

# Exploratory Graphics (xGx): Promoting the purposeful exploration of PKPD data

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# We come from many disciplines...

Chemical Engineering

Statistics

Pharmacology

Mathematics

Physics

Pharmacometrics

Biophysics

Pharmacy

Bioinformatics

Molecular biology

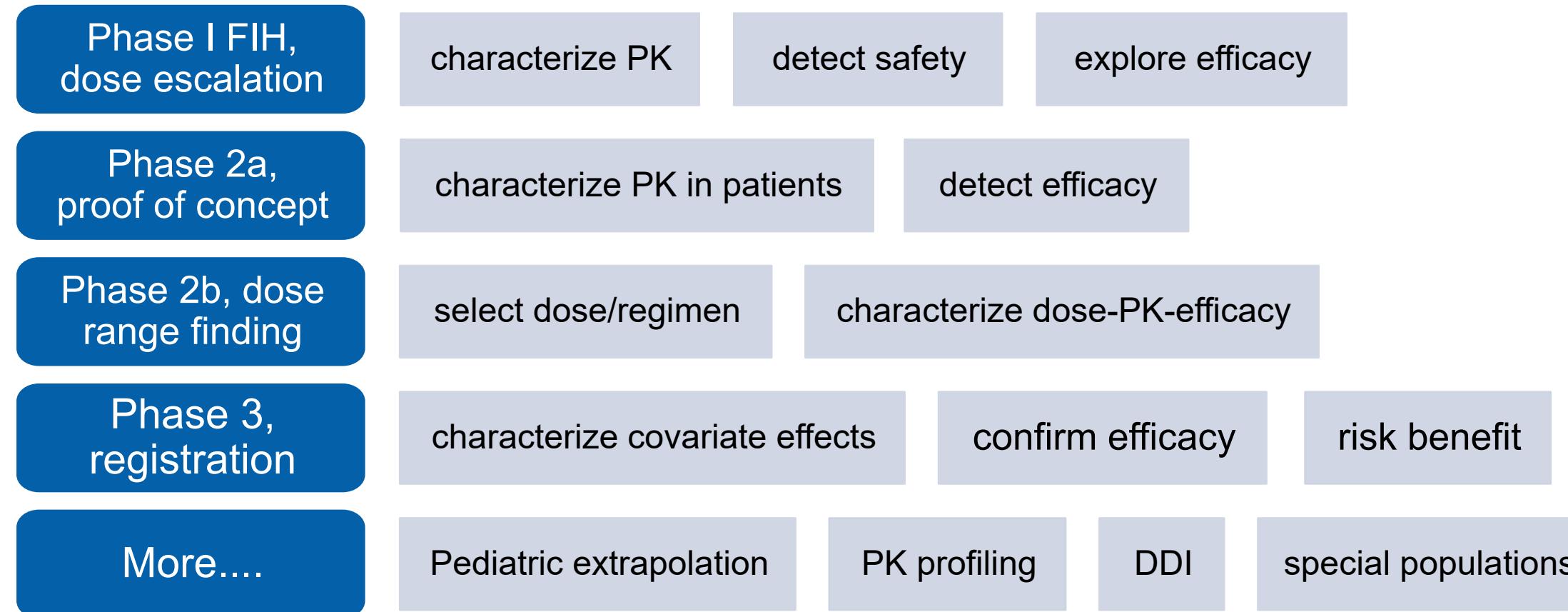
Computer Engineering

Mathematical Modeling



# What we do is driven by the relevant questions

Each phase of development has its own questions



**xGx Website:**  
**<https://opensource.nibr.com/xgx>**



# **Website for Exploratory Graphics (xGx)**

<https://opensource.nibr.com/xgx/>

## **Objectives**

- ✓ Provide structured approach for purposeful exploration of PKPD data
- ✓ Provide a teaching tool for exploring PKPD data with R
- ✓ Improve efficiency and code readability for exploratory analyses
- ✓ Improve quality of exploratory PKPD graphics

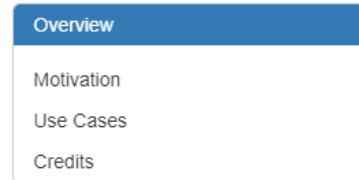
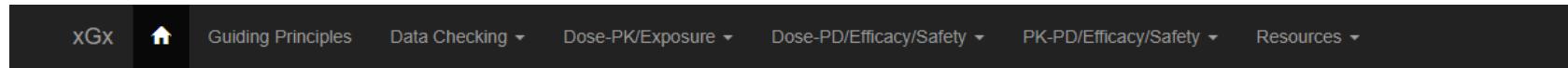
## **Key message**

Don't just look at your data, but look at it in a structured way



# Website for Exploratory Graphics (xGx)

<https://opensource.nibr.com/xgx/>



## Exploratory Graphics (xGx) Overview

Exploratory plots can be helpful in understanding general behavior of data. They should be used as a first step before approaching modeling, and could even uncover useful insights that can be quickly communicated to project teams without extensive effort.

Visit the [Guiding Principles](#) page to get an overview of the general principles to follow when exploring PK/PD data.

This website is composed of Rmarkdown documents, which could be used as templates for generating exploratory plots. The Rmarkdown documents can be accessed on [GitHub](#).

Many of the codes on this website use functions that we have found to be helpful while exploring PK/PD data. We compiled these helpful functions into the xgxr R-package, which is available on [CRAN](#), and [GitHub](#).

This website displays suggested plots to pursue when exploring different PK/PD datasets, with a focus on exploring the Dose-Exposure-Response relationship. This site is a collection of exploratory plots and code, and could serve as a checklist of graphs someone might create for certain projects.

Some suggestions may be repetitive, so use your judgment to choose the best plot for your purpose and dataset. These plots are for exploratory benefit, and are not all expected to be included in a final report.

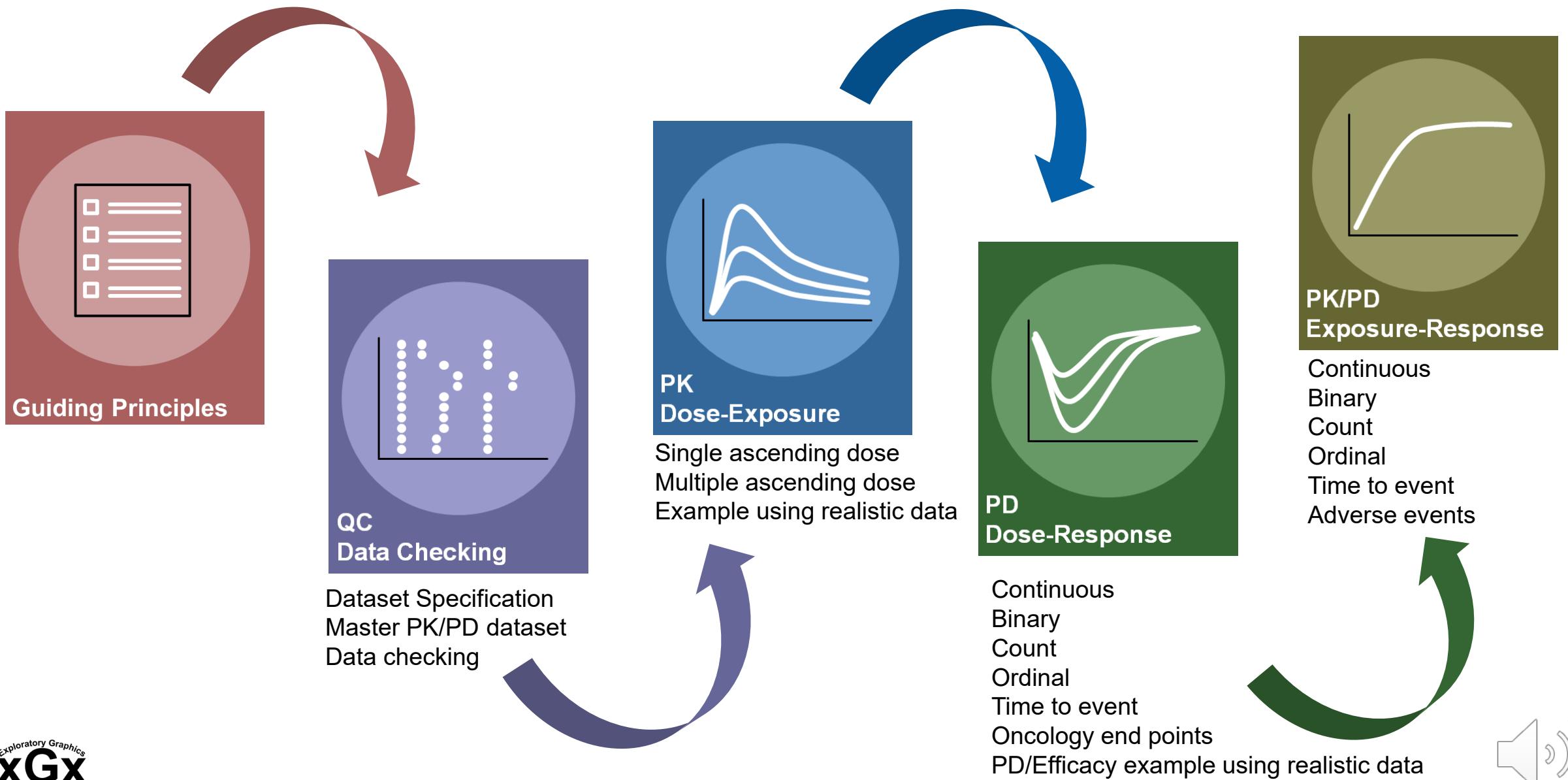
Use the navigation menus at the top of the page, or click on an icon below to find the topic for your specific needs.

