79421 |    -1.061 |     1.132 |   -0.4511 |    0.6865 |
## |.....................|    0.4919 |   0.08306 |   -0.2067 |    -1.269 |
## |.....................|    0.7179 |     1.469 |    0.7516 |...........|
## |    U|    -329.79421 |    -1.738 |     3.499 |   -0.6540 |     2.742 |
## |.....................|     1.428 |     1.460 |    0.7491 |   0.04909 |
## |.....................|     2.601 |     2.891 |     2.570 |...........|
## |    X|    -329.79421 |    0.1759 |     33.08 |    0.5199 |     15.52 |
## |.....................|     1.428 |     1.460 |    0.7491 |   0.04909 |
## |.....................|     2.601 |     2.891 |     2.570 |...........|
## |    F| Forward Diff. |    -75.74 |     162.6 |    -2.627 |     81.57 |
## |.....................|    -3.479 |     9.066 |     301.2 |    -68.23 |
## |.....................|   -0.2334 |     2.707 |    0.8559 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   27|    -341.90636 |    -1.042 |     1.131 |   -0.5189 |    0.6198 |
## |.....................|    0.5547 |   0.07241 |   -0.2430 |    -1.138 |
## |.....................|    0.7522 |     1.367 |    0.7502 |...........|
## |    U|    -341.90636 |    -1.719 |     3.498 |   -0.7218 |     2.675 |
## |.....................|     1.502 |     1.419 |    0.5863 |   0.05536 |
## |.....................|     2.614 |     2.851 |     2.569 |...........|
## |    X|    -341.90636 |    0.1793 |     33.05 |    0.4859 |     14.52 |
## |.....................|     1.502 |     1.419 |    0.5863 |   0.05536 |
## |.....................|     2.614 |     2.851 |     2.569 |...........|
## |    F| Forward Diff. |    -46.38 |     6.342 |     4.172 |     1.895 |
## |.....................|     5.733 |     5.058 |    -101.9 |    -12.08 |
## |.....................|   -0.7518 |  -0.01094 |   -0.4199 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   28|    -338.69230 |    -1.000 |     1.086 |   -0.4770 |    0.5512 |
## |.....................|    0.5306 |   0.03551 |   -0.1714 |    -1.003 |
## |.....................|    0.8236 |     1.337 |    0.7969 |...........|
## |    U|     -338.6923 |    -1.677 |     3.454 |   -0.6799 |     2.607 |
## |.....................|     1.474 |     1.279 |    0.9072 |   0.06178 |
## |.....................|     2.641 |     2.840 |     2.588 |...........|
## |    X|     -338.6923 |    0.1869 |     31.61 |    0.5067 |     13.56 |
## |.....................|     1.474 |     1.279 |    0.9072 |   0.06178 |
## |.....................|     2.641 |     2.840 |     2.588 |...........|
## |   29|    -342.79306 |    -1.020 |     1.115 |   -0.5053 |    0.5961 |
## |.....................|    0.5456 |   0.05903 |   -0.2022 |    -1.090 |
## |.....................|    0.7766 |     1.357 |    0.7662 |...........|
## |    U|    -342.79306 |    -1.697 |     3.482 |   -0.7082 |     2.652 |
## |.....................|     1.492 |     1.368 |    0.7695 |   0.05764 |
## |.....................|     2.623 |     2.847 |     2.575 |...........|
## |    X|    -342.79306 |    0.1832 |     32.52 |    0.4925 |     14.18 |
## |.....................|     1.492 |     1.368 |    0.7695 |   0.05764 |
## |.....................|     2.623 |     2.847 |     2.575 |...........|
## |    F| Forward Diff. |     1.724 |     58.94 |   -0.2822 |     27.59 |
## |.....................|    -2.077 |    -1.575 |     140.0 |   -0.4683 |
## |.....................|   -0.9441 |   -0.1534 |   -0.3682 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   30|    -343.68927 |    -1.016 |     1.090 |   -0.5235 |    0.5784 |
## |.....................|    0.5066 |   0.05247 |   -0.2199 |    -1.094 |
## |.....................|    0.8252 |     1.360 |    0.7997 |...........|
```

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## |    U|    -343.68927 |    -1.693 |     3.457 |   -0.7264 |     2.634 |
## |.....................|     1.445 |     1.343 |    0.6901 |   0.05745 |
## |.....................|     2.642 |     2.848 |     2.589 |...........|
## |    X|    -343.68927 |    0.1840 |     31.74 |    0.4836 |     13.93 |
## |.....................|     1.445 |     1.343 |    0.6901 |   0.05745 |
## |.....................|     2.642 |     2.848 |     2.589 |...........|
## |    F| Forward Diff. |     9.818 |    -41.54 |     3.537 |    -18.75 |
## |.....................|   -0.7872 |    -3.875 |    -62.69 | -0.007460 |
## |.....................|   -0.6899 |   -0.3491 |   -0.5067 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   31|    -344.36847 |    -1.019 |     1.107 |   -0.5846 |    0.5689 |
## |.....................|    0.5148 |   0.05486 |   -0.2171 |    -1.087 |
## |.....................|    0.8594 |     1.377 |    0.8300 |...........