

```
output: rmarkdown::github_document
```

```
install.packages("tinytex") tinytex::install_tinytex() tinytex::reinstall_tinytex()
```

```
## load required R packages
```

```
library(ggplot2)
```

```
## Warning: package 'ggplot2' was built under R version 4.2.3
```

```
library(dplyr)
```

```
## Warning: package 'dplyr' was built under R version 4.2.3
```

```
##
```

```
## Attaching package: 'dplyr'
```

```
## The following objects are masked from 'package:stats':
```

```
##
```

```
## filter, lag
```

```
## The following objects are masked from 'package:base':
```

```
##
```

```
## intersect, setdiff, setequal, union
```

```
#install.packages("PKNCA")
```

```
library(PKNCA)
```

```
##
```

```
## Attaching package: 'PKNCA'
```

```
## The following object is masked from 'package:stats':
```

```
##
```

```
## filter
```

```
#install.packages('pander')
```

```
library(pander)
```

```
library(tidyr)
```

```
## Warning: package 'tidyr' was built under R version 4.2.3
```

```
#load the sample_data dataset
```

```
data <- read.csv("C:\\Users\\Grzegorz_Sterkowski\\Documents\\Pharma\\my_NCA_repo\\dataset\\sample_data.csv")
```

```
head(data)
```

```
##   ID Time  Amt      Conc Age Weight Gender      Race Dose AGECAT
## 1  1 0.00 5000  0.000000  56    94   Male Hispanic 5000      0
## 2  1 0.25   0  8.612809  56    94   Male Hispanic 5000      0
## 3  1 0.50   0 19.436818  56    94   Male Hispanic 5000      0
## 4  1 1.00   0 34.006699  56    94   Male Hispanic 5000      0
## 5  1 2.00   0 30.228800  56    94   Male Hispanic 5000      0
## 6  1 3.00   0 31.299610  56    94   Male Hispanic 5000      0
```

```
###
##ID Time Amt Conc Age Weight Gender Race Dose AGECAT
##1 1 0.00 5000 0.000000 56 94 Male Hispanic 5000 0
##2 1 0.25 0 8.612809 56 94 Male Hispanic 5000 0
##3 1 0.50 0 19.436818 56 94 Male Hispanic 5000 0
##4 1 1.00 0 34.006699 56 94 Male Hispanic 5000 0
##5 1 2.00 0 30.228800 56 94 Male Hispanic 5000 0
##6 1 3.00 0 31.299610 56 94 Male Hispanic 5000 0
##7 1 4.00 0 24.979117 56 94 Male Hispanic 5000 0

#summarising the data
summary(data)
```

```
##           ID           Time           Amt           Conc
## Min.      : 1.0    Min.      : 0.000    Min.      : 0.0    Min.      : 0.00
## 1st Qu.: 38.0    1st Qu.: 0.875    1st Qu.: 0.0    1st Qu.: 22.77
## Median : 75.5    Median : 3.500    Median : 0.0    Median : 50.12
## Mean     : 75.5    Mean      : 6.396    Mean      : 972.2    Mean      : 65.98
## 3rd Qu.:113.0    3rd Qu.: 9.000    3rd Qu.: 0.0    3rd Qu.: 95.35
## Max.     :150.0    Max.      :24.000    Max.      :20000.0    Max.      :400.17
##                                     NA's      :13
##           Age           Weight           Gender           Race
## Min.      :38.0    Min.      :55.00    Length:1800    Length:1800
## 1st Qu.:47.0    1st Qu.:64.00    Class :character    Class :character
## Median :51.0    Median :71.00    Mode  :character    Mode  :character
## Mean      :50.5    Mean      :70.94
## 3rd Qu.:55.0    3rd Qu.:77.00
## Max.      :61.0    Max.      :94.00
##
##           Dose           AGECAT
## Min.      : 5000    Min.      :0.00
## 1st Qu.: 5000    1st Qu.:0.00
## Median :10000    Median :0.00
## Mean      :11667    Mean      :0.38
## 3rd Qu.:20000    3rd Qu.:1.00
## Max.      :20000    Max.      :1.00
##
```

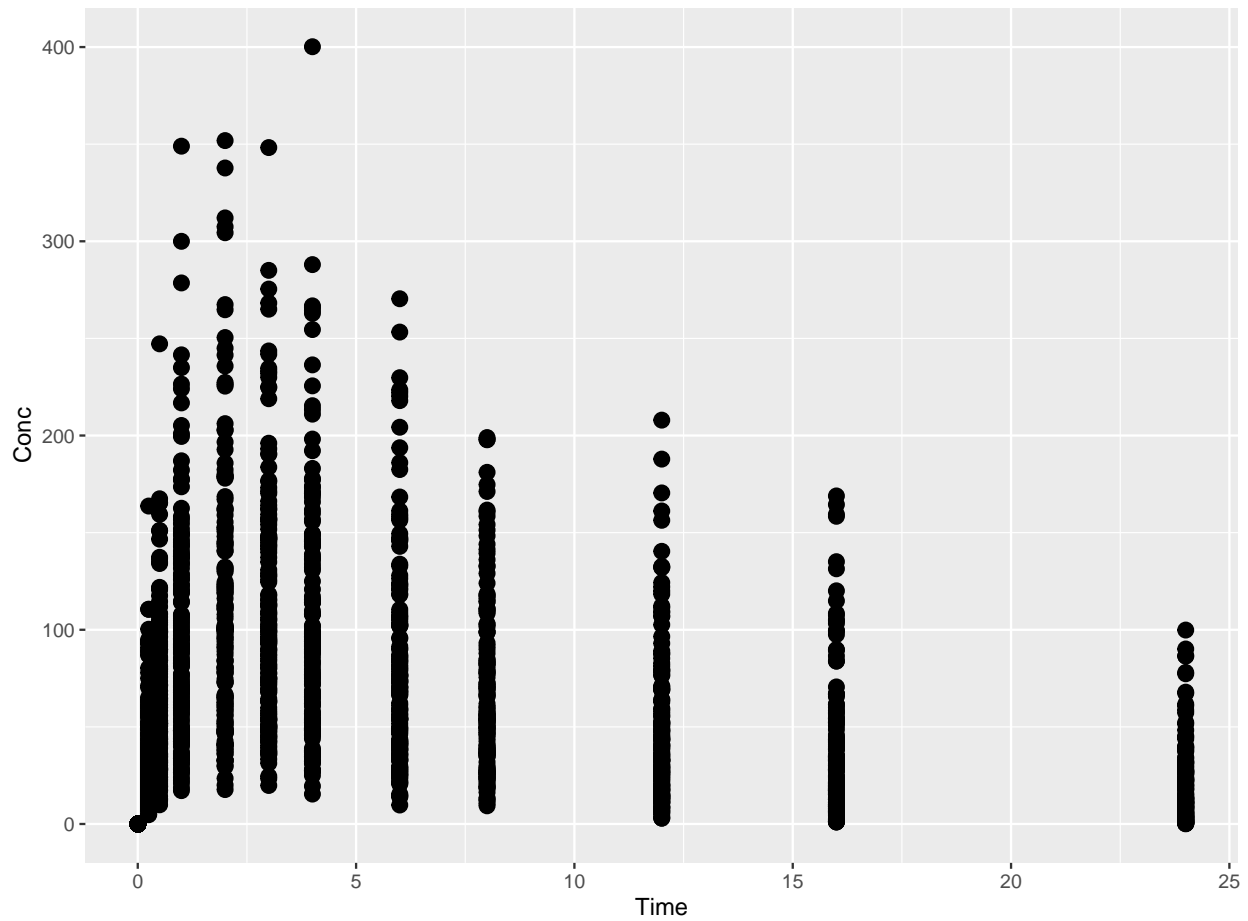
```
#number of subject in the study
n_distinct(data$ID)
```

```
## [1] 150
```