The graphs on this website were created with [Good Graphics Principles](#) in mind. Also check out the [Presentation Checklist](#) for useful tips on creating presentations of your results.



# Site-map

Looking at the data in a structured way



# Provide a teaching tool with R

## Guiding Principles

### Provide overview of the data

- Concentration vs Nominal time (median  $\pm$  5-95% CI)
- Normalized Concentration vs Nominal time (median  $\pm$  5-95% CI)

### Assess PK linearity

- NCA of dose-normalized AUC and Cmax vs dose

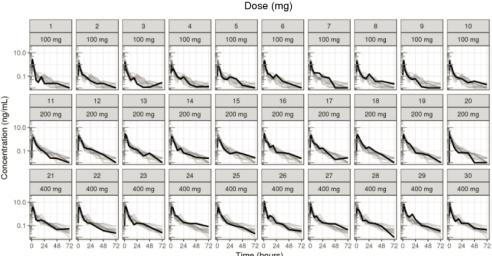
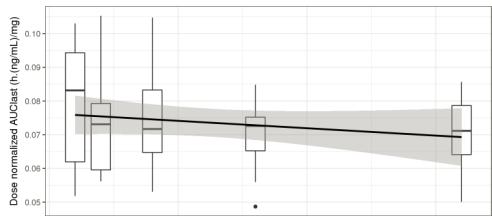
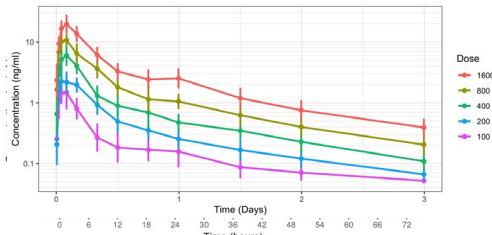
### Explore variability

- Spaghetti plots, grouped by dosing regimen

### Explore irregularities in profiles

- Individual plots of all patients (one patient per panel)

## Graphs



## R Codes

```
gg <- ggplot(data = data_to_plot, aes(x = NT, y = DV, group = DOSE, color = DOSE_label))
gg <- gg + theme_bw(base_size = 12)
gg <- gg + stat_summary(geom = "errorbar", width = 0.5, size = 1,
fun.data = function(y){
  y <- stats::na.omit(y)
  data.frame(
    y = mean(y),
    ymin = mean(y)-qt(0.975,length(y))*sqrt(stats::var(y)/length(y)),
    ymax = mean(y)+qt(0.975,length(y))*sqrt(stats::var(y)/length(y)))
}) +
stat_summary(geom = "point", size = 2, fun.y = mean) +
stat_summary(geom = "line", size = 1, fun.y = mean)
gg <- gg + scale_y_log10() + annotation_logticks(base = 10, sides = "1", color = rgb(0.5,0.5,0.5))
gg <- gg + scale_x_continuous(breaks = seq(0,96,6))
gg <- gg + xlab("Time (hours)") + ylab("Concentration (ng/mL)")
gg <- gg + guides(color= guide_legend(title="Dose"))
gg
```

```
AUClast <- my.data[my.data$HT==2&!is.na(my.data$DV),]
AUClast <- data.frame(stack(sapply(split(AUClast,AUClast$ID),function(df) trapz(df$time,df$DV))))
names(AUClast) <- c("AUC","ID")

AUClast$ID <- as.numeric(as.character(AUClast$ID))
AUClast <- AUClast[order(AUClast$ID),]
AUClast <- merge(AUClast,unique(my.data[c("ID","DOSE","DOSE_label")]), by = "ID")

gg <- ggplot(data = AUClast, aes(x = DOSE, y = AUC/DOSE))
gg <- gg + geom_boxplot(aes(group = DOSE)) + geom_smooth(method = "lm",color = "black")
gg + ylab("Dose normalized AUClast (h.(ng/mL)/mg)") + xlab("Dose (mg)")
```

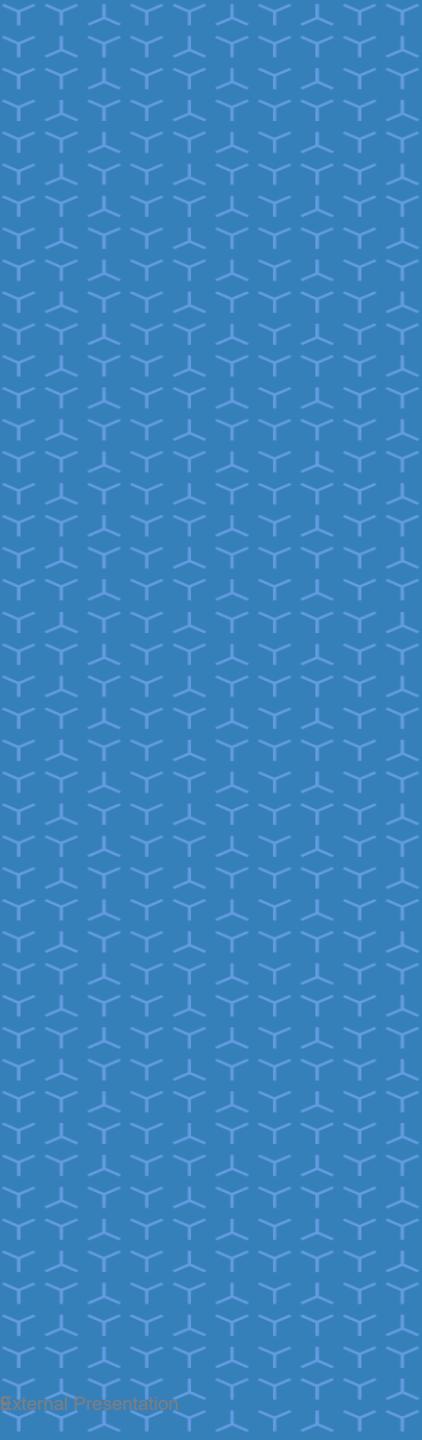
```
data_to_plot <- my.data[my.data$HT==2,]

data_to_plot2 <- NULL
for(id in unique(my.data$ID)){
  if(is.null(data_to_plot2)){
    data_to_plot2 <- data.frame(data_to_plot[data_to_plot$DOSE==data_to_plot$ID==id,]$DOSE, , ID2 = id)
  }else{
    data_to_plot2 <- rbind(data_to_plot,
                           data.frame(data_to_plot[data_to_plot$DOSE==data_to_plot$ID==id,]$DOSE, , ID2 = id))
  }
}

temp <- data_to_plot2
data_to_plot2 <- data_to_plot2[!(data_to_plot2$ID2 == temp$ID2),]
data_to_plot2$ID2 <- temp$ID2

gg <- ggplot() + theme_bw(base_size = 12)
gg <- gg + geom_line(data = data_to_plot2, aes(x = time, y = DV, group = ID2), size = 1, color = rgb(0.5,0.5,0.5), alpha = 0.3)
gg <- gg + geom_line(data = data_to_plot, aes(x = time, y = DV,group = ID), size = 1)
gg <- gg + scale_y_log10() + annotation_logticks(base = 10, sides = "1", color = rgb(0.5,0.5,0.5))
gg <- gg + scale_x_continuous(breaks = seq(0,96,24))
gg <- gg + xlab("Time (hours)") + ylab("Concentration (ng/mL)")
gg <- gg + theme(legend.position="none")
gg
```