|
## |    U|    -344.36847 |    -1.696 |     3.474 |   -0.7875 |     2.624 |
## |.....................|     1.455 |     1.352 |    0.7025 |   0.05781 |
## |.....................|     2.655 |     2.855 |     2.601 |...........|
## |    X|    -344.36847 |    0.1835 |     32.28 |    0.4550 |     13.80 |
## |.....................|     1.455 |     1.352 |    0.7025 |   0.05781 |
## |.....................|     2.655 |     2.855 |     2.601 |...........|
## |    F| Forward Diff. |     4.944 |    -8.388 |     1.873 |    -3.596 |
## |.....................|   -0.7000 |    -3.024 |    -3.733 |     1.793 |
## |.....................|   -0.4410 |   -0.5132 |   -0.5241 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   32|    -344.67781 |    -1.020 |     1.128 |   -0.6988 |    0.5439 |
## |.....................|    0.5182 |   0.05939 |   -0.2234 |    -1.093 |
## |.....................|    0.8945 |     1.445 |    0.9109 |...........|
## |    U|    -344.67781 |    -1.697 |     3.495 |   -0.9017 |     2.599 |
## |.....................|     1.459 |     1.370 |    0.6741 |   0.05750 |
## |.....................|     2.669 |     2.881 |     2.632 |...........|
## |    X|    -344.67781 |    0.1833 |     32.95 |    0.4059 |     13.46 |
## |.....................|     1.459 |     1.370 |    0.6741 |   0.05750 |
## |.....................|     2.669 |     2.881 |     2.632 |...........|
## |   33|    -344.70010 |    -1.020 |     1.151 |   -0.8423 |    0.5114 |
## |.....................|    0.5223 |   0.06425 |   -0.2325 |    -1.101 |
## |.....................|    0.9385 |     1.531 |     1.013 |...........|
## |    U|     -344.7001 |    -1.697 |     3.518 |    -1.045 |     2.567 |
## |.....................|     1.464 |     1.388 |    0.6336 |   0.05712 |
## |.....................|     2.686 |     2.914 |     2.673 |...........|
## |    X|     -344.7001 |    0.1833 |     33.72 |    0.3516 |     13.03 |
## |.....................|     1.464 |     1.388 |    0.6336 |   0.05712 |
## |.....................|     2.686 |     2.914 |     2.673 |...........|
## |    F| Forward Diff. |     4.431 |     2.571 |  -0.04517 |     4.364 |
## |.....................|     3.297 |     1.912 |    -31.88 |    -1.826 |
## |.....................|    0.1427 |  -0.04735 |   -0.3846 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   34|    -344.62203 |    -1.027 |     1.198 |    -1.043 |    0.4175 |
## |.....................|    0.3698 |   0.06957 |   -0.2366 |    -1.116 |
## |.....................|     1.000 |     1.668 |     1.208 |...........|
## |    U|    -344.62203 |    -1.703 |     3.565 |    -1.245 |     2.473 |
## |.....................|     1.283 |     1.409 |    0.6154 |   0.05642 |
## |.....................|     2.710 |     2.967 |     2.749 |...........|
## |    X|    -344.62203 |    0.1820 |     35.35 |    0.2878 |     11.86 |
```

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## |.....................|     1.283 |     1.409 |    0.6154 |   0.05642 |
## |.....................|     2.710 |     2.967 |     2.749 |...........|
## |   35|    -344.86973 |    -1.024 |     1.172 |   -0.9325 |    0.4686 |
## |.....................|    0.4532 |   0.06643 |   -0.2307 |    -1.107 |
## |.....................|    0.9664 |     1.593 |     1.101 |...........|
## |    U|    -344.86973 |    -1.700 |     3.539 |    -1.135 |     2.524 |
## |.....................|     1.382 |     1.397 |    0.6415 |   0.05682 |
## |.....................|     2.697 |     2.938 |     2.707 |...........|
## |    X|    -344.86973 |    0.1826 |     34.43 |    0.3213 |     12.48 |
## |.....................|     1.382 |     1.397 |    0.6415 |   0.05682 |
## |.....................|     2.697 |     2.938 |     2.707 |...........|
## |    F| Forward Diff. |    -3.522 |     23.57 |   -0.4293 |     10.89 |
## |.....................|  -0.01928 |     3.252 |     17.36 |    -3.526 |
## |.....................|    0.3809 |   0.08984 |   -0.3096 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   36|    -344.91616 |    -1.029 |     1.164 |   -0.9893 |    0.4367 |
## |.....................|    0.5429 |   0.06986 |   -0.2210 |    -1.094 |
## |.....................|    0.9697 |     1.628 |     1.217 |...........|
## |    U|    -344.91616 |    -1.705 |     3.531 |    -1.192 |     2.492 |
## |.....................|     1.488 |     1.410 |    0.6851 |   0.05747 |
## |.....................|     2.698 |     2.952 |     2.753 |...........|
## |    X|    -344.91616 |    0.1817 |     34.17 |    0.3035 |     12.09 |
## |.....................|     1.488 |     1.410 |    0.6851 |   0.05747 |
## |.....................|     2.698 |     2.952 |     2.753 |...........|
## |    F| Forward Diff. |    -11.77 |     8.248 |    -1.846 |     6.407 |
## |.....................