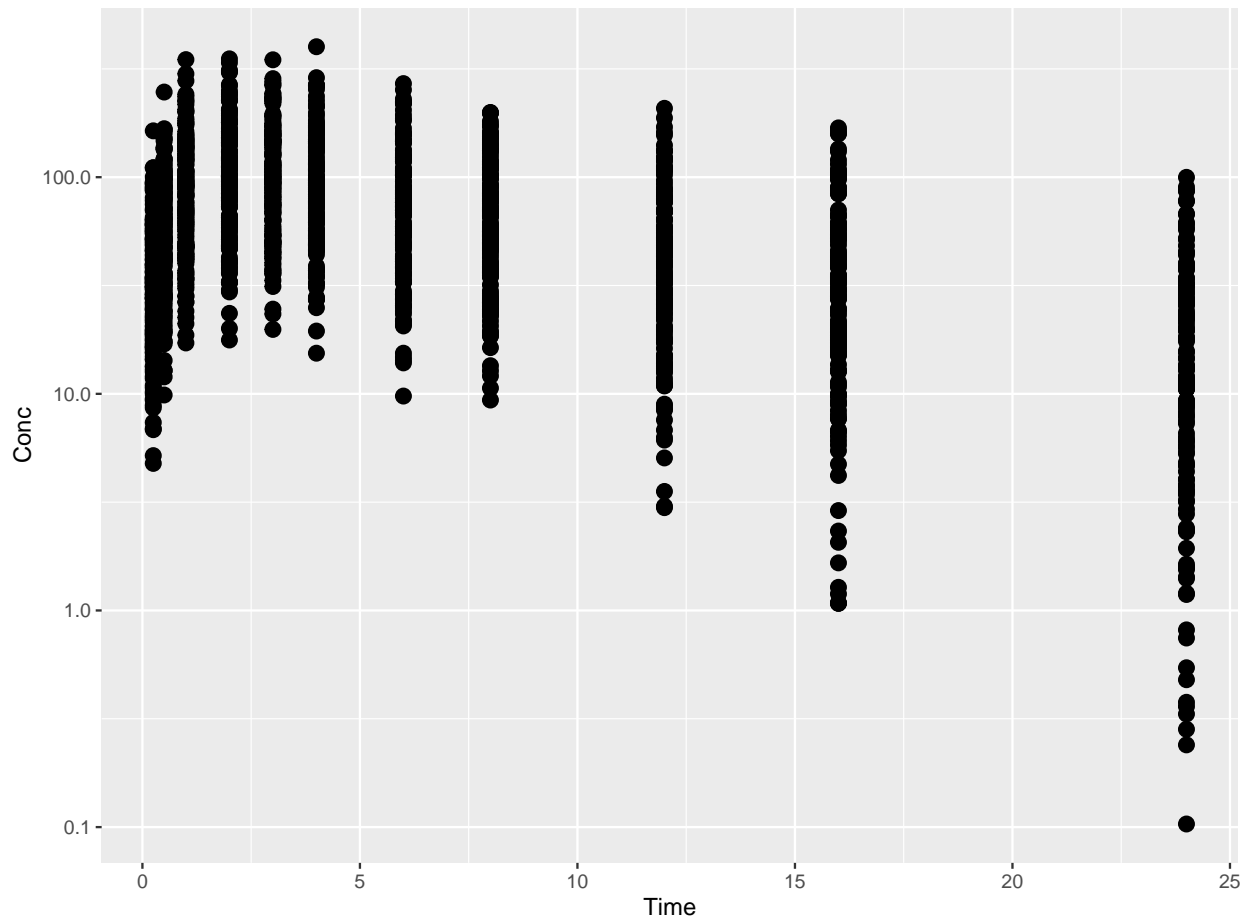
```
#####visualisation of the data
```

```
ggplot(data, aes(x=Time, y=Conc)) +
  geom_point(size=3)
```

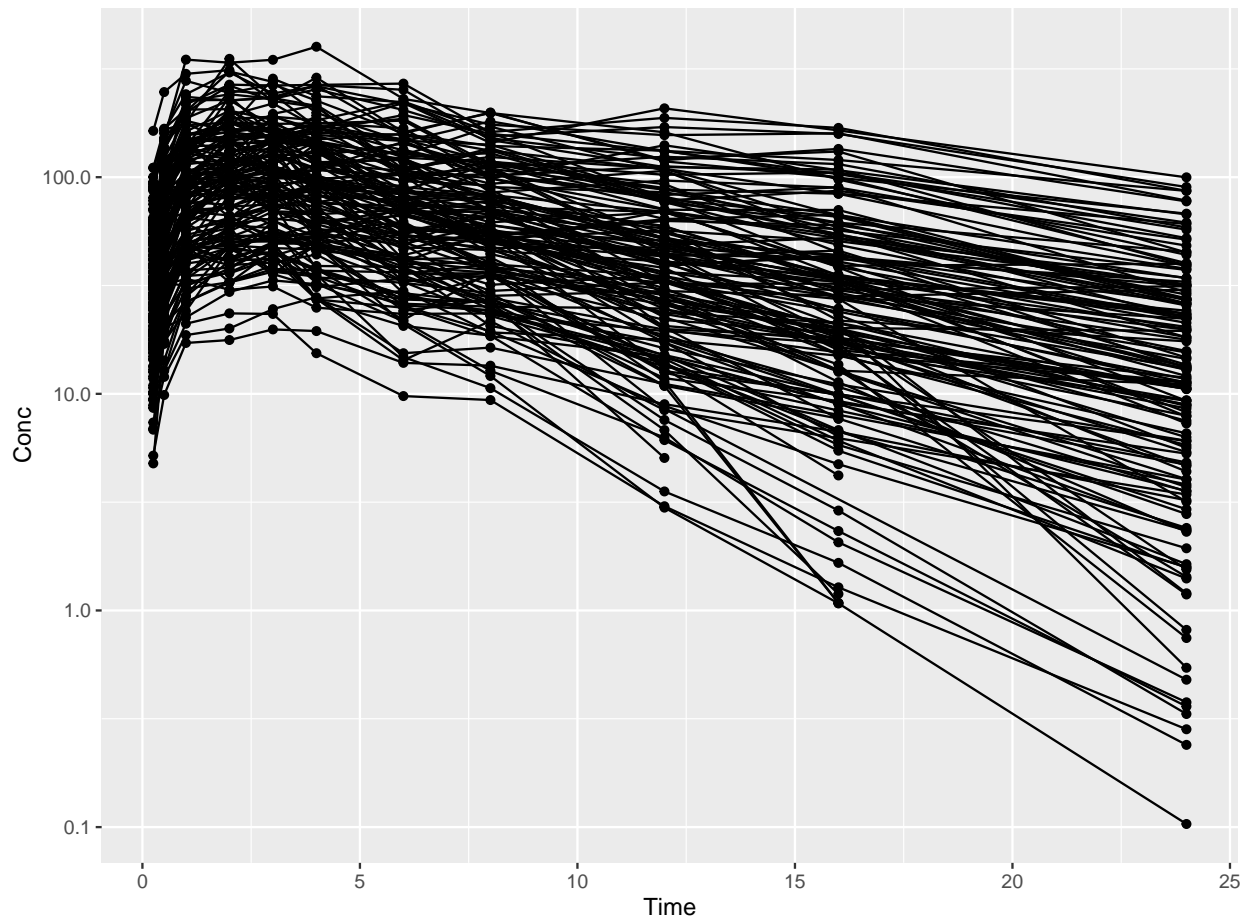
```
## Warning: Removed 13 rows containing missing values or values outside the scale range
## ('geom_point()').
```