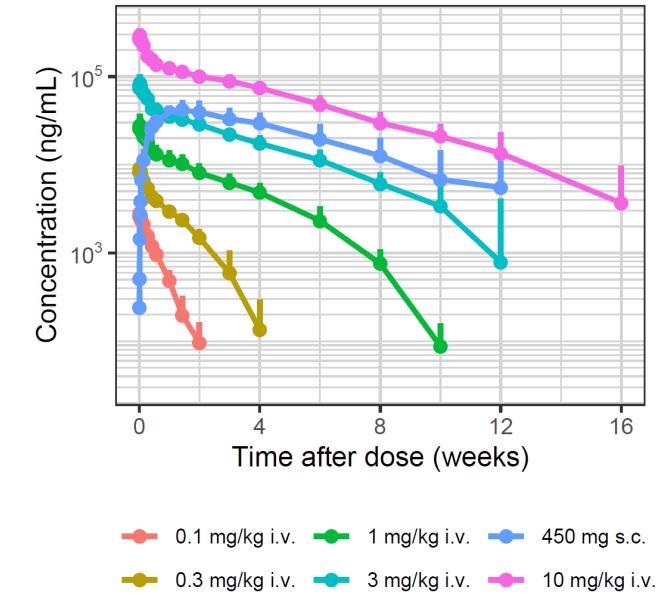
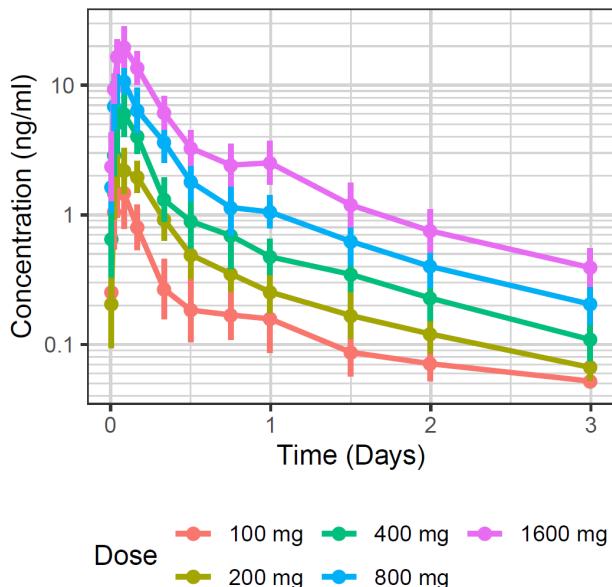
# **Explore your data with relevant questions**



# Explore PK by relevant questions

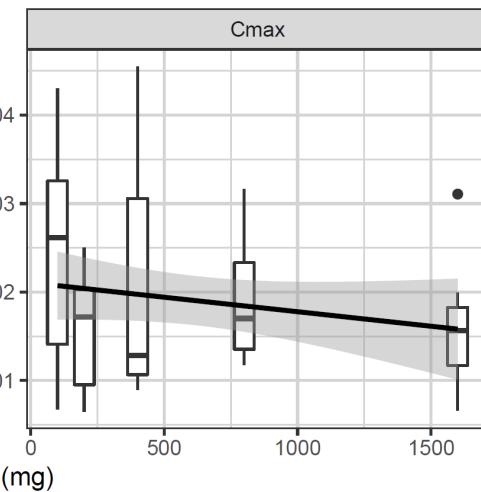
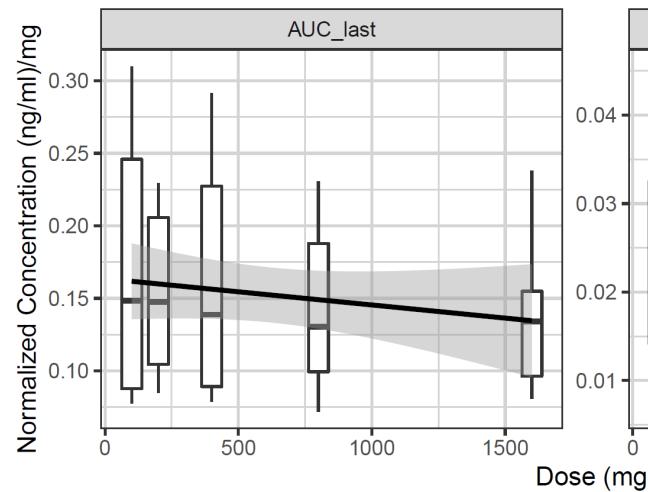
Assess trends over time

- How many compartments do you observe?
- Do you observe nonlinear clearance? at which doses?



Assess dose linearity

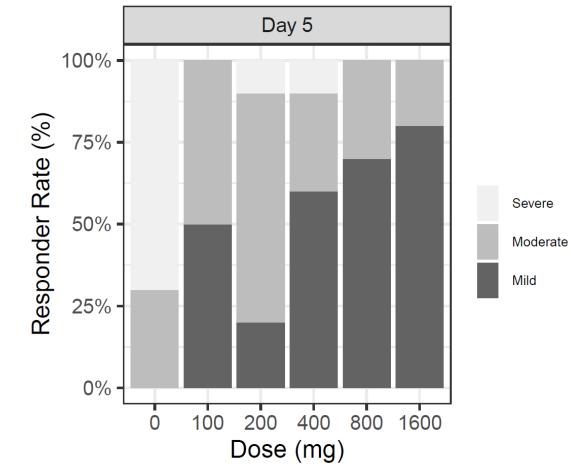
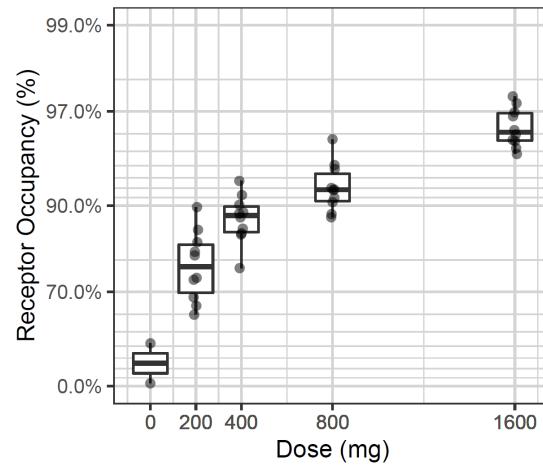
- Is dose-normalized exposure consistent across dose?



# Explore PD by relevant questions

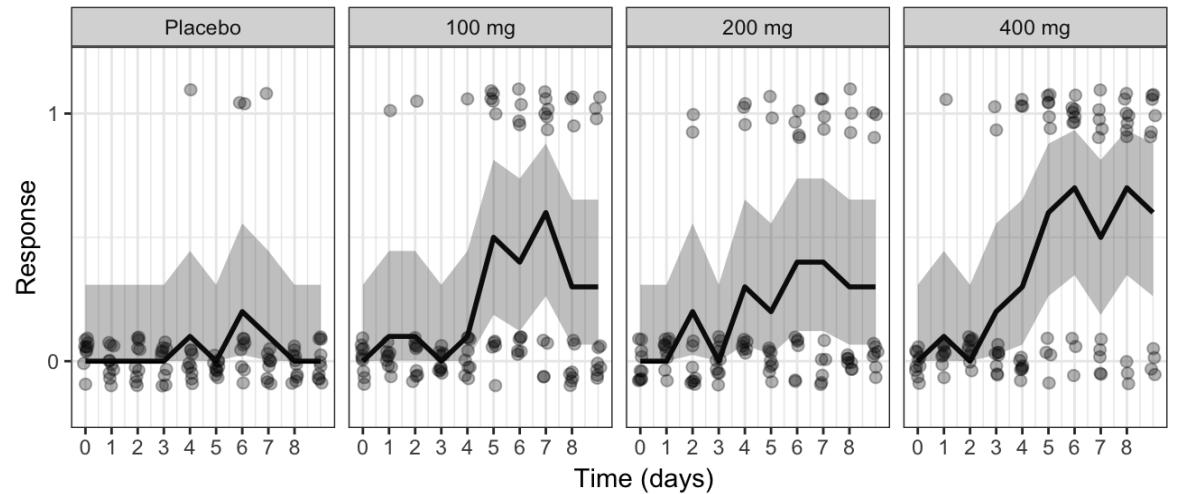
Assess trends by dose

- Is there a relationship with dose?
- Is there a plateau?
- What is Emax? ED50?