|     2.751 |     3.966 |     24.98 |   -0.6909 |
## |.....................|    0.3990 |    0.1590 |   -0.3351 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   37|    -345.05825 |    -1.024 |     1.183 |    -1.049 |    0.3882 |
## |.....................|    0.5250 |   0.06427 |   -0.2305 |    -1.069 |
## |.....................|    0.9496 |     1.654 |     1.355 |...........|
## |    U|    -345.05825 |    -1.701 |     3.550 |    -1.252 |     2.444 |
## |.....................|     1.467 |     1.388 |    0.6427 |   0.05865 |
## |.....................|     2.690 |     2.962 |     2.808 |...........|
## |    X|    -345.05825 |    0.1826 |     34.82 |    0.2859 |     11.52 |
## |.....................|     1.467 |     1.388 |    0.6427 |   0.05865 |
## |.....................|     2.690 |     2.962 |     2.808 |...........|
## |    F| Forward Diff. |    -6.077 |    -5.591 |    0.3526 |    -1.823 |
## |.....................|     3.856 |     1.502 |    -24.48 |     5.925 |
## |.....................|    0.2160 |   0.08923 |   -0.2875 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   38|    -345.02941 |    -1.012 |     1.180 |    -1.124 |    0.3794 |
## |.....................|    0.4898 |   0.05886 |   -0.2317 |    -1.097 |
## |.....................|    0.9028 |     1.621 |     1.483 |...........|
## |    U|    -345.02941 |    -1.688 |     3.548 |    -1.327 |     2.435 |
## |.....................|     1.425 |     1.368 |    0.6373 |   0.05732 |
## |.....................|     2.672 |     2.949 |     2.858 |...........|
## |    X|    -345.02941 |    0.1848 |     34.73 |    0.2654 |     11.41 |
## |.....................|     1.425 |     1.368 |    0.6373 |   0.05732 |
## |.....................|     2.672 |     2.949 |     2.858 |...........|
## |   39|    -345.19411 |    -1.018 |     1.182 |    -1.084 |    0.3843 |
## |.....................|    0.5082 |   0.06158 |   -0.2282 |    -1.083 |
```

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## |.....................|    0.9278 |     1.639 |     1.415 |.........|
## |    U|    -345.19411 |    -1.694 |     3.550 |    -1.287 |     2.440 |
## |.....................|     1.447 |     1.378 |    0.6529 |   0.05800 |
## |.....................|     2.682 |     2.956 |     2.831 |.........|
## |    X|    -345.19411 |    0.1837 |     34.80 |    0.2762 |     11.47 |
## |.....................|     1.447 |     1.378 |    0.6529 |   0.05800 |
## |.....................|     2.682 |     2.956 |     2.831 |.........|
## |    F| Forward Diff. |     9.886 |    -4.710 |    -1.040 |    0.8441 |
## |.....................|     2.661 |    0.3637 |    -4.321 |     2.644 |
## |.....................|   0.09536 |    0.1001 |   -0.2795 |.........|
## |-----+--------------+----------+----------+----------+----------|
## |   40|    -345.13014 |    -1.030 |     1.189 |    -1.109 |    0.3779 |
## |.....................|    0.4786 |   0.06476 |   -0.2249 |    -1.091 |
## |.....................|    0.9163 |     1.614 |     1.473 |.........|
## |    U|    -345.13014 |    -1.707 |     3.557 |    -1.312 |     2.433 |
## |.....................|     1.412 |     1.390 |    0.6674 |   0.05758 |
## |.....................|     2.677 |     2.947 |     2.854 |.........|
## |    X|    -345.13014 |    0.1814 |     35.04 |    0.2693 |     11.40 |
## |.....................|     1.412 |     1.390 |    0.6674 |   0.05758 |
## |.....................|     2.677 |     2.947 |     2.854 |.........|
## |   41|    -345.02683 |    -1.031 |     1.189 |    -1.091 |    0.3814 |
## |.....................|    0.4958 |   0.06232 |   -0.2231 |    -1.088 |
## |.....................|    0.9239 |     1.630 |     1.435 |.........|
## |    U|    -345.02683 |    -1.708 |     3.556 |    -1.294 |     2.437 |
## |.....................|     1.432 |     1.381 |    0.6757 |   0.05775 |
## |.....................|     2.680 |     2.953 |     2.839 |.........|
## |    X|    -345.02683 |    0.1813 |     35.03 |    0.2741 |     11.44 |
## |.....................|     1.432 |     1.381 |    0.6757 |   0.05775 |
## |.....................|     2.680 |     2.953 |     2.839 |.........|
## |   42|    -345.18380 |    -1.025 |     1.186 |    -1.083 |    0.3837 |
## |.....................|    0.5062 |   0.06131 |   -0.2250 |    -1.085 |
## |.....................|    0.9278 |     1.639 |     1.415 |.........|
## |    U|     -345.1838 |    -1.702 |     3.553 |    -1.286 |     2.439 |
## |.....................|     1.445 |     1.377 |    0.6671 |   0.05791 |
## |.....................|     2.682 |     2.956 |     2.831 |.........|
## |    X|     -345.1838 |    0.1824 |     34.92 |    0.2764 |     11.46 |
## |.....................