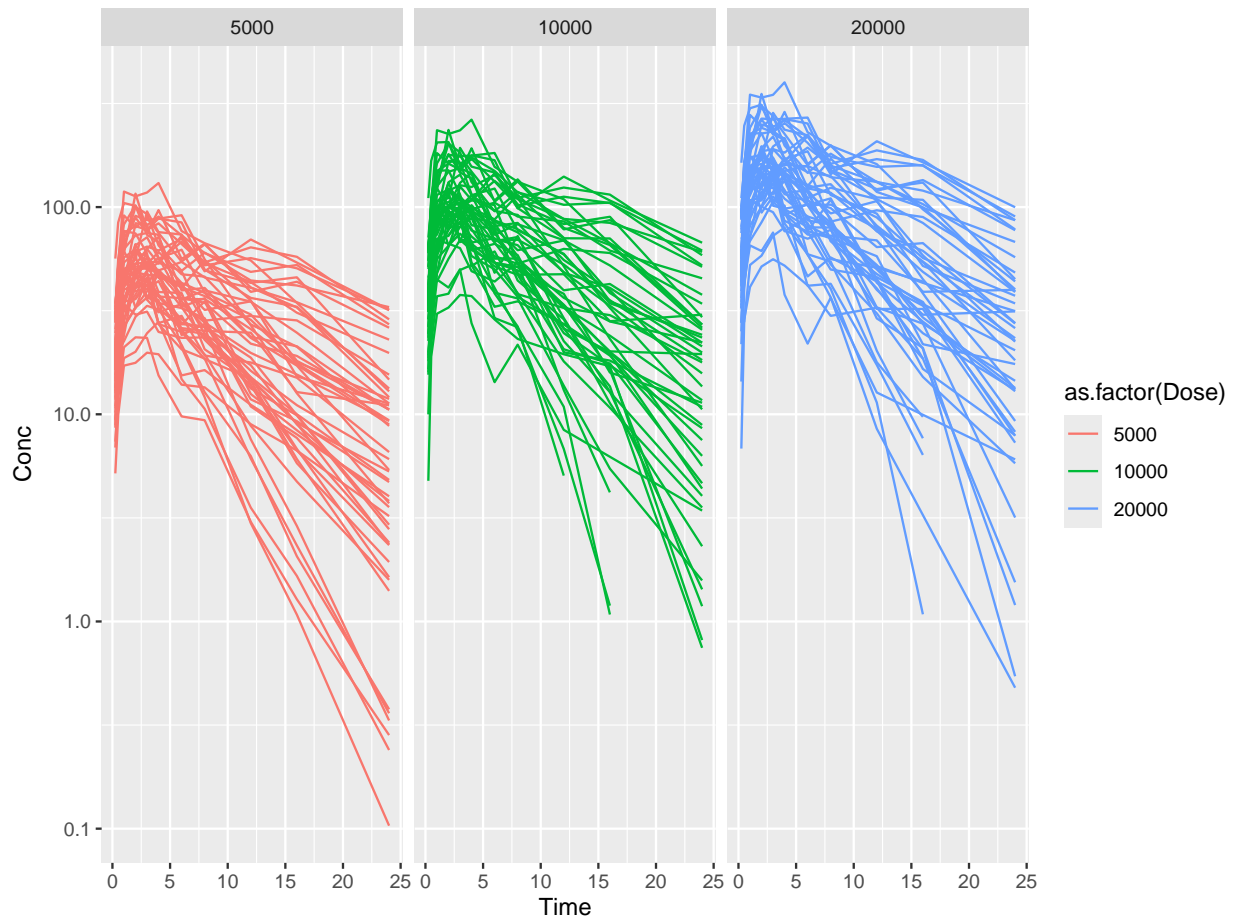
```
# plot of data with log transformation  
ggplot(data %>% filter(!is.na(Conc), Conc > 0), aes(x=Time, y=Conc)) +  
  geom_point(size=3)+  
  scale_y_log10()
```



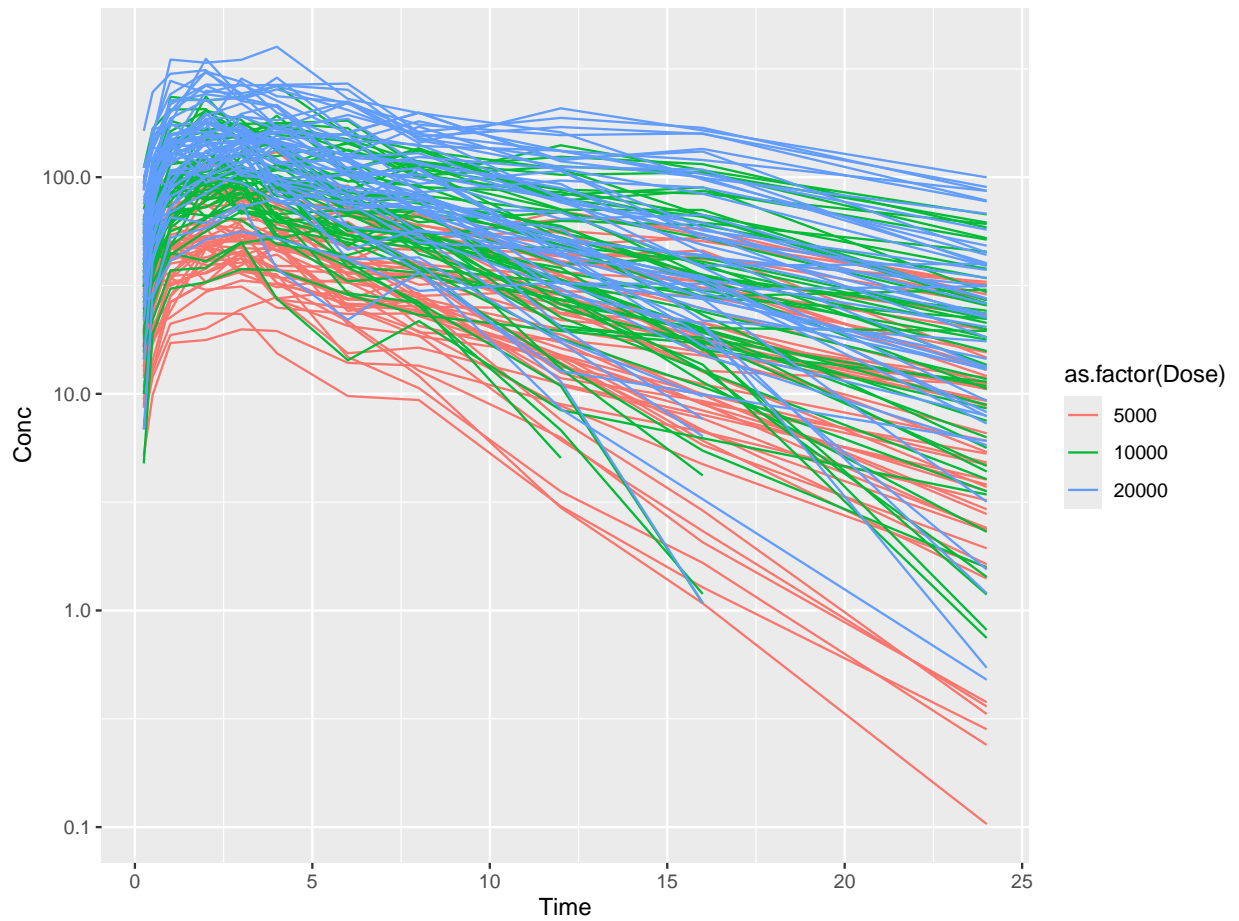
```
# plot with the lines by Subject ID
ggplot(data %>% filter(!is.na(Conc), Conc > 0), aes(Time, Conc)) + geom_point() +
  geom_line(aes(group=ID)) +
  scale_y_log10()
```