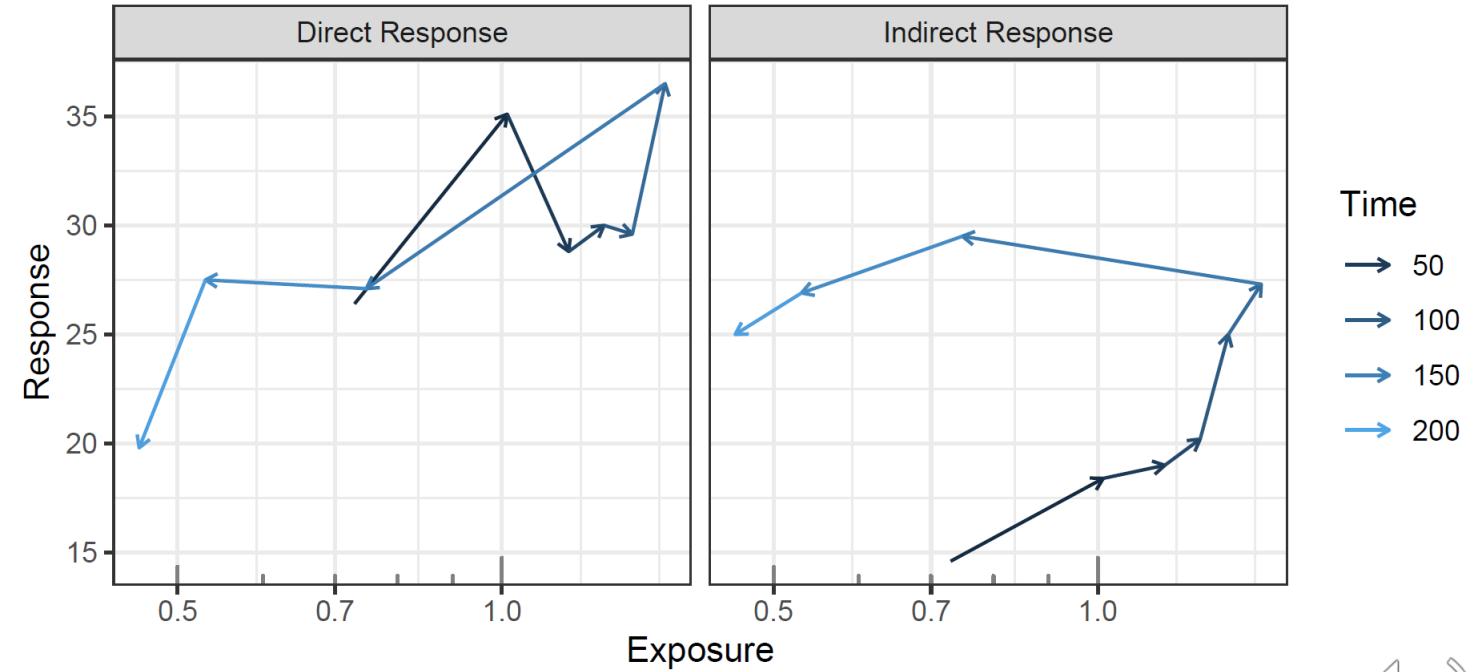
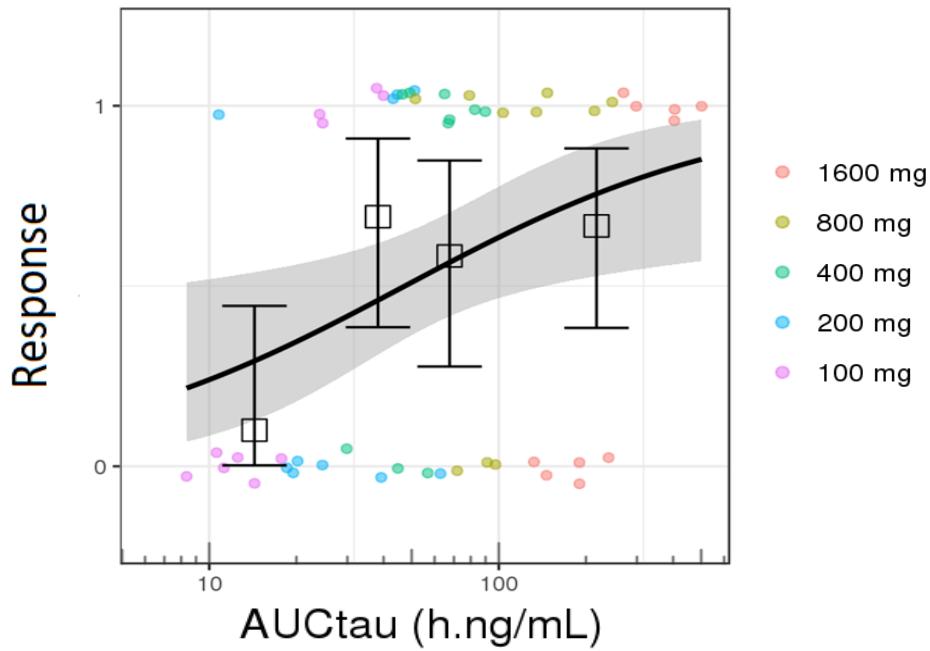
Assess trends over time

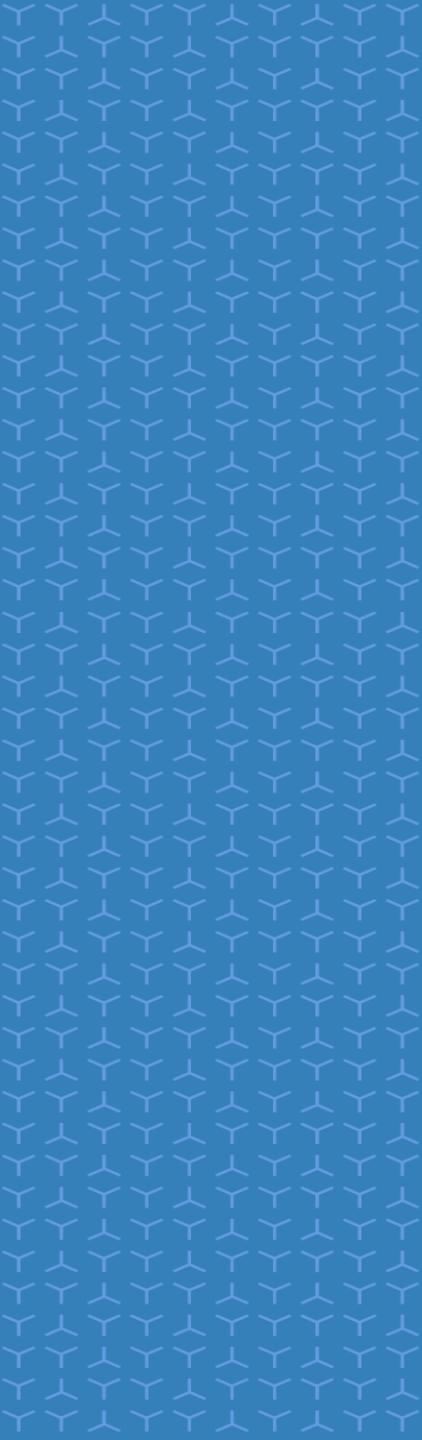
- General trends over time?
- How quickly is response detected?
- When does response reach steady state?



# Explore Exposure-Response relationship by relevant questions

- Positive/negative relationship?
- Is there a delay between the exposure and the response?





# **xgxr: R package to improve code readability and efficiency for PKPD plots**

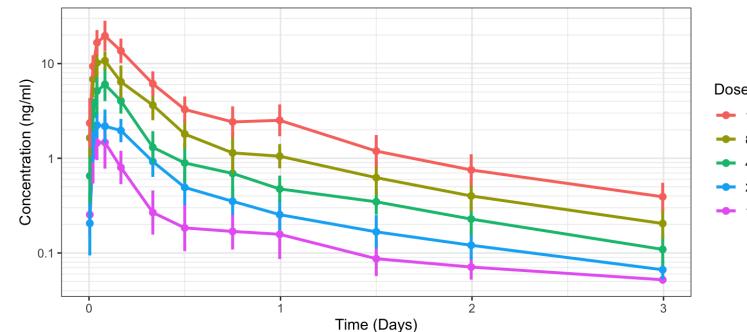


# xgxr: an R package to improve code readability

<https://cran.r-project.org/web/packages/xgxr/index.html>

- Useful functions for plotting, e.g. nice log scale, unit conversions
- Vignette apply to PK & PD examples

Graph to explore PK



R Code before xgxr

```
gg <- ggplot(data = pk_data, aes(x = NOMTIME,
y = LIDV, group= DOSE, color = TRTACT_high2low)) + theme_bw()

gg <- gg + stat_summary(geom = "errorbar", width = 0.5, size = 1,
fun.data = function(y){
  y <- stats::na.omit(y)
  data.frame(y = mean(y),
  ymin = mean(y)-qt(0.975,length(y))*sqrt(stats::var(y)/length(y)),
  ymax = mean(y)+qt(0.975,length(y))*sqrt(stats::var(y)/length(y))))}

gg <- gg + stat_summary(geom = "point", size = 2, fun.y = mean)
gg <- gg + stat_summary(geom = "line", size = 1, fun.y = mean)

gg <- gg + scale_y_log10(minor_breaks =
(rep(seq(1,9),21))*10^(rep(seq(-10,10), each = 9)))

gg <- gg + scale_x_continuous(breaks=seq(0,max(my.data$TIME/24)+1,1))

gg <- gg + labs(x = "Time (Days)", y = "Concentration (ng/ml)",
color = "Dose")
```

R Code after xgxr

xgxr functions make plotting PKPD data more efficient:

```
gg <- xgx_plot(data = pk_data, aes(x = NOMTIME,
y = LIDV, group= DOSE, color = TRTACT_high2low))

gg <- gg + xgx_geom_ci(conf_level = .95)

gg <- gg + xgx_scale_y_log10()

gg <- gg + xgx_scale_x_time_units(units_dataset = "hours",
units_plot = "days")

gg <- gg + labs(y = "Concentration (ng/ml)", color = "Dose")
```



## **Plot theme functions**

- `xgx_theme()` – set the global plotting theme
- `xgx_plot()` – make a plot and set the theme for that one plot

## **Tabulation functions**

- `xgx_check_data()` – provide summary tables that check data
- `xgx_summarize_covariates()` – summarize covariate information



## Plotting functions

- `xgx_geom_ci()` – plot mean & confidence intervals under different distribution assumptions (e.g. normal, lognormal, binomial)
- `xgx_geom_pi()` – plot median & percentile intervals

## Plot scaling functions

- `xgx_scale_y_log10()` – change y axis to log10 scale, nicely spaced major & minor gridlines
- `xgx_scale_x_time_units()` – convert time units for plotting
- `xgx_scale_y_reverselog10()` – scale y axis nicely for receptor occupancy data, increases resolution around 100%. Scales according to  $-\log_{10}(1-x)$ .
- `xgx_scale_y_percentchangelog10()` – scale y axis nicely for percent change data, increases resolution around -100%. Scales according to  $\log(PCHG + 100\%)$ .