|     1.445 |     1.377 |    0.6671 |   0.05791 |
## |.....................|     2.682 |     2.956 |     2.831 |.........|
## |   43|    -345.22055 |    -1.021 |     1.184 |    -1.084 |    0.3840 |
## |.....................|    0.5073 |   0.06146 |   -0.2267 |    -1.083 |
## |.....................|    0.9278 |     1.639 |     1.415 |.........|
## |    U|    -345.22055 |    -1.698 |     3.551 |    -1.286 |     2.440 |
## |.....................|     1.446 |     1.378 |    0.6594 |   0.05796 |
## |.....................|     2.682 |     2.956 |     2.831 |.........|
## |    X|    -345.22055 |    0.1831 |     34.86 |    0.2763 |     11.47 |
## |.....................|     1.446 |     1.378 |    0.6594 |   0.05796 |
## |.....................|     2.682 |     2.956 |     2.831 |.........|
## |    F| Forward Diff. |     2.485 |     2.582 |    -1.103 |     2.911 |
## |.....................|     2.370 |    0.1692 |     6.635 |     2.339 |
## |.....................|   0.09461 |    0.1021 |   -0.2850 |.........|
## |-----+--------------+----------+----------+----------+----------|
## |   44|    -345.22605 |    -1.022 |     1.183 |    -1.084 |    0.3834 |
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## |.....................|    0.5054 |   0.06154 |   -0.2286 |    -1.084 |
## |.....................|    0.9277 |     1.638 |     1.417 |.....      |
## |    U|    -345.22605 |    -1.698 |     3.550 |    -1.287 |     2.439 |
## |.....................|     1.444 |     1.378 |    0.6509 |   0.05792 |
## |.....................|     2.682 |     2.956 |     2.832 |.....      |
## |    X|    -345.22605 |    0.1830 |     34.83 |    0.2761 |     11.46 |
## |.....................|     1.444 |     1.378 |    0.6509 |   0.05792 |
## |.....................|     2.682 |     2.956 |     2.832 |.....      |
## |    F| Forward Diff. |    0.5852 |    -4.187 |   -0.7407 |    0.4514 |
## |.....................|     2.606 |    0.2797 |    -5.780 |     2.272 |
## |.....................|   0.08827 |   0.09989 |   -0.2833 |.....      |
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   45|    -345.23770 |    -1.022 |     1.184 |    -1.085 |    0.3831 |
## |.....................|    0.5037 |   0.06160 |   -0.2276 |    -1.085 |
## |.....................|    0.9274 |     1.637 |     1.421 |.....      |
## |    U|     -345.2377 |    -1.699 |     3.551 |    -1.288 |     2.439 |
## |.....................|     1.442 |     1.378 |    0.6557 |   0.05788 |
## |.....................|     2.682 |     2.955 |     2.833 |.....      |
## |    X|     -345.2377 |    0.1829 |     34.86 |    0.2758 |     11.46 |
## |.....................|     1.442 |     1.378 |    0.6557 |   0.05788 |
## |.....................|     2.682 |     2.955 |     2.833 |.....      |
## |    F| Forward Diff. |    0.3681 |    0.1693 |   -0.9122 |     1.939 |
## |.....................|     2.340 |    0.2850 |     3.745 |     2.106 |
## |.....................|   0.09263 |   0.09840 |   -0.2750 |.....      |
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   46|    -345.24620 |    -1.022 |     1.184 |    -1.088 |    0.3817 |
## |.....................|    0.5008 |   0.06174 |   -0.2286 |    -1.086 |
## |.....................|    0.9267 |     1.635 |     1.427 |.....      |
## |    U|     -345.2462 |    -1.699 |     3.552 |    -1.291 |     2.437 |
## |.....................|     1.438 |     1.379 |    0.6509 |   0.05783 |
## |.....................|     2.681 |     2.955 |     2.836 |.....      |
## |    X|     -345.2462 |    0.1829 |     34.87 |    0.2750 |     11.44 |
## |.....................|     1.438 |     1.379 |    0.6509 |   0.05783 |
## |.....................|     2.681 |     2.955 |     2.836 |.....      |
## |    F| Forward Diff. |   -0.1990 |    -2.545 |   -0.7559 |    0.9475 |
## |.....................|     2.384 |    0.4113 |    -2.437 |     1.872 |
## |.....................|   0.08815 |   0.09296 |   -0.2791 |.....      |
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   47|    -345.26500 |    -1.022 |     1.186 |    -1.094 |    0.3791 |
## |.....................|    0.4962 |   0.06193 |   -0.2282 |    -1.088 |
## |.....................|    0.9252 |     1.632 |     1.441 |.....      |
## |    U|      -345.265 |    -1.699 |     3.553 |    -1.297 |     2.435 |
## |.....................|     1.433 |     1.379 |    0.6528 |   0.05776 |
## |.....................|     2.681 |     2.953 |     2.841 |.....      |
## |    X|      -345.265 |    0.1829 |     34.92 |    0.2733 |     11.41 |
## |.....................|     1.433 |     1.379 |    0.6528 |   0.05776 |
## |.....................|     2.681 |     2.953 |     2.841 |.....      |
## |   48|    -345.29799 |    -1.022 |     1.188 |    -1.114 |    0.3722 |
## |.....................|    0.4845 |   0.06292 |   -0.2293 |    -1.090 |
## |.....................|    0.9207 |     1.622 |     1.484 |.....      |
## |    U|    -345.29799 |    -1.699 |     3.556 |    -1.317 |     2.428 |
## |.....................|     1.419 |     1.383 |    0.6478 |   0.05764 |
```