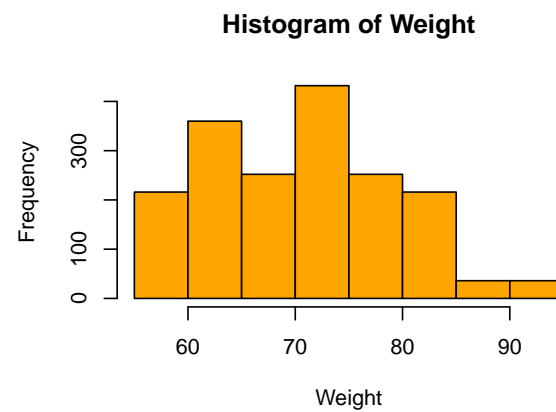
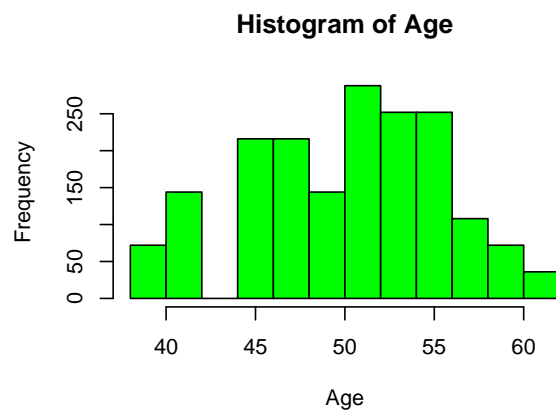
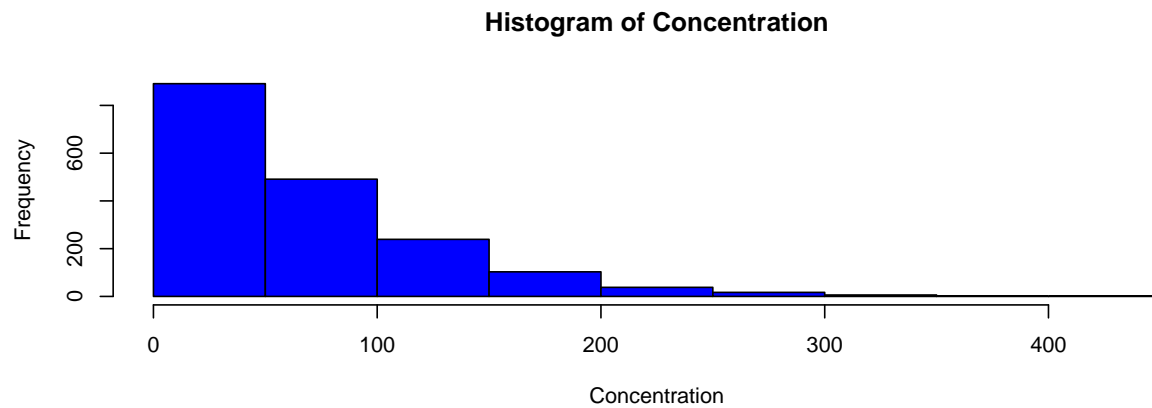
```
# create 3 plots split by Dose
ggplot(data %>% filter(!is.na(Conc), Conc > 0), aes(Time, Conc, colour=as.factor(Dose))) +
  geom_line(aes(group=ID)) +
  facet_grid(~Dose) +
  scale_y_log10()
```



```
# create split by Dose  
ggplot(data %>% filter(!is.na(Conc), Conc > 0), aes(Time, Conc, colour=as.factor(Dose))) +  
  geom_line(aes(group=ID)) +  
  scale_y_log10()
```



```
# histograms of quantitative variables
layout(matrix(c(1, 1, 2, 3), 2, 2, byrow = TRUE)) # Define plotting grid layout
hist(data$Conc, main = "Histogram of Concentration", xlab = "Concentration", col = "blue")
hist(data$Age, main = "Histogram of Age", xlab = "Age", col = "green")
hist(data$Weight, main = "Histogram of Weight", xlab = "Weight", col = "orange")
```



```
# median and 0.25 and 0.75 quantile of log(concentration) vs time
ggplot(data,aes(Time,Conc))+
  geom_line(aes(group=ID),color="black",alpha=0.2)+
  geom_ribbon(mapping = aes(x = Time, y = Conc,),
    stat = "summary",
    fun.ymin = function(y) {quantile(y,0.25)},
    fun.ymax = function(y) {quantile(y,0.75)},
    fun.y = median, alpha =0.3)+
  geom_line(data= data[!is.na(data$Conc),], mapping = aes(x = Time, y = Conc),
    stat = "summary",
    fun.y = median, alpha =1,size=2 ) +
  scale_y_log10()+ ## log10 on y axis
  theme_bw()
```

```
## Warning in geom_ribbon(mapping = aes(x = Time, y = Conc, ), stat = "summary", :
## Ignoring unknown parameters: 'fun.ymin', 'fun.ymax', and 'fun.y'
```

```
## Warning: Using 'size' aesthetic for lines was deprecated in ggplot2 3.4.0.
## i Please use 'linewidth' instead.
## This warning is displayed once every 8 hours.
## Call 'lifecycle::last_lifecycle_warnings()' to see where this warning was
## generated.
```



```
## Warning in geom_line(data = data[!is.na(data$Conc), ], mapping = aes(x = Time,
## : Ignoring unknown parameters: 'fun.y'

## Warning in scale_y_log10(): log-10 transformation introduced infinite values.
## log-10 transformation introduced infinite values.
## log-10 transformation introduced infinite values.

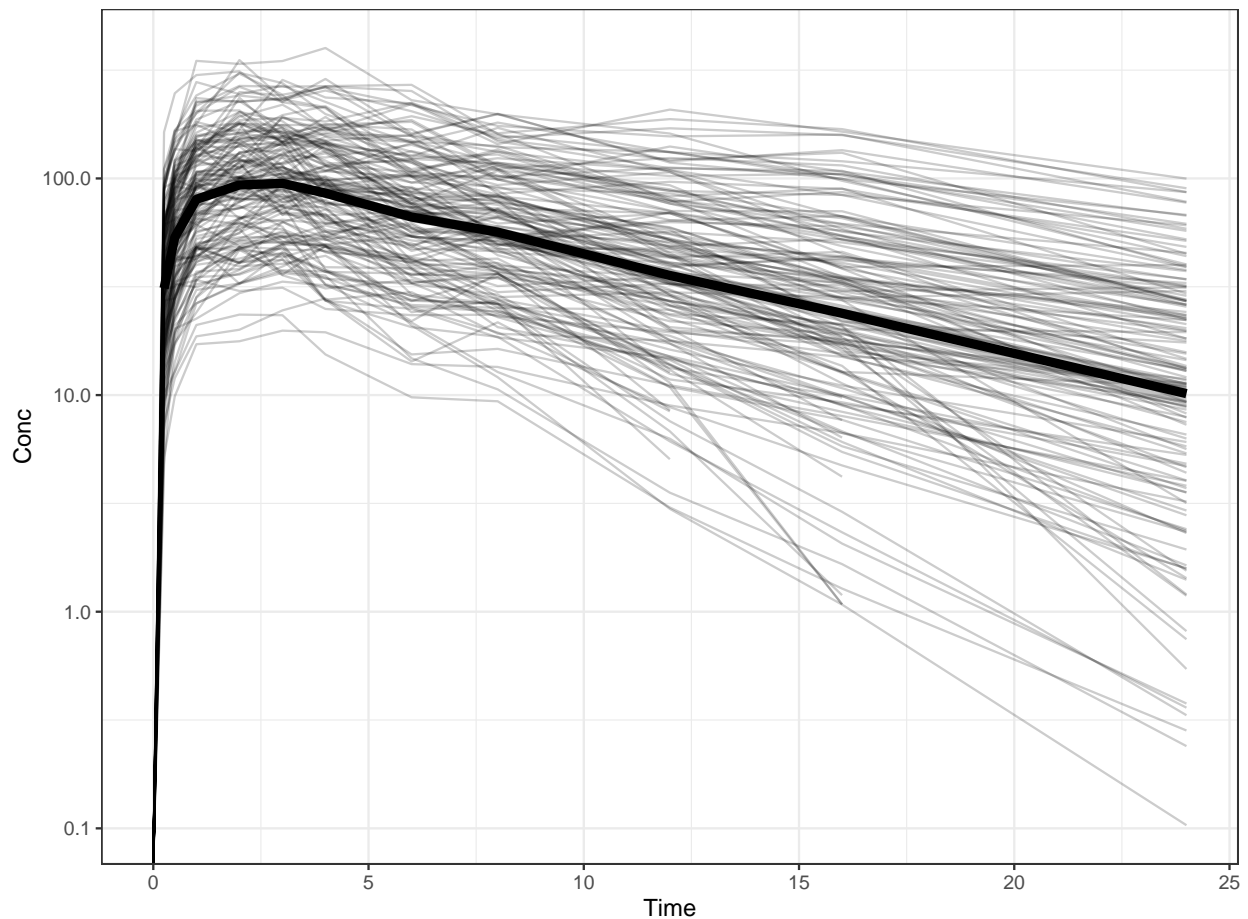
## Warning: Removed 163 rows containing non-finite outside the scale range
## ('stat_summary()').

## No summary function supplied, defaulting to 'mean_se()'

## Warning: Removed 150 rows containing non-finite outside the scale range
## ('stat_summary()').

## No summary function supplied, defaulting to 'mean_se()'

## Warning: Removed 10 rows containing missing values or values outside the scale range
## ('geom_line()').
```



```

# median and 0.25 and 0.75 quantile of log(concentration) vs time by doses
ggplot(data,aes(Time,Conc))+
  geom_line(aes(group=ID),color="black",alpha=0.2)+
  geom_ribbon(mapping = aes(x = Time, y = Conc,fill=as.factor(Dose)),
    stat = "summary",
    fun.ymin = function(y) {quantile(y,0.25)},
    fun.ymax = function(y) {quantile(y,0.75)},
    fun.y = median, alpha =0.3)+
  geom_line(data= data[!is.na(data$Conc),], mapping = aes(x = Time, y = Conc,linetype=as.factor(Dose)),
    stat = "summary",
    fun.y = median, alpha =1,size=2 ) +
  scale_y_log10()+ ## log10 on y axis
  theme_bw()