## Saving and annotating functions

- `xgx_annotate_status()` – add draft status watermark to figures
- `xgx_annotate_filenames()` – add metadata to bottom of figures
- `xgx_save()` – **save figures including status watermark & metadata**
- `xgx_save_table()` – saves table to csv including source metadata



# **PKPD Exploratory Graphics (xGx) Cheat Sheet v.1.0**



# xGx Cheat Sheet

- Single page reference sheet
- Guiding principles for PKPD exploration

## PKPD Exploratory Graphics (xGx) Cheat Sheet v1.0

<http://opensource.nibr.com/xgx>

### Introduction, Background, Motivation

Data exploration is a key first step of any data analysis. Often an exploratory plot can quickly answer a question of interest and could be used in place of more complex analyses or to inform next steps.

In this cheat sheet, we provide a list of assessments to perform during exploratory analysis of exposure-response (PK, PD and PKPD) data in order to encourage a structured approach to data exploration.

#### Key Message

Don't just look at your data – look at it in a structured way

#### Objectives

- ✓ Provide structured approach for purposeful exploration of PKPD data
- ✓ Provide a teaching tool for exploring PKPD data with R
- ✓ Improve efficiency and code readability for exploratory analyses
- ✓ Improve quality of exploratory PKPD graphics

### Data Checking

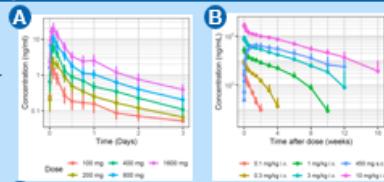
A first important step to data exploration is to check the quality of your data. For PK/PD data, we recommend to check for:

- incorrect timing of dosing and observations (e.g. nonzero pre-dose PK observations)
- erroneous duplication of data
- large discrepancies between actual time and nominal time (i.e. per-protocol time of sample collection)
- outlying data points

### PK, Dose-Exposure

Get an overview of the PK data by plotting a summary measure of central tendency +/- variability (e.g. mean +/- SE, [mean \(95% CI\)](#)), over time, grouped by dose or assigned treatment (Figure A, B)

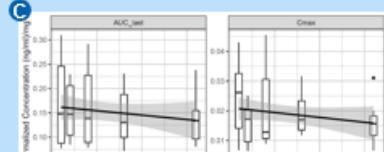
- Q How many compartments does the PK appear to have?  
Q Do you detect any nonlinear clearance (e.g. dramatic drop in elimination phase on log scale)?



Both linear and log scale should be used for exploring PK data. See section on Technical Considerations (Scales) for further details.

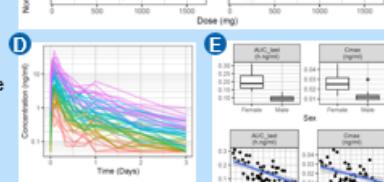
**Assess PK linearity** by looking for trends in the plot of dose vs dose normalized PK metric (e.g. AUC or Ctrough) (Figure C)

- Assessing linearity of PK is important for understanding how dose adjustments will impact the response

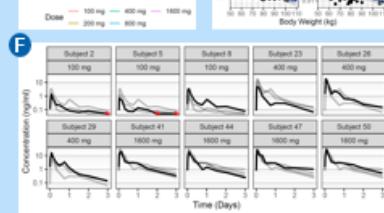
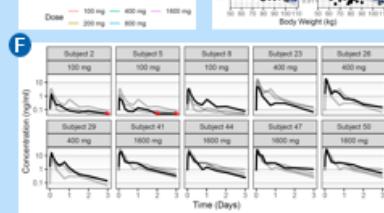


**Assess extent and sources of variability**

- Assess size of variability by using [spaghetti plots](#) or [confidence intervals](#) (Figure D)
- Assess sources of between subject variability by stratifying by covariates (Figure E)
- Assess sources of within subject variability using individual plots (Figure F)



See section on Technical Considerations (Variability) for details on within vs between subject variability, explained vs unexplained variability, and consequences of high variability.



### PD, Efficacy, Safety, Dose-Response

Determine data type of the endpoint of interest, and choose appropriate exploratory plots for this data type, (e.g. [continuous](#), [binary](#), [ordinal](#)).

See section on Technical Considerations for:

- Determining whether any correction is needed (e.g. change from baseline, placebo adjusted).
- Choosing the appropriate scale for your endpoint.

Assess trends with dose: Summary of PD/efficacy/safety vs dose, (e.g. [Mean \(95% CI\) of PD vs dose](#)) (Figure G, H)

- Q Do you see a relationship between dose and response?

Q Is a plateau observed at higher doses?

- Q What would you guess the ED50 to be? ED90? (you can check your expectations against your future model)

Assess trends over time by plotting [summary plots of the endpoint against time](#) (Figure I, J)

- Q Does the response change over time?

Q Is tolerance observed (e.g. rebounding, returning to baseline, overshooting)?

- Q How long does it take the PD to reach steady state (if there is a steady state)?

Assess extent and sources of variability

- Assess size of variability by using [spaghetti plots](#) or [confidence intervals](#) (Figure K)
- Assess sources of between subject variability by stratifying by covariates (Figure L)
- Assess sources of within subject variability using individual plots (Figure M)

See section on Technical Considerations (Variability) for further details

### PKPD, Exposure-Response/Safety

Plot PK and PD on the same time scale to get an idea of the trends of both over time. Look at both summary plots and individual plots (Figure N)

- Q How long is the delay between changes in PK and changes in PD?

Q How long after steady state PK does PD reach steady state (if at all)?

Get an overall idea of the relationship between PK and PD by plotting [PD on the vertical axis against different PK metrics on the horizontal axis](#) (Figure O)

- Q Is it a positive relationship?

Q How strong is the relationship?

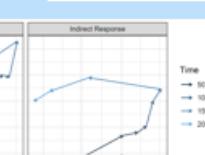
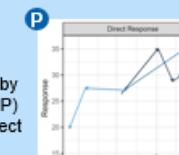
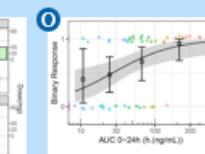
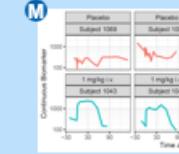
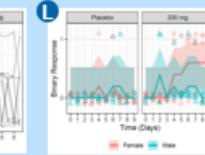
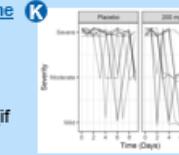
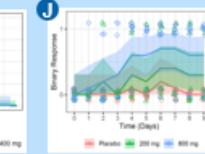
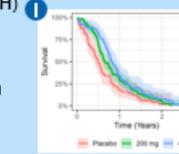
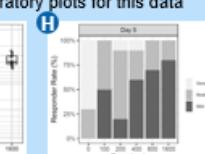
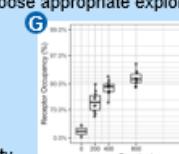
Q Is there a lot of between subject variability?

Get an idea of the time delay of the PKPD relationship by plotting [individual hysteresis plots of PD vs PK](#) (Figure P)

- Q Is the observed relationship between PK and PD direct (straight line in hysteresis path) or indirect (looping behavior in the hysteresis path)?

Be aware of situations that can impact interpretation, e.g.:

- Dose interruptions
- Intercurrent events (e.g. nonresponder drop-out before responders)



# xGx Cheat Sheet

- Technical considerations
- Useful plotting functions
- PKPD exploration Checklist

**Technical Considerations**

### Variability

Variability is not the same as noise. Variability is a characteristic of living systems and may in itself be a signal if appropriately represented (e.g covariate effects, diurnal effects, disease progression). Variability has two key characteristics:

- 1) Inter-subject (between subject) vs Intra-subject (within subject)
- 2) Explained vs Unexplained

The table below shows examples of the different types of variability, and mitigation steps for high variability in each category.

Type of Variability	Examples	Mitigation Steps
Explained between subject variability	Traditional covariates (e.g. age, weight, sex, race)	Individualized therapy may be an option to reduce between subject variability
Unexplained between subject variability	Unaccounted for covariates	Therapeutic drug monitoring could be attempted to adjust dose based on observed PK and/or PD during therapy
Explained within subject variability	Circadian rhythms, seasonal effects, food effects, disease progression	Depending on the explanation, you might suggest dosing accordingly
Unexplained within subject variability	Residual error, poor absorption, other unaccounted for effects	PK: could be difficult to address, unless there is a large therapeutic window in which case it may not be an issue. There may be a need for reformulation of the product. PD: may require multiple and/or appropriately timed measures of the endpoint and/or baseline in order to get a good idea of the "true" drug effect. Protocol assessment schedules for future studies should be designed accordingly.