```
## |.....................|     2.679 |     2.950 |     2.858 |.....|
## |    X|    -345.29799 |    0.1829 |     35.01 |    0.2680 |     11.33 |
## |.....................|     1.419 |     1.383 |    0.6478 |   0.05764 |
## |.....................|     2.679 |     2.950 |     2.858 |.....|
## |   49|    -345.35149 |    -1.023 |     1.196 |    -1.169 |    0.3523 |
## |.....................|    0.4509 |   0.06553 |   -0.2316 |    -1.098 |
## |.....................|    0.9082 |     1.595 |     1.604 |.....|
## |    U|    -345.35149 |    -1.699 |     3.563 |    -1.371 |     2.408 |
## |.....................|     1.379 |     1.393 |    0.6377 |   0.05727 |
## |.....................|     2.674 |     2.939 |     2.905 |.....|
## |    X|    -345.35149 |    0.1828 |     35.28 |    0.2538 |     11.11 |
## |.....................|     1.379 |     1.393 |    0.6377 |   0.05727 |
## |.....................|     2.674 |     2.939 |     2.905 |.....|
## |    F| Forward Diff. |    -1.708 |    -1.201 |    -1.014 |     1.764 |
## |.....................|    0.4513 |     2.628 |     2.568 |   -0.7001 |
## |.....................|   0.01229 |  -0.02617 |   -0.2529 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   50|    -345.35521 |    -1.018 |     1.221 |    -1.222 |    0.2883 |
## |.....................|    0.4563 |   0.06218 |   -0.2344 |    -1.114 |
## |.....................|    0.9026 |     1.581 |     1.791 |.....|
## |    U|    -345.35521 |    -1.694 |     3.588 |    -1.425 |     2.344 |
## |.....................|     1.386 |     1.380 |    0.6249 |   0.05651 |
## |.....................|     2.672 |     2.934 |     2.979 |.....|
## |    X|    -345.35521 |    0.1837 |     36.17 |    0.2405 |     10.42 |
## |.....................|     1.386 |     1.380 |    0.6249 |   0.05651 |
## |.....................|     2.672 |     2.934 |     2.979 |.....|
## |    F| Forward Diff. |     4.538 |     11.29 |    0.7404 |    0.9252 |
## |.....................|     1.406 |    0.9457 |     1.626 |    -4.376 |
## |.....................|   0.03691 |   -0.1386 |   -0.2090 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   51|    -345.43038 |    -1.018 |     1.220 |    -1.235 |    0.2851 |
## |.....................|    0.4387 |   0.05995 |   -0.2358 |    -1.106 |
## |.....................|    0.9164 |     1.597 |     1.890 |.....|
## |    U|    -345.43038 |    -1.695 |     3.587 |    -1.437 |     2.341 |
## |.....................|     1.365 |     1.372 |    0.6187 |   0.05689 |
## |.....................|     2.677 |     2.940 |     3.018 |.....|
## |    X|    -345.43038 |    0.1836 |     36.14 |    0.2375 |     10.39 |
## |.....................|     1.365 |     1.372 |    0.6187 |   0.05689 |
## |.....................|     2.677 |     2.940 |     3.018 |.....|
## |    F| Forward Diff. |     3.473 |     4.485 |    0.7477 |   -0.8112 |
## |.....................|    0.7004 |  -0.01260 |    -3.564 |    -2.272 |
## |.....................|    0.1143 |   -0.1231 |   -0.1950 |.....|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   52|    -345.46141 |    -1.020 |     1.217 |    -1.242 |    0.2904 |
## |.....................|    0.4314 |   0.06267 |   -0.2360 |    -1.100 |
## |.....................|    0.8242 |     1.650 |     2.068 |.....|
## |    U|    -345.46141 |    -1.697 |     3.584 |    -1.445 |     2.346 |
## |.....................|     1.356 |     1.382 |    0.6177 |   0.05715 |
## |.....................|     2.642 |     2.961 |     3.088 |.....|
## |    X|    -345.46141 |    0.1833 |     36.02 |    0.2358 |     10.44 |
## |.....................|     1.356 |     1.382 |    0.6177 |   0.05715 |
## |.....................|     2.642 |     2.961 |     3.088 |.....|
```

```