```

```

## Warning in geom_ribbon(mapping = aes(x = Time, y = Conc, fill =
## as.factor(Dose)), : Ignoring unknown parameters: 'fun.ymin', 'fun.ymax', and
## 'fun.y'

```

```

## Warning in geom_line(data = data[!is.na(data$Conc), ], mapping = aes(x = Time,
## : Ignoring unknown parameters: 'fun.y'

```

```

## Warning in scale_y_log10(): log-10 transformation introduced infinite values.
## log-10 transformation introduced infinite values.
## log-10 transformation introduced infinite values.

```

```

## Warning: Removed 163 rows containing non-finite outside the scale range
## ('stat_summary()').

```

```

## No summary function supplied, defaulting to 'mean_se()'

```

```

## Warning: Removed 150 rows containing non-finite outside the scale range
## ('stat_summary()').

```

```

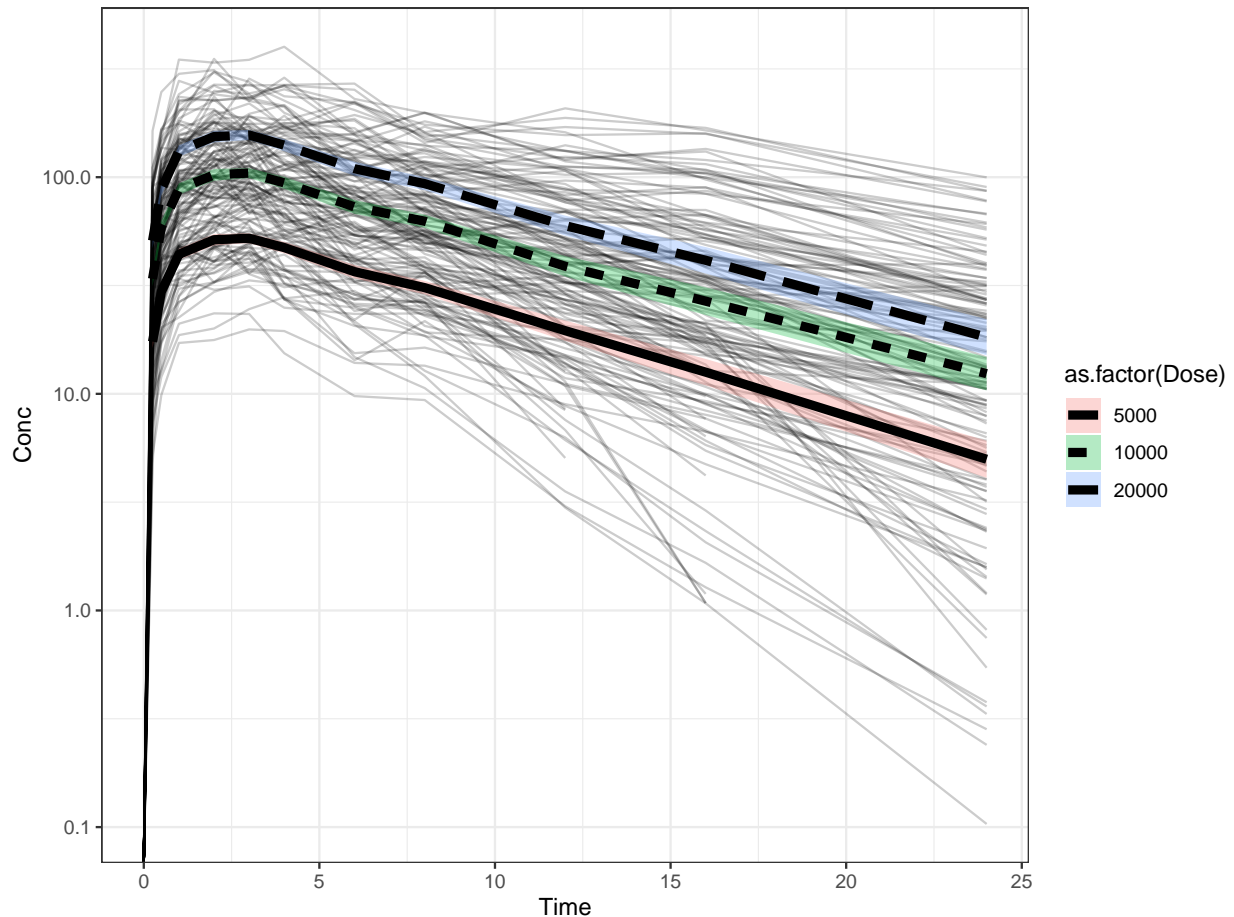
## No summary function supplied, defaulting to 'mean_se()'

```

```

## Warning: Removed 10 rows containing missing values or values outside the scale range
## ('geom_line()').