### PD Data corrections (e.g. change from baseline, placebo adjusted, fold normal)

Consider whether correcting by a reference value will provide a clearer representation of your data (see table below)

Reference value	Situation that might benefit from data correction
Baseline	If there is high inter-subject variability and high correlation between baseline value and endpoint
Normal	If the goal is to compare to normal ranges (e.g. upper limit of normal for lab markers)
Placebo	To more clearly reveal drug effect, especially for primary endpoints which are often compared against placebo

When performing PD data correction:

- Consider whether to use absolute difference ( $y - y^*$ ), ratio to reference ( $y/y^*$ ) or percent change from reference ( $(y-y^*)/y^*$ ).
- Give special care to axis scales and confidence intervals for ratios and percent change from baseline (see section on Scales).
- Give special care when there is high within subject variability, e.g. use multiple baseline values for one individual (see section on Variability).

### Scales

Axis scales should reflect the distribution of data and/or the question being answered

<b>PK</b> <ul style="list-style-type: none"> <li>Log scale helps identify # of compartments, linearity of elimination, &amp; visualize wide range of doses on same plot.</li> <li>Linear scale focuses attention on <math>C_{max}</math>, which may be important for drugs with narrow therapeutic window &amp; <math>C_{max}</math>-driven safety.</li> </ul>	
<b>PD</b> <ul style="list-style-type: none"> <li>Log scale works well for PD markers that can change over several orders of magnitude.</li> <li>Linear scale is preferred when the PD measure can be both positive or negative, or when there are less than 2 orders of magnitude between the minimum and maximum value.</li> <li>For percent change from baseline, use the <code>xgx_scale_y_percentchangelog10()</code> function to increase the resolution around -100% (Figure Q)</li> <li>For receptor occupancy, use the <code>xgx_scale_y_reverselog10()</code> function to increase the resolution around 100% occupancy (Figure R)</li> </ul>	

**Authors:** Alison Margolskee, Feriba Khanshan, Andrew Stein, Camille Vong, Yu-Yun Ho, Mick Looby

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**Useful Plotting Functions - xgxr package**

### Plot theme functions

`xgx_theme()` – set the global plotting theme  
`xgx_plot()` – make a plot and set the theme for that one plot

### Tabulation functions

`xgx_check_data()` – provide summary tables that check data  
`xgx_summarize_covariates()` – summarize covariate information

### Plotting functions

`xgx_geom_ci()` – plot mean & confidence intervals under different distribution assumptions (e.g. normal, lognormal, binomial)  
`xgx_geom_pi()` – plot median & percentile intervals  
`xgx_geom_individuals()` – coming soon  
`xgx_geom_spaghetti()` – coming soon

### Plot scaling functions

`xgx_scale_y_log10()` – change y axis to log10 scale  
`xgx_scale_x_time_units()` – convert time units for plotting  
`xgx_scale_y_reverselog10()` – scale y axis nicely for receptor occupancy data, increases resolution around 100%. Scales according to  $-\log_{10}(1-x)$ .  
`xgx_scale_y_percentchangelog10()` – scale y axis nicely for percent change data, increases resolution around -100%. Scales according to  $\log(PCHG + 100\%)$ .

### Saving and annotating functions

`xgx_annotation_status()` – add draft status watermark to figures  
`xgx_annotation_filenames()` – add metadata to bottom of figures  
`xgx_save()` – save figures including status watermark & metadata  
`xgx_save_table()` – saves table to csv including source metadata

See <https://cran.r-project.org/web/packages/xgxr> for more details

**PKPD Exploratory Graphics Checklist**

- Identify data type and choose appropriate graph types (PD)
- Identify axis scale that reflects distribution of data (PK, PD)
- Provide an overview of the data (PK, PD)
- Determine whether data corrections are needed (PD)
- Assess trends over time (PK, PD)
- Assess trends by dose (PD)
- Assess PK linearity (PK)
- Assess extent and sources of variability (PK, PD)
- Get an overview of the relationship between exposure and response (PKPD)
- Explore delays between exposure and response (PKPD)

**Resources**

See <https://github.com/Novartis/xgx/tree/master/Resources> for:

- Fundamental PK principles introduction
- Fundamental PD principles introduction
- Uncertainty Assessment - Pedigree table
- Graphics Principles Cheat Sheet
- Presentation check list

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# **Example applying Rmarkdown page to new dataset**



## Overview

Motivation

Use Cases

Credits

# Exploratory Graphics (xGx)

## Overview

Exploratory plots can be helpful in understanding general behavior of data. They should be used as a first step before approaching modeling, and could even uncover useful insights that can be quickly communicated to project teams without extensive effort.

Visit the [Guiding Principles](#) page to get an overview of the general principles to follow when exploring PK/PD data.

This website is composed of Rmarkdown documents, which could be used as templates for generating exploratory plots. The Rmarkdown documents can be accessed on [GitHub](#).

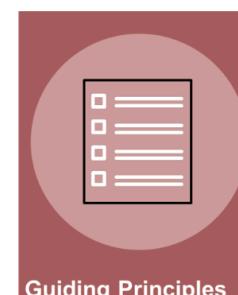
Many of the codes on this website use functions that we have found to be helpful while exploring PK/PD data. We compiled these helpful functions into the `xgxr` R-package, which is available on [CRAN](#), and [GitHub](#). Check out the [xgxr package website](#) for more information and examples on how to use the `xgxr` package functions.

This website displays suggested plots to pursue when exploring different PK/PD datasets, with a focus on exploring the Dose-Exposure-Response relationship. This site is a collection of exploratory plots and code, and could serve as a checklist of graphs someone might create for certain projects.

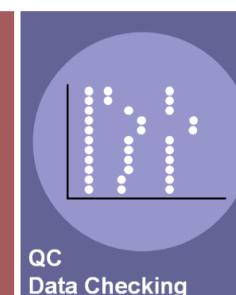
Some suggestions may be repetitive, so use your judgment to choose the best plot for your purpose and dataset. These plots are for exploratory benefit, and are not all expected to be included in a final report.

Use the navigation menus at the top of the page, or click on an icon below to find the topic for your specific needs.

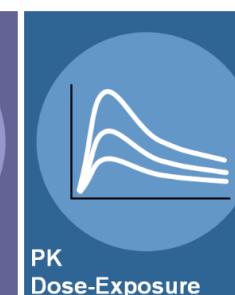
The graphs on this website were created with [Good Graphics Principles](#) in mind. Also check out the [Presentation Checklist](#) for useful tips on creating presentations of your results.



Guiding Principles



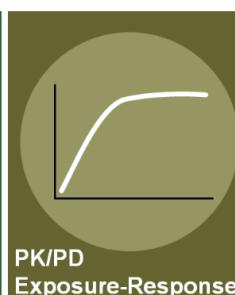
QC Data Checking



PK Dose-Exposure



PD Dose-Response



PK/PD Exposure-Response



**Overview**

Motivation  
Use Cases  
Credits

# Exploratory Graphics Overview

Exploratory plots can be helpful in understanding general trends in PK/PD data before approaching modeling, and could even uncover useful insights without extensive effort.

Visit the [Guiding Principles](#) page to get an overview of the general principles to follow when exploring PK/PD data.

This website is composed of RMarkdown documents, which could be used as templates for generating exploratory plots. The RMarkdown documents can be accessed on [GitHub](#).

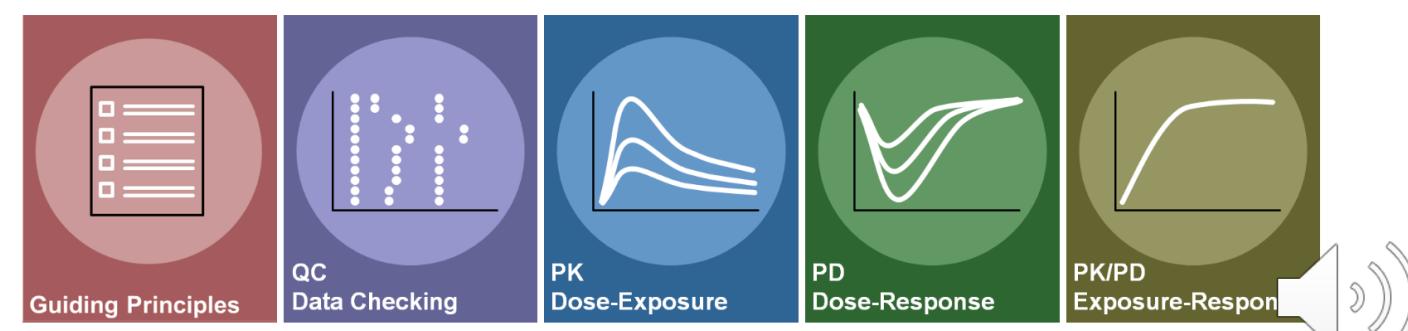
Many of the codes on this website use functions that we have found to be helpful while exploring PK/PD data. We compiled these helpful functions into the `xgxr` R-package, which is available on [CRAN](#), and [GitHub](#). Check out the [xgxr package website](#) for more information and examples on how to use the `xgxr` package functions.

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The graphs on this website were created with [Good Graphics Principles](#) in mind. Also check out the [Presentation Checklist](#) for useful tips on creating presentations of your results.