## |    F| Forward Diff. |    0.4441 |    -1.469 |    0.4862 |    -1.587 |
## |.....................|    0.3042 |     1.272 |    -7.026 |   -0.9367 |
## |.....................|   -0.5449 |    0.1037 |   -0.1645 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   53|    -345.50918 |    -1.022 |     1.213 |    -1.251 |    0.2959 |
## |.....................|    0.4226 |   0.06019 |   -0.2355 |    -1.100 |
## |.....................|    0.8817 |     1.651 |     2.267 |...........|
## |    U|    -345.50918 |    -1.699 |     3.580 |    -1.454 |     2.351 |
## |.....................|     1.345 |     1.373 |    0.6199 |   0.05719 |
## |.....................|     2.664 |     2.961 |     3.167 |...........|
## |    X|    -345.50918 |    0.1829 |     35.89 |    0.2336 |     10.50 |
## |.....................|     1.345 |     1.373 |    0.6199 |   0.05719 |
## |.....................|     2.664 |     2.961 |     3.167 |...........|
## |    F| Forward Diff. |    -2.731 |    -5.683 |   0.04001 |    -1.848 |
## |.....................|   -0.2755 |    0.1414 |    -6.845 |   -0.8212 |
## |.....................|   -0.1508 |    0.1513 |   -0.1432 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   54|    -345.54444 |    -1.022 |     1.214 |    -1.264 |    0.2946 |
## |.....................|    0.4165 |   0.05919 |   -0.2358 |    -1.094 |
## |.....................|    0.8911 |     1.595 |     2.466 |...........|
## |    U|    -345.54444 |    -1.698 |     3.582 |    -1.467 |     2.350 |
## |.....................|     1.338 |     1.369 |    0.6186 |   0.05748 |
## |.....................|     2.667 |     2.939 |     3.245 |...........|
## |    X|    -345.54444 |    0.1830 |     35.93 |    0.2306 |     10.49 |
## |.....................|     1.338 |     1.369 |    0.6186 |   0.05748 |
## |.....................|     2.667 |     2.939 |     3.245 |...........|
## |   55|    -345.54975 |    -1.021 |     1.216 |    -1.278 |    0.2933 |
## |.....................|    0.4102 |   0.05813 |   -0.2362 |    -1.087 |
## |.....................|    0.9010 |     1.537 |     2.677 |...........|
## |    U|    -345.54975 |    -1.698 |     3.583 |    -1.481 |     2.349 |
## |.....................|     1.331 |     1.365 |    0.6172 |   0.05778 |
## |.....................|     2.671 |     2.917 |     3.328 |...........|
## |    X|    -345.54975 |    0.1831 |     35.98 |    0.2275 |     10.47 |
## |.....................|     1.331 |     1.365 |    0.6172 |   0.05778 |
## |.....................|     2.671 |     2.917 |     3.328 |...........|
## |    F| Forward Diff. |   -0.1019 |    -2.055 |   -0.4564 |   -0.3945 |
## |.....................|   -0.8270 |   -0.7636 |    -2.048 |     2.525 |
## |.....................|  0.003658 |   -0.2432 |   -0.1423 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   56|    -345.60631 |    -1.021 |     1.204 |    -1.205 |    0.3203 |
## |.....................|    0.4222 |   0.05767 |   -0.2322 |    -1.088 |
## |.....................|    0.9354 |     1.514 |     3.095 |...........|
## |    U|    -345.60631 |    -1.698 |     3.572 |    -1.408 |     2.376 |
## |.....................|     1.345 |     1.363 |    0.6349 |   0.05774 |
## |.....................|     2.685 |     2.908 |     3.493 |...........|
## |    X|    -345.60631 |    0.1831 |     35.57 |    0.2447 |     10.76 |
## |.....................|     1.345 |     1.363 |    0.6349 |   0.05774 |
## |.....................|     2.685 |     2.908 |     3.493 |...........|
## |    F| Forward Diff. |    0.6977 |    -3.065 |   -0.2102 |   -0.8336 |
## |.....................|    -1.003 |    -1.222 |     1.629 |     2.236 |
## |.....................|    0.2379 |   -0.1605 |   -0.1062 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
```

```
## |   57|    -345.66118 |    -1.021 |     1.199 |    -1.175 |    0.3340 |
## |.....................|    0.4345 |   0.05828 |   -0.2306 |    -1.092 |
## |.....................|    0.9291 |     1.509 |     3.521 |...........|
## |    U|    -345.66118 |    -1.698 |     3.567 |    -1.378 |     2.390 |
## |.....................|     1.360 |     1.366 |    0.6419 |   0.05756 |
## |.....................|     2.682 |     2.906 |     3.661 |...........|
## |    X|    -345.66118 |    0.1830 |     35.40 |    0.2522 |     10.91 |
## |.....................|     1.360 |     1.366 |    0.6419 |   0.05756 |
## |.....................|     2.682 |     2.906 |     3.661 |...........|
## |    F| Forward Diff. |  -0.05334 |    -1.952 |   -0.1915 |   -0.3361 |
## |.....................|   -0.7279 |    -1.067 |     6.622 |     1.231 |
## |.....................|    0.1996 |  -0.06695 |  -0.08874 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   58|    -345.75183 |    -1.021 |     1.201 |    -1.177 |    0.3350 |
## |.....................|    0.4398 |   0.05956 |   -0.2321 |    -1.096 |
## |.....................|    0.9144 |     1.538 |     4.628 |...........|
## |    U|    -345.75183 |    -1.698 |     3.569 |    -1.380 |     2.391 |
## |.....................|     1.366 |     1.370 |    0.6354 |   0.05734 |
## |.....................|     2.676 |     2.917 |     4.097 |...........|
## |    X|    -345.75183 |    0.1831 |     35.47 |    0.2515 |     10.92 |
## |.....................|     1.366 |     1.370 |    0.6354 |   0.05734 |
## |.....................