```



```
# median and 0.25-and-0.75_quantile_of_log(concentration)_vs_time_grouped_by_dose_by_gender
#####
ggplot(data, aes(Time, Conc)) +
  geom_line(aes(group=ID), color="black", alpha=0.2) +
  geom_ribbon(mapping = aes(x = Time, y = Conc, fill=Gender, group = paste(Gender, Dose)),
    stat = "summary",
    fun.ymin = function(y) {quantile(y, 0.25)},
    fun.ymax = function(y) {quantile(y, 0.75)},
    fun.y = median, alpha = 0.3) +
  geom_line(data = data[!is.na(data$Conc), ], mapping = aes(x = Time, y = Conc,
    colour=Gender,
    linetype=Gender),
    stat = "summary",
    fun.y = median, alpha = 1, size = 2) +
  scale_y_log10() +
  facet_grid(~Dose) + # try (~ Race ) here
  theme_bw()
```

```
## Warning in geom_ribbon(mapping = aes(x = Time, y = Conc, fill = Gender, :
## Ignoring unknown parameters: 'fun.ymin', 'fun.ymax', and 'fun.y'
```

```
## Warning in geom_line(data = data[!is.na(data$Conc), ], mapping = aes(x = Time,
## : Ignoring unknown parameters: 'fun.y'
```

```
## Warning in scale_y_log10(): log-10 transformation introduced infinite values.
## log-10 transformation introduced infinite values.
## log-10 transformation introduced infinite values.

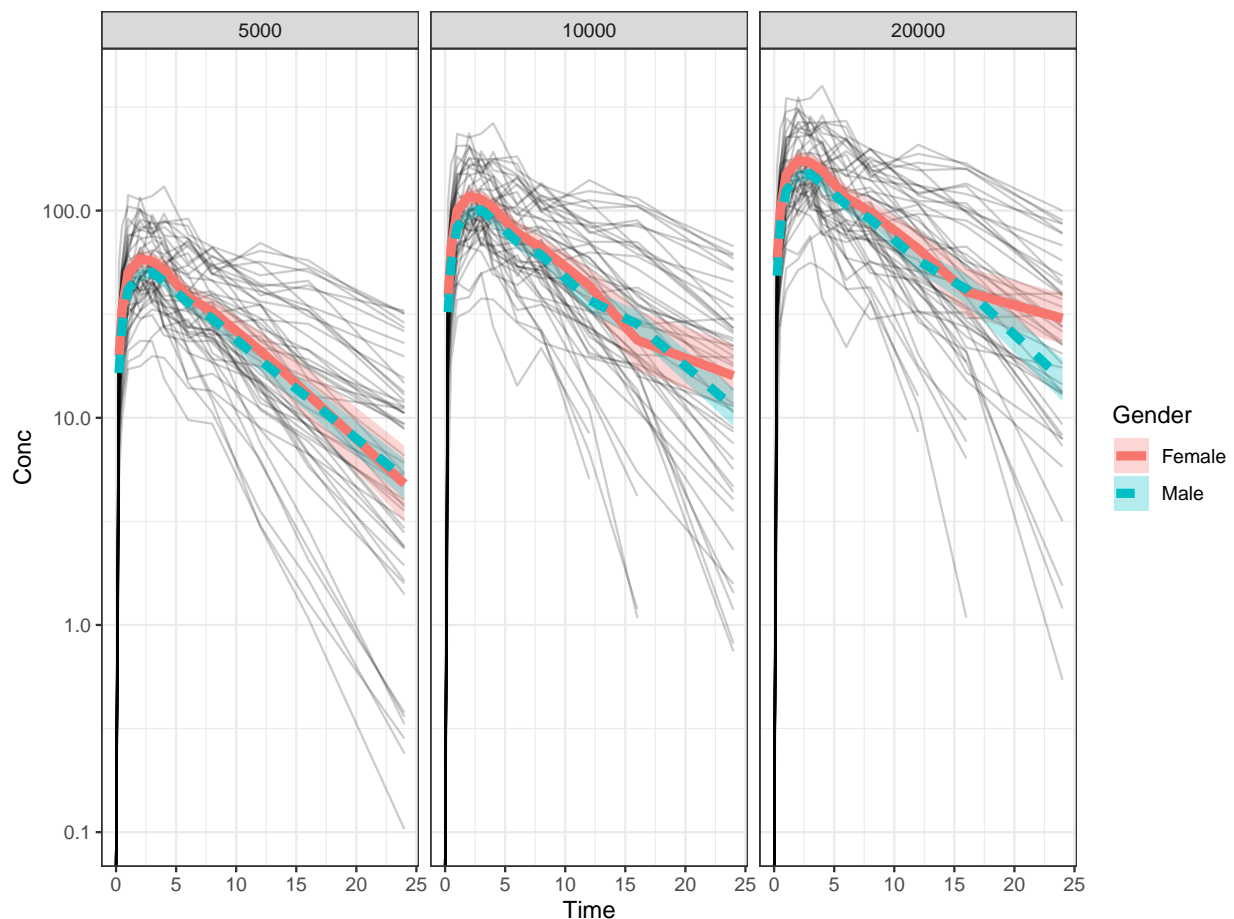
## Warning: Removed 163 rows containing non-finite outside the scale range
## ('stat_summary()').

## No summary function supplied, defaulting to 'mean_se()'
## No summary function supplied, defaulting to 'mean_se()'
## No summary function supplied, defaulting to 'mean_se()'

## Warning: Removed 150 rows containing non-finite outside the scale range
## ('stat_summary()').

## No summary function supplied, defaulting to 'mean_se()'
## No summary function supplied, defaulting to 'mean_se()'
## No summary function supplied, defaulting to 'mean_se()'

## Warning: Removed 10 rows containing missing values or values outside the scale range
## ('geom_line()').
```



```
#####
#### noncompartmental analysis

## obtaining dose data from original dataset
dose_data <- data.frame(
  Subject = unique(data$ID),
  Time = 0,
  Dose = 5000 # The dose values (from your dataset)
)

#creating Dose object
dose_obj <- PKNCAdose(
  dose_data,                                # Raw dosing dataset
  Dose ~ Time | Subject                     # Formula: Dose depends on Time, grouped by ID
)

# obtaining concentration-time data from original dataset
conc_data <- data.frame(
  Subject = data$ID,
  Time = data$Time,
  Concentration = data$Conc
)

#creating Concentration object
conc_obj <- PKNCAconc(
  conc_data[!is.na(conc_data$Concentration), ], # Filter rows where concentration values are not NA
  Concentration ~ Time | Subject                # Formula: Concentration as a function of Time, grouped by ID
)

#creation of the PK object
PK_object <- PKNCAdata(
  data.conc = conc_obj, # Concentration-time object
  data.dose = dose_obj  # Dosing object
)

#obtaining overall results for PK_object as AUC last, Cmax, tmax, halflife
results<-pk.nca(PK_object)
```

```
## =====>----- 19% | ETA: 4s =====>-----
## 20% | ETA: 6s =====>----- 22% | ETA: 7s
## =====>----- 23% | ETA: 8s =====>-----
## 25% | ETA: 8s =====>----- 28% | ETA: 8s
## =====>----- 30% | ETA: 8s =====>-----
## 32% | ETA: 9s =====>----- 35% | ETA: 8s
## =====>----- 37% | ETA: 8s =====>-----
## 39% | ETA: 8s =====>----- 40% | ETA: 8s
## =====>----- 41% | ETA: 9s =====>-----
## 43% | ETA: 9s =====>----- 45% | ETA: 9s
## =====>----- 46% | ETA: 9s =====>-----
## 47% | ETA: 9s =====>----- 49% | ETA: 9s
## =====>----- 51% | ETA: 8s =====>-----
## 53% | ETA: 8s =====>----- 56% | ETA: 7s
```

```
## =====>----- 58% | ETA: 7s =====>-----
## 61% | ETA: 6s =====>----- 63% | ETA: 6s
## =====>----- 67% | ETA: 6s =====>-----
## 69% | ETA: 5s =====>----- 72% | ETA: 5s
## =====>----- 75% | ETA: 4s =====>-----
## 77% | ETA: 4s =====>----- 80% | ETA: 3s
## =====>----- 82% | ETA: 3s =====>-----
## 85% | ETA: 2s =====>----- 87% | ETA: 2s
## =====>----- 89% | ETA: 2s =====>-----
## 92% | ETA: 1s =====>----- 96% | ETA: 1s
## =====>----- 99% | ETA: 0s
```

```
pander::pander(summary(results))
```