## Motivation

# Two ways to get the R codes and graphics

The screenshot shows a web browser window with the URL [opensource.nibr.com](https://opensource.nibr.com). The page title is "PK/PD, Exposure-Response - Continuous". The left sidebar has a "Overview" tab selected, followed by "Setup", "Load Dataset", "Provide an overview of the data", "Explore variability", "Explore Exposure-Response Relationship", and "R Session Info". The main content area starts with an "Overview" section by Alison Margolskee and Fariba Khanshan, followed by "Setup", "Load Dataset", and "Provide an overview of the data" sections.

## PK/PD, Exposure-Response - Continuous

Alison Margolskee, Fariba Khanshan

### Overview

This document contains exploratory plots for continuous PD data as well as the R code that generates them. The plots presented here are based on simulated data (see: [PKPD Datasets](#)). Data specifications can be found in the [Data Specification](#) section. A Rmarkdonw template to generate this page can be found on [Rmarkdown-Template](#). You may also want to look at the [Continuous Dose PK/PD](#) dataset for your reference ([download dataset](#)).

### Setup

### Load Dataset

### Provide an overview of the data

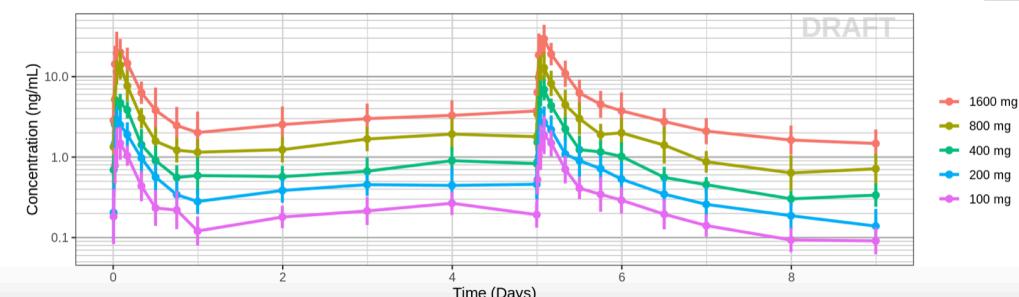
Summarize the data in a way that is easy to visualize the general trend of PD over time and between doses. Using summary statistics can be helpful, e.g. Mean +/- SE, or median, 5th & 95th percentiles. Consider either coloring by dose or faceting by dose. Depending on the amount of data one graph may be better than the other.

### PK and PD marker over time, colored by Dose, mean (95% CI) percentiles by nominal time

Observe the overall shape of the average profiles. Does the effect appear to increase and decrease quickly on a short time scale, or does it occur over a longer time scale? Do the PK and PD profiles appear to be on the same time scale, or does the PD seem delayed compared to the PK? Is there clear separation between the profiles for different doses? Does the effect appear to increase with increasing dose? Do you detect a saturation of the effect?

Code

Download the Rmarkdown documents and use them as templates



```

1 ---  

2 title: "PK/PD, Exposure-Response - Continuous"  

3 author: "Alison Margolskee, Fariba Khanshan"  

4 output:  

5   html_document:  

6     toc: true  

7     toc_float: true  

8     code_folding: hide  

9 ---  

10  

11 ## Overview  

12 <!--START_EXPLANATION-->  

13 This document contains exploratory plots for continuous PD data as well as the R code that  

  are based on simulated data ([see: PKPD Datasets](PKPD_Datasets.html)). Data specification  

  Rmarkdown template to generate this page can be found on [Rmarkdown-Template](Rmarkdown/Mu  

  may also download the Multiple Ascending Dose PK/PD dataset for your reference ([download  

  dataset](Data/Multiple_Ascending_Dose_Dataset2.csv)).  

14 <!--END_EXPLANATION-->  

15 ## Setup  

16  

17 ```{r, error = TRUE, warning=FALSE, message=FALSE}  

18 library(ggplot2)  

19 library(dplyr)  

20 library(tidyr)  

21 library(xgxr)  

22  

23 #flag for labeling figures as draft  

24 status = "DRAFT"  

25  

26 ## ggplot settings  

27 xgx_theme_set()  

28  

29 #directories for saving individual graphs  

30 dirs = list(  

31   parent_dir= tempdir(),  

32   rscript_dir = "./",  

33   rscript_name = "Example.R",  

34   results_dir = "./",  

35   filename_prefix = "",  

36   filename = "Example.png")  

37 ```

```

```

1 ---  

2 title: "PK/PD, Exposure-Response - Continuous"  

3 author: "Alison Margolskee, Fariba Khanshan"  

4 output:  

5   html_document:  

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14 <!--END_EXPLANATION-->  

15 ## Setup  

16  

17 ```{r, error = TRUE, warning=FALSE, message=FALSE}  

18 library(ggplot2)  

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32   rscript_dir = "./",  

33   rscript_name = "Example.R",  

34   results_dir = "./",  

35   filename_prefix = "",  

36   filename = "Example.png")  

37 ```

```

Add your name  
here

Might want to label  
your figure if working  
with non-validated  
dataset

Might want to  
specify directory if  
you plan on saving  
your outputs



# Two ways to get the R codes and graphics

opensource.nibr.com

xGx Guiding Principles Data Checking Dose-PK/Exposure Dose-PD/Efficacy/Safety PK-PD/Efficacy/Safety Resources

Overview

- Setup
- Load Dataset
- Provide an overview of the data
- Explore variability
- Explore Exposure-Response Relationship
- R Session Info

PK/PD, Exposure-Response - Continuous

Alison Margolskee, Fariba Khanshan

Code Show All Code Hide All Code

Overview

This document contains exploratory plots for continuous PD data as well as the R code that generates them. The plots presented here are based on simulated data (see: [PKPD Datasets](#)). Data specifications can be accessed or modified in the R script. The R code used to generate this page can be found on [Rmarkdown-Template](#). You may also download the [PKPD Datasets](#) and the [Ascending Dose PK/PD dataset](#) for your reference ([download dataset](#)).

Show all codes

Setup

Load Dataset

Provide an overview of the data

PK and PD marker over time, colored by Dose, mean (95% CI) percentiles by nominal time

DRAFT

Concentration (ng/ml)

Time (Days)

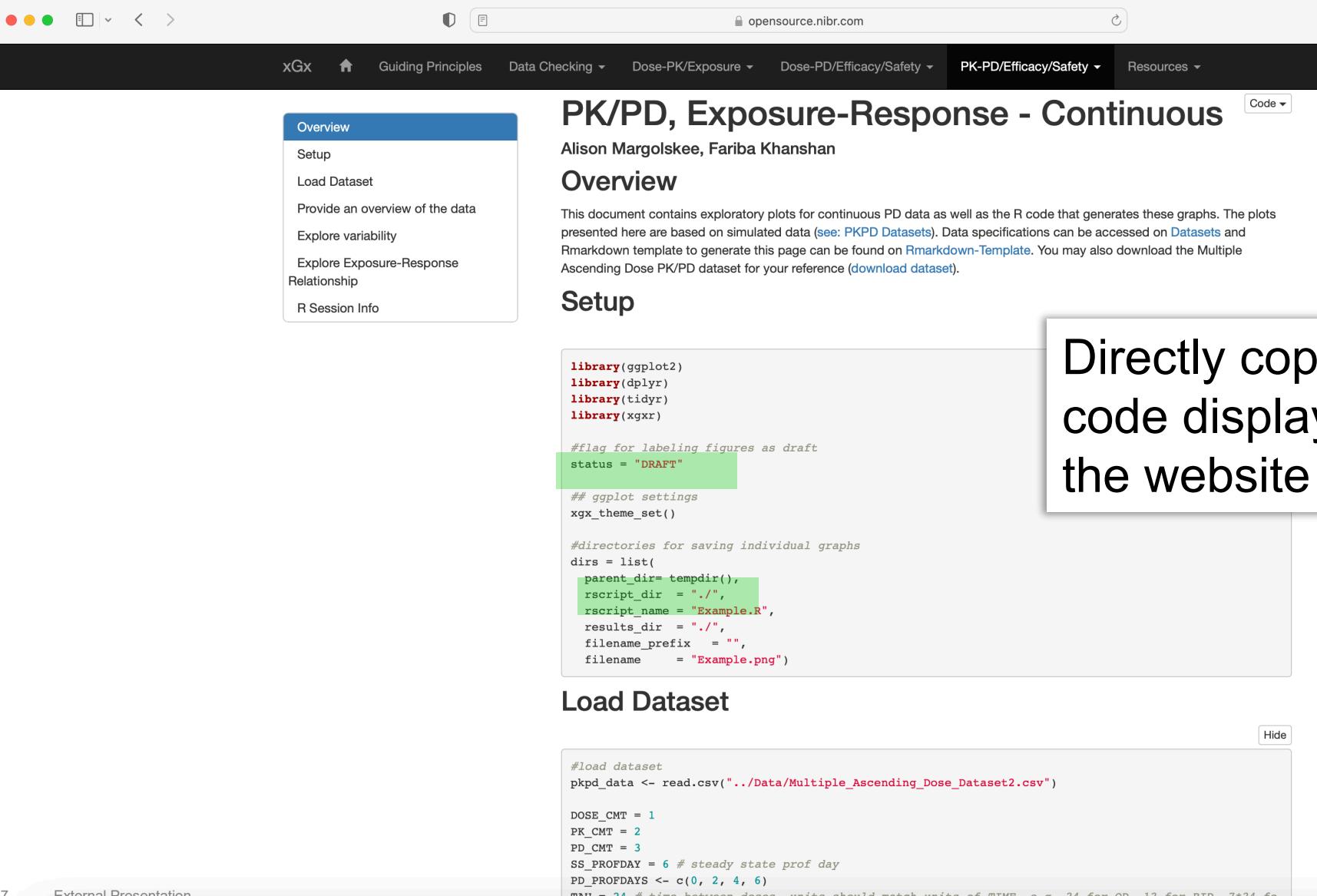
1600 mg  
800 mg  
400 mg  
200 mg  
100 mg