|     2.676 |     2.917 |     4.097 |...........|
## |    F| Forward Diff. |    0.2449 |    0.4778 |  -0.07210 |    0.4745 |
## |.....................|   -0.2649 |   -0.4023 |     1.859 |   0.03094 |
## |.....................|    0.1034 |    0.1284 |  -0.04568 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   59|    -345.79039 |    -1.022 |     1.198 |    -1.165 |    0.3408 |
## |.....................|    0.4523 |   0.06042 |   -0.2313 |    -1.100 |
## |.....................|    0.8901 |     1.442 |     5.732 |...........|
## |    U|    -345.79039 |    -1.699 |     3.565 |    -1.368 |     2.396 |
## |.....................|     1.381 |     1.374 |    0.6388 |   0.05717 |
## |.....................|     2.667 |     2.880 |     4.532 |...........|
## |    X|    -345.79039 |    0.1829 |     35.35 |    0.2546 |     10.98 |
## |.....................|     1.381 |     1.374 |    0.6388 |   0.05717 |
## |.....................|     2.667 |     2.880 |     4.532 |...........|
## |    F| Forward Diff. |    -1.173 |    -1.716 |  -0.04189 |   -0.4429 |
## |.....................|    0.1937 |   -0.1167 |    -3.021 |   -0.6586 |
## |.....................|  -0.04412 |   -0.1293 |  -0.03152 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
## |   60|    -345.82417 |    -1.021 |     1.199 |    -1.164 |    0.3397 |
## |.....................|    0.4528 |   0.06174 |   -0.2309 |    -1.098 |
## |.....................|    0.8887 |     1.446 |     6.840 |...........|
## |    U|    -345.82417 |    -1.698 |     3.566 |    -1.367 |     2.395 |
## |.....................|     1.381 |     1.379 |    0.6405 |   0.05727 |
## |.....................|     2.667 |     2.882 |     4.969 |...........|
## |    X|    -345.82417 |    0.1830 |     35.38 |    0.2549 |     10.97 |
## |.....................|     1.381 |     1.379 |    0.6405 |   0.05727 |
## |.....................|     2.667 |     2.882 |     4.969 |...........|
## |    F| Forward Diff. |    0.1492 |    0.2725 | -0.008961 |    0.1091 |
## |.....................|    0.1388 |    0.5464 |     1.784 |   0.07601 |
## |.....................|  -0.04585 |  -0.09354 |  -0.02025 |...........|
## |-----+---------------+-----------+-----------+-----------+-----------|
```

```
## |   61|    -345.82417 |    -1.021 |     1.199 |    -1.164 |    0.3397 |
## |.....................|    0.4528 |   0.06174 |   -0.2309 |    -1.098 |
## |.....................|    0.8887 |     1.446 |     6.840 |...........|
## |    U|    -345.82417 |    -1.698 |     3.566 |    -1.367 |     2.395 |
## |.....................|     1.381 |     1.379 |    0.6405 |   0.05727 |
## |.....................|     2.667 |     2.882 |     4.969 |...........|
## |    X|    -345.82417 |    0.1830 |     35.38 |    0.2549 |     10.97 |
## |.....................|     1.381 |     1.379 |    0.6405 |   0.05727 |
## |.....................|     2.667 |     2.882 |     4.969 |...........|
## calculating covariance matrix
## done
```

```
## → Calculating residuals/tables
```

```
## ✔ done
```

```
## → compress origData in nlmixr2 object, save 9504
```

```
## → compress parHistData in nlmixr2 object, save 8240
```

3.10 Estimating individual Exposures - Full

estimation, TDM, Last Timepoint, No observation

```
## TDM
orig_data <- two_cmt_TDM_pk_fit$origData
indv_cl <- data.frame(ID = two_cmt_TDM_pk_fit$ID, Clearance = two_cmt_TDM_pk_fit$cl)

tdm_indiv_AUC<- merge(orig_data, indv_cl, by = 'ID')
tdm_indiv_AUC <- tdm_indiv_AUC %>% mutate(AUC = AMT/Clearance) %>% select(ID, AUC)

tdm_indiv_AUC <- tdm_indiv_AUC %>%
  group_by(ID) %>%
  summarize(tdm_AUC = first(AUC), .groups = "drop")

## Last Time POint
last_tp_indv_cl <- data.frame(ID = two_cmt_last_tp_pk_fit$ID, Clearance = two_cmt_last_t
p_pk_fit$cl)

last_tp_indiv_exposure <- merge(last_time_point, last_tp_indv_cl, by = 'ID')
last_tp_indiv_exposure <- last_tp_indiv_exposure %>% mutate(AUC = AMT/Clearance) %>% sel
ect(ID, AUC)

last_tp_AUC <- last_tp_indiv_exposure %>%
  group_by(ID) %>%
  summarize(last_tp_AUC = first(AUC), .groups = "drop")

## Full-Estimation
full_est_indv_cl <- data.frame(ID = full_estimation_pk_fit$ID, Clearance = full_estimati
on_pk_fit$cl)

full_est_indiv_exposure <- merge(busulfan_First_Dose_dataset, full_est_indv_cl, by = 'I
D')
full_est_indiv_exposure <- full_est_indiv_exposure %>% mutate(AUC = AMT/Clearance) %>% s
elect(ID, AUC)

full_est_AUC <- full_est_indiv_exposure %>%
  group_by(ID) %>%
  summarize(full_estimation_AUC = first(AUC), .groups = "drop")

compare_auc <- merge(full_est_AUC, tdm_indiv_AUC, by = "ID")
compare_auc <- merge(compare_auc, last_tp_AUC, by = "ID")
compare_auc <- merge(compare_auc, no_tp_AUC, by = "ID")