Table 1: auclast, cmax, aucinf.obs: geometric mean and geometric coefficient of variation; tmax: median and range; half.life: arithmetic mean and standard deviation; N: number of subjects (continued below)

start	end	N	auclast	cmax	tmax	half.life
0	24	150	1080 [76.3]	.	.	.
0	Inf	150	.	107 [65.9]	3.00 [1.00, 6.00]	7.75 [4.17]

aucinf.obs
.
1260 [86.1]

```
# Obtaining subject-level NCA results
param_table <- as.data.frame(results)

head(param_table)
```

```
## # A tibble: 6 x 6
##   Subject start   end Pptestcd  PPORRES exclude
##   <int> <dbl> <dbl> <chr>      <dbl> <chr>
## 1     1     0    24 auclast    382.   <NA>
## 2     1     0   Inf cmax      34.0   <NA>
## 3     1     0   Inf tmax       1    <NA>
## 4     1     0   Inf tlast     24    <NA>
## 5     1     0   Inf clast.obs  5.30   <NA>
## 6     1     0   Inf lambda.z  0.0829 <NA>
```

```
#aggregating the data from original dataset to add 'Gender' and 'Dose' level to the subject-level NCA r
data_grouped <- data %>%
  group_by(ID) %>%
  summarize(Dose = first(Dose), Gender = first(Gender))

# left join aggregated data to param table by = c('Subject' = 'ID'))
param_table <- param_table %>%
```

```
left_join(data_grouped %>% select(ID, Dose, Gender), by = c('Subject' = 'ID'))

head(param_table)
```

```
## # A tibble: 6 x 8
##   Subject start   end PTESTCD   PPORRES exclude Dose Gender
##   <int> <dbl> <dbl> <chr>     <dbl> <chr>   <int> <chr>
## 1     1     0    24 auclast   382.   <NA>   5000 Male
## 2     1     0   Inf cmax     34.0   <NA>   5000 Male
## 3     1     0   Inf tmax      1    <NA>   5000 Male
## 4     1     0   Inf tlast    24    <NA>   5000 Male
## 5     1     0   Inf clast.obs  5.30   <NA>   5000 Male
## 6     1     0   Inf lambda.z  0.0829 <NA>   5000 Male
```

```
#pivot PTESTCD and PPORRES columns
```

```
data_wide <- param_table %>%
  pivot_wider(names_from = PTESTCD, values_from = PPORRES)
```

```
#adding the Clearance and Volume parameters to NCA subject level parameter table
```

```
data_wide <- data_wide %>%
  mutate(
    CL = Dose / aucinf.obs,          # Clearance
    Vd = CL / lambda.z              # Volume of distribution
  )
```

```
# View the reshaped dataset
```

```
head(data_wide)
```

```
## # A tibble: 6 x 22
##   Subject start   end exclude Dose Gender auclast cmax tmax tlast clast.obs
##   <int> <dbl> <dbl> <chr>   <int> <chr>   <dbl> <dbl> <dbl> <dbl>   <dbl>
## 1     1     0    24 <NA>    5000 Male   382.   NA    NA    NA    NA
## 2     1     0   Inf <NA>    5000 Male    NA  34.0    1    24    5.30
## 3     2     0    24 <NA>    5000 Male  1199.   NA    NA    NA    NA
## 4     2     0   Inf <NA>    5000 Male    NA  100.    2    24   32.9
## 5     3     0    24 <NA>    5000 Male   459.   NA    NA    NA    NA
## 6     3     0   Inf <NA>    5000 Male    NA  53.9    3    24    2.34
## # i 11 more variables: lambda.z <dbl>, r.squared <dbl>, adj.r.squared <dbl>,
## #   lambda.z.time.first <dbl>, lambda.z.n.points <dbl>, clast.pred <dbl>,
## #   half.life <dbl>, span.ratio <dbl>, aucinf.obs <dbl>, CL <dbl>, Vd <dbl>
```

```
# Summary statistics for AUCLAST, CMAX, TMAX, and other NCA parameters
```

```
summary_stats <- data_wide %>%
  group_by(Dose, Gender) %>%
  summarize(
    median_auclast = median(auclast, na.rm = TRUE),          # Median AUCLAST
    median_cmax = median(cmax, na.rm = TRUE),                # Median CMAX
    median_tmax = median(tmax, na.rm = TRUE),                # Median TMAX
    q1_auclast = quantile(auclast, probs = 0.25, na.rm = TRUE), # 25th Percentile AUCLAST
    q3_auclast = quantile(auclast, probs = 0.75, na.rm = TRUE), # 75th Percentile AUCLAST
  )
```

```

median_tlast = median(tlast, na.rm = TRUE),          # Median TLAST
median_half_life = median(half.life, na.rm = TRUE),  # Median Half-Life
median_CL = median(CL, na.rm = TRUE),               # Median Clearance
median_Vd = median(Vd, na.rm = TRUE),              # Median Volume of Distribution
n = n_distinct(Subject)                             # Number of Distinct Subjects
)

```

```

## 'summarise()' has grouped output by 'Dose'. You can override using the
## '.groups' argument.

```

```

print(summary_stats)

```

```

## # A tibble: 6 x 12
## # Groups:   Dose [3]
##   Dose Gender median_auclast median_cmax median_tmax q1_auclast q3_auclast
##   <int> <chr>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>
## 1  5000 Female      581.       51.6        2       476.      1060.
## 2  5000 Male       576.       58.5        3       415.       774.
## 3 10000 Female     1145.      105.        3       979.     2093.
## 4 10000 Male     1152.      114.        3       828.     1575.
## 5 20000 Female     1718.      157.        3      1477.     3166.
## 6 20000 Male     1693.      173.        3      1236.     2355.
## # i 5 more variables: median_tlast <dbl>, median_half_life <dbl>,
## #   median_CL <dbl>, median_Vd <dbl>, n <int>

```

```

#Dose Gender median_auclast median_cmax median_tmax q1_auclast q3_auclast median_tlast
#<int> <chr>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>      <dbl>
#1  5000 Female      581.       51.6        2       476.      1060.       24
#2  5000 Male       576.       58.5        3       415.       774.       24
#3 10000 Female     1145.      105.        3       979.     2093.       24
#4 10000 Male     1152.      114.        3       828.     1575.       24
#5 20000 Female     1718.      157.        3      1477.     3166.       24
#6 20000 Male     1693.      173.        3      1236.     2355.       24

```

```

#BOX PLOT of median AUCLast by Gender
ggplot(data_wide, aes(x=factor(Dose), y=auclast, fill=Gender)) +
  geom_boxplot() +
  labs(title="AUC Last by Dose and Gender", x="Dose", y="AUC Last") +
  theme_minimal()

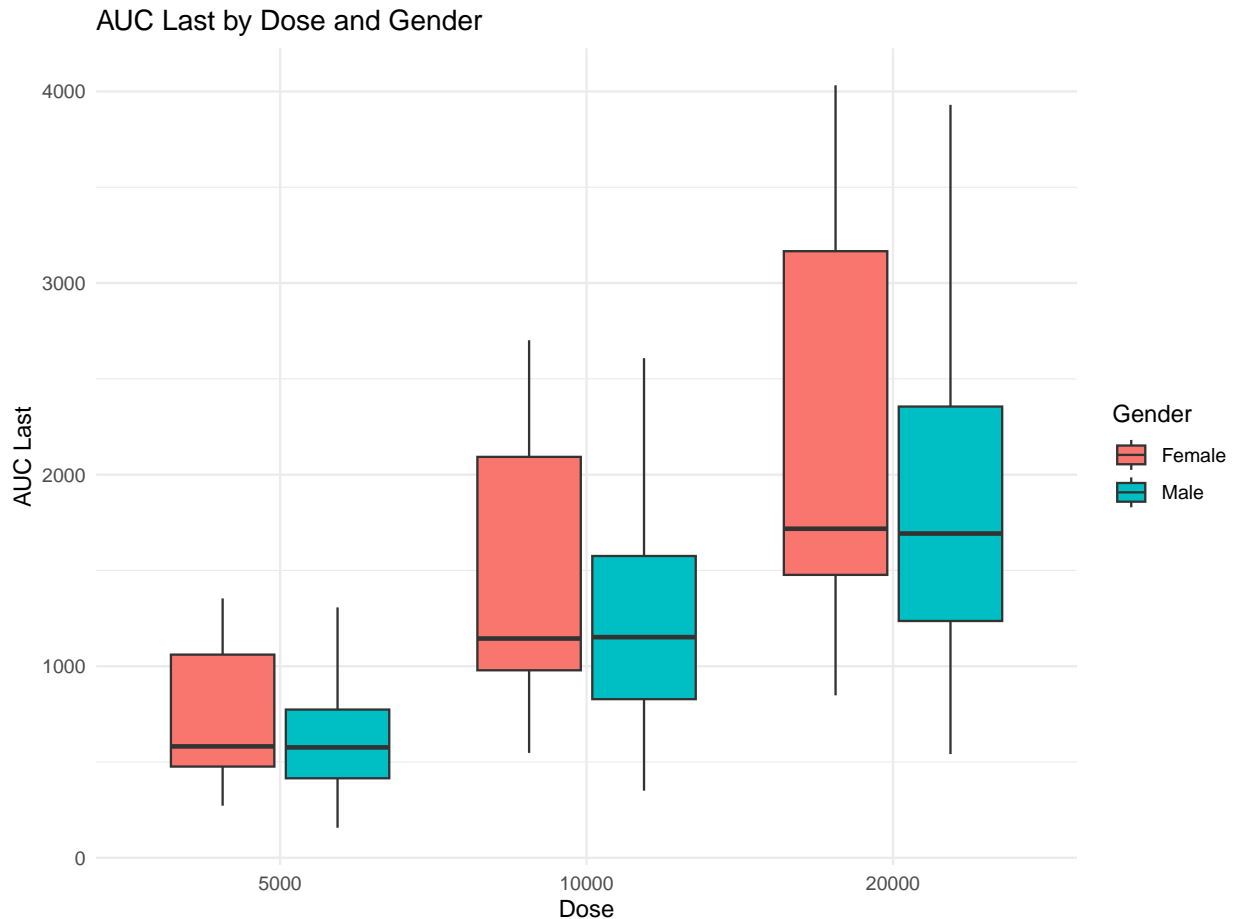
```

```

## Warning: Removed 150 rows containing non-finite outside the scale range
## ('stat_boxplot()').

```

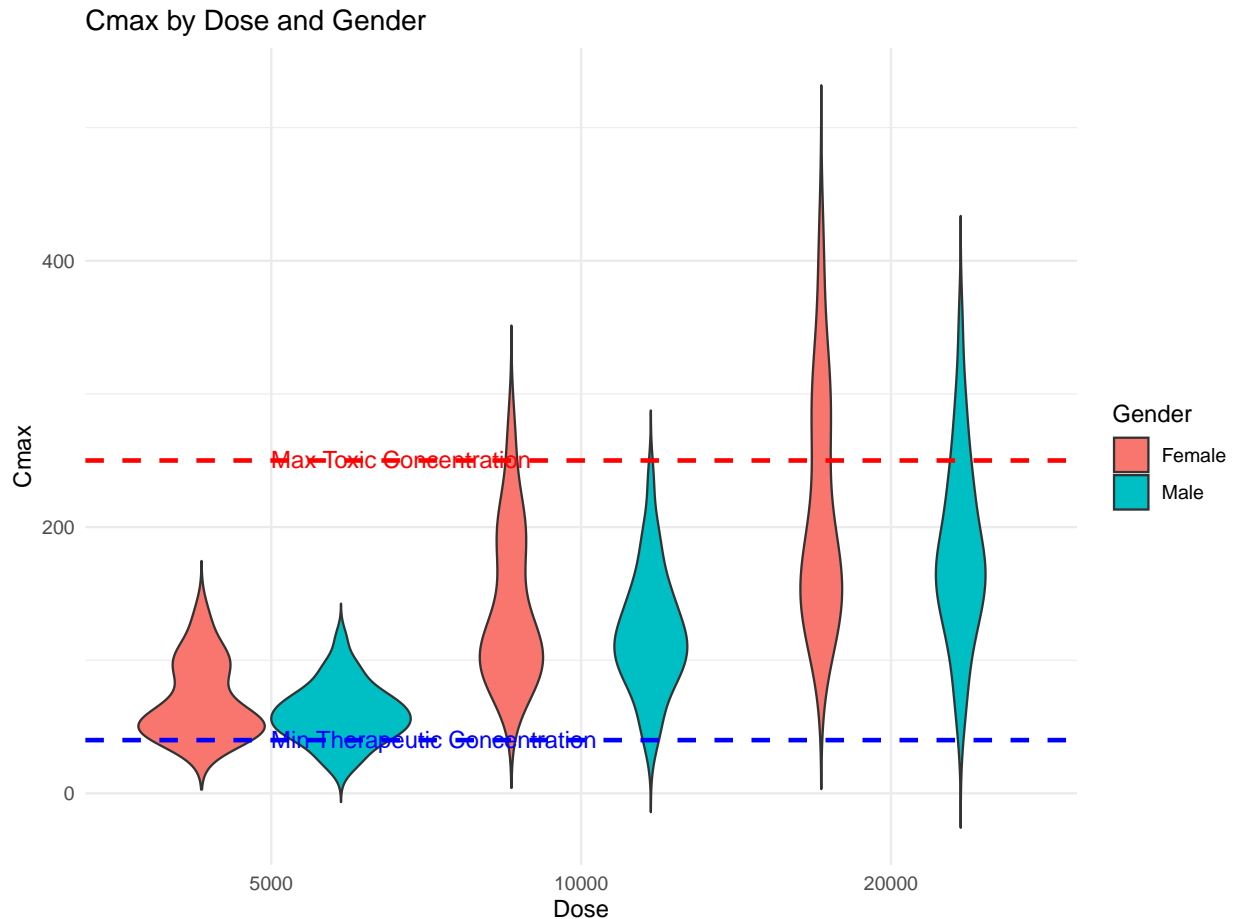




```
#Violin PLOT of median Cmax by Gender MEC and MTC lines
min_therapeutic_concentration <- 40 # theoretical value for MEC
max_toxic_concentration <- 250 # theoretical value for MTC

ggplot(data_wide, aes(x = factor(Dose), y = cmax, fill = Gender)) +
  geom_violin(trim=FALSE) +
  labs(
    title = "Cmax by Dose and Gender",
    x = "Dose",
    y = "Cmax"
  ) +
  theme_minimal() +
  geom_hline(yintercept = min_therapeutic_concentration, color = "blue", linetype = "dashed", size = 1.0) +
  geom_hline(yintercept = max_toxic_concentration, color = "red", linetype = "dashed", size = 1.0) +
  annotate("text", x = 1, y = min_therapeutic_concentration + 0.5,
    label = "Min Therapeutic Concentration", color = "blue", size = 4, hjust = 0) +
  annotate("text", x = 1, y = max_toxic_concentration + 0.5,
    label = "Max Toxic Concentration", color = "red", size = 4, hjust = 0)
```

```
## Warning: Removed 150 rows containing non-finite outside the scale range
## ('stat_ydensity()').
```



```
#scatterplot of Cmax vs Tmax by Gender
ggplot(data_wide, aes(x=tmax, y=cmax, color=Gender)) +
  geom_point() +
  geom_smooth(method="loess", formula = y ~ splines::bs(x, 3), se=TRUE) ## have chosen the loess fitting
  labs(title="Cmax vs Tmax by Gender", x="Tmax", y="Cmax") +
  theme_minimal()
```

```
## Warning: Removed 150 rows containing non-finite outside the scale range
## ('stat_smooth()').
```

```
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : pseudoinverse used at -0.015775 -0.015775 -0.028086
```

```
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : neighborhood radius 4.0106
```

```
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : reciprocal condition number 1.0517e-47
```

```
## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : There are other near singularities as well. 12.734
```

```

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : pseudoinverse used at
## -0.015775 -0.015775 -0.028086

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : neighborhood radius
## 4.0106

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : reciprocal condition
## number 1.0517e-47

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : There are other near
## singularities as well. 12.734

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : pseudoinverse used at -0.01405 -0.015397 -0.06381

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : neighborhood radius 4.5929

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : reciprocal condition number 3.4904e-46

## Warning in simpleLoess(y, x, w, span, degree = degree, parametric = parametric,
## : There are other near singularities as well. 18.437

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : pseudoinverse used at
## -0.01405 -0.015397 -0.06381

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : neighborhood radius
## 4.5929

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : reciprocal condition
## number 3.4904e-46

## Warning in predLoess(object$y, object$x, newx = if (is.null(newdata)) object$x
## else if (is.data.frame(newdata))
## as.matrix(model.frame(delete.response(terms(object))), : There are other near
## singularities as well. 18.437

```

```
## Warning: Removed 150 rows containing missing values or values outside the scale range
## ('geom_point()').
```

```
## Warning: Removed 40 rows containing missing values or values outside the scale range
## ('geom_smooth()').
```