compare_auc[] <- lapply(compare_auc, function(x) if(is.numeric(x)) round(x, 0) else x)
print(compare_auc)
```

```
##      ID full_estimation_AUC tdm_AUC last_tp_AUC no_tp_AUC
## 1  1002                1040    1088        1088      1089
## 2  1006                1267    1214        1214      1200
## 3  1014                1079    1107        1116      1137
## 4  1022                1195    1467        1467      1246
## 5  1027                1152    1724        1725      1601
## 6  1043                1190    1269        1306      1157
## 7  1046                1102    1193        1268      1281
## 8  1050                1221    1251        1222      1329
## 9  1051                1177     966         966      1150
## 10 1052                1142    1184        1259      1151
## 11 1079                1144    1126        1122      1062
## 12 1083                1574    1157        1157      1470
## 13 1087                1232    1245        1245      1330
## 14 1088                1137     810         810       948
## 15 1098                1143    1242        1354      1467
## 16 1109                1307    1389        1464      1390
## 17 1110                1324    1330        1378      1405
## 18 1111                1390    1153        1153      1134
## 19 1113                1096     844         844      1040
## 20 1127                1100    1093        1125      1139
## 21 1132                1291    1030        1030      1131
## 22 1140                 752     965         965      1115
```

3.11 Compare across estimation methods

```
# Convert to long format
df_long <- compare_auc %>%
  pivot_longer(cols = -ID, names_to = "Method", values_to = "AUC")

# Order methods for nicer plotting
df_long$Method <- factor(df_long$Method, levels = c("full_estimation_AUC", "tdm_AUC", "l
ast_tp_AUC", "no_tp_AUC"))

# Set common y-axis limits
y_limits <- c(750, 1750)

# --- Full vs TDM
df_tdm <- compare_auc %>%
  select(ID, Full = full_estimation_AUC, TDM = tdm_AUC) %>%
  pivot_longer(cols = -ID, names_to = "Method", values_to = "AUC") %>%
  mutate(Method = factor(Method, levels = c("Full", "TDM")))

p_tdm <- ggplot(df_tdm, aes(x = Method, y = AUC)) +
  geom_boxplot(alpha = 0.3, aes(fill = Method, color = Method)) +
  geom_jitter(aes(color = Method), width = 0.1, alpha = 0.7, size = 2) +
  geom_line(aes(group = ID), color = "grey60", alpha = 0.6) +
  scale_fill_manual(values = c("Full" = "#F8766D", "TDM" = "#00BFC4")) +
  scale_color_manual(values = c("Full" = "#F8766D", "TDM" = "#00BFC4")) +
  theme_bw() +
  labs(title = "TDM", x = "", y = "AUC") +
  theme(legend.position = "none",
        plot.title = element_text(hjust = 0.5)
        ) +
  scale_y_continuous(limits = y_limits)

# --- Full vs Last TP
df_last <- compare_auc %>%
  select(ID, Full = full_estimation_AUC, Last_TP = last_tp_AUC) %>%
  pivot_longer(cols = -ID, names_to = "Method", values_to = "AUC") %>%
  mutate(Method = factor(Method, levels = c("Full", "Last_TP")))

p_last <- ggplot(df_last, aes(x = Method, y = AUC)) +
  geom_boxplot(alpha = 0.3, aes(fill = Method, color = Method)) +
  geom_jitter(aes(color = Method), width = 0.1, alpha = 0.7, size = 2) +
  geom_line(aes(group = ID), color = "grey60", alpha = 0.6) +
  scale_fill_manual(values = c("Full" = "#F8766D", "Last_TP" = "#7CAE00")) +
  scale_color_manual(values = c("Full" = "#F8766D", "Last_TP" = "#7CAE00")) +
  theme_bw() +
  labs(title = "Last TP", x = "", y = "AUC") +
  theme(legend.position = "none",
        axis.title.y = element_blank(),
        axis.text.y = element_blank(),
        axis.ticks.y = element_blank(),
        plot.title = element_text(hjust = 0.5)
        ) +
```

```
  scale_y_continuous(limits = y_limits)

# --- Full vs No TP
df_no <- compare_auc %>%
  select(ID, Full = full_estimation_AUC, No_Obs = no_tp_AUC) %>%
  pivot_longer(cols = -ID, names_to = "Method", values_to = "AUC") %>%
  mutate(Method = factor(Method, levels = c("Full", "No_Obs")))

p_no <- ggplot(df_no, aes(x = Method, y = AUC)) +
  geom_boxplot(alpha = 0.3, aes(fill = Method, color = Method)) +
  geom_jitter(aes(color = Method), width = 0.1, alpha = 0.7, size = 2) +
  geom_line(aes(group = ID), color = "grey60", alpha = 0.6) +
  scale_fill_manual(values = c("Full" = "#F8766D", "No_Obs" = "#C77CFF")) +
  scale_color_manual(values = c("Full" = "#F8766D", "No_Obs" = "#C77CFF")) +
  theme_bw() +
  labs(title = "No Obs", x = "", y = "AUC") +
  theme(legend.position = "none",
        axis.title.y = element_blank(),
        axis.text.y = element_blank(),
        axis.ticks.y = element_blank(),
        plot.title = element_text(hjust = 0.5)
        ) +
  scale_y_continuous(limits = y_limits)

wrap_plots(p_tdm, p_last, p_no, ncol = 3)
```