Exploratory Graphics

XGx

QC PK PD PKPD

# Two ways to get the R codes and graphics



The screenshot shows a web browser window with the URL [opensource.nibr.com](https://opensource.nibr.com). The page title is "PK/PD, Exposure-Response - Continuous". A sidebar on the left has a "Overview" tab selected, containing links for Setup, Load Dataset, Provide an overview of the data, Explore variability, Explore Exposure-Response Relationship, and R Session Info. The main content area has a "Code" button at the top right. Below it, the "Overview" section contains text about the document's purpose and how it was generated. The "Setup" section contains the following R code:

```
library(ggplot2)
library(dplyr)
library(tidyr)
library(xgxr)

#flag for labeling figures as draft
status = "DRAFT"

## ggplot settings
xgx_theme_set()

#directories for saving individual graphs
dirs = list(
  parent_dir= tempdir(),
  rscript_dir = "./",
  rscript_name = "Example.R",
  results_dir = "./",
  filename_prefix = "",
  filename = "Example.png")
```

A callout box on the right says "Directly copy the code displayed on the website". The "Load Dataset" section contains the following R code:

```
#load dataset
pkpd_data <- read.csv("../Data/Multiple_Ascending_Dose_Dataset2.csv")

DOSE_CMT = 1
PK_CMT = 2
PD_CMT = 3
SS_PROFDAY = 6 # steady state prof day
PD_PROF_DAYS <- c(0, 2, 4, 6)
TAU = 24 # time between doses, units should match units of TIME, e.g. 24 for QD, 12 for BID, 7*24 for CTD
```



```

38
39 ## Load Dataset
40
41 ````{r, error = TRUE, warning=FALSE, message=FALSE}
42 #load dataset
43 pkpd_data <- read.csv("./Data/Multiple_Ascending_Dose_Dataset2.csv")
44
45 DOSE_CMT = 1
46 PK_CMT = 2
47 PD_CMT = 3
48 SS_PROFDAY = 6 # steady state prof day
49 PD_PROF_DAYS <- c(0, 2, 4, 6)
50 TAU = 24 # time between doses, units should match units of TIME, e.g. 24 for QD, 12 for BID, 7*24 for Q1W (when units of TIME are h)
51
52 #ensure dataset has all the necessary columns
53 pkpd_data = pkpd_data %>%
54   mutate(
55     ID = ID, #ID column
56     TIME = TIME, #TIME column name
57     NOMTIME = NOMTIME, #NOMINAL TIME column name
58     PROFDAY = 1 + floor(NOMTIME / 24), #PROFILE DAY day associated with profile, e.g. day of dose administration
59     LIDV = LIDV, #DEPENDENT VARIABLE column name
60     CENS = CENS, #CENSORING column name
61     CMT = CMT, #COMPARTMENT column
62     DOSE = DOSE, #DOSE column here (numeric value)
63     TRTACT = TRTACT, #DOSE REGIMEN column here (character, with units),
64     LIDV_NORM = LIDV/DOSE,
65     LIDV_UNIT = EVENTU,
66     DAY_label = ifelse(PROFDAY > 0, paste("Day", PROFDAY), "Baseline")
67   )

```



# PKPD dataset specification

R 3.6.1> View(pkpd\_data)

	TIME	TIM2	NT	LIDV	ID	CMT	DOSE	AMT	ROUTE	MGKG	NAME	UNIT	TRT
1	0.000	-571.117	NA	145.0000	1001	4	0.2151	0.000	2	0.003	PD	pg/mL	0.003 mg/kg i.v.
2	547.117	-24.000	NA	137.0000	1001	4	0.2151	0.000	2	0.003	PD	pg/mL	0.003 mg/kg i.v.
3	570.533	-0.583	0	95.3000	1001	4	0.2151	0.000	2	0.003	PD	pg/mL	0.003 mg/kg i.v.
4	570.533	-0.583	0	0.0000	1001	5	0.2151	0.000	2	0.003	PK	ng/mL	0.003 mg/kg i.v.
5	571.117	0.000	0	0.0000	1001	2	0.2151	1.434	2	0.003	IV Drug administration	nmol	0.003 mg/kg i.v.
6	572.133	1.017	1	0.0000	1001	5	0.2151	0.000	2	0.003	PK	ng/mL	0.003 mg/kg i.v.
7	573.117	2.000	2	0.0000	1001	5	0.2151	0.000	2	0.003	PK	ng/mL	0.003 mg/kg i.v.
8	575.117	4.000	4	95.3000	1001	4	0.2151	0.000	2	0.003	PD	pg/mL	0.003 mg/kg i.v.

ID = ID

TIME = TIM2

NOMTIME = NT

EVID = 0

LIDV = LIDV

CENS = 0

CMT = CMT

DOSE = MGKG

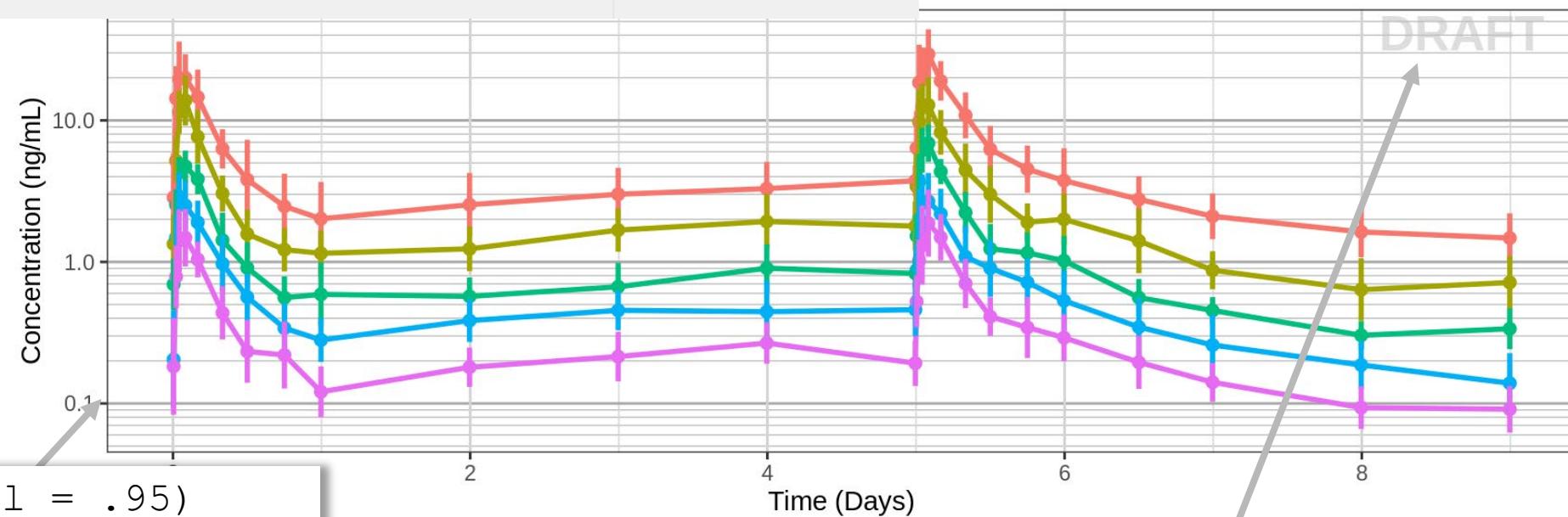
TRTACT = TRT

LIDV\_NORM = LIDV/MGKG

LIDV\_UNIT = UNIT



```
148 + ````{r, error = TRUE, cache = TRUE, fig.width = 10, fig.height = 3, warning = FALSE, message= FALSE}
149
150 #PK data
151 gg <- ggplot(data = pk_data,
152                 aes(x = NOMTIME,y = LIDV, color = TRTACT_high2low, fill = TRTACT_high2low))
153 gg <- gg + xgx_stat_ci(conf_level = .95)
154 gg <- gg + xgx_annotate_status(status)
155 gg <- gg + xgx_scale_x_time_units(units_dataset = time_units_dataset,
156                                         units_plot      = time_units_plot)
157 gg <- gg + guides(color = guide_legend(""), fill = guide_legend(""))
158 gg <- gg + xgx_scale_y_log10()
159 gg <- gg + labs(y = conc_label)
160 print(gg)
--
```



xgx\_stat\_ci(conf\_level = .95)  
Plots mean and 95% CI with one line of code

xgx\_scale\_y\_log10  
Makes nicely spaced grid lines for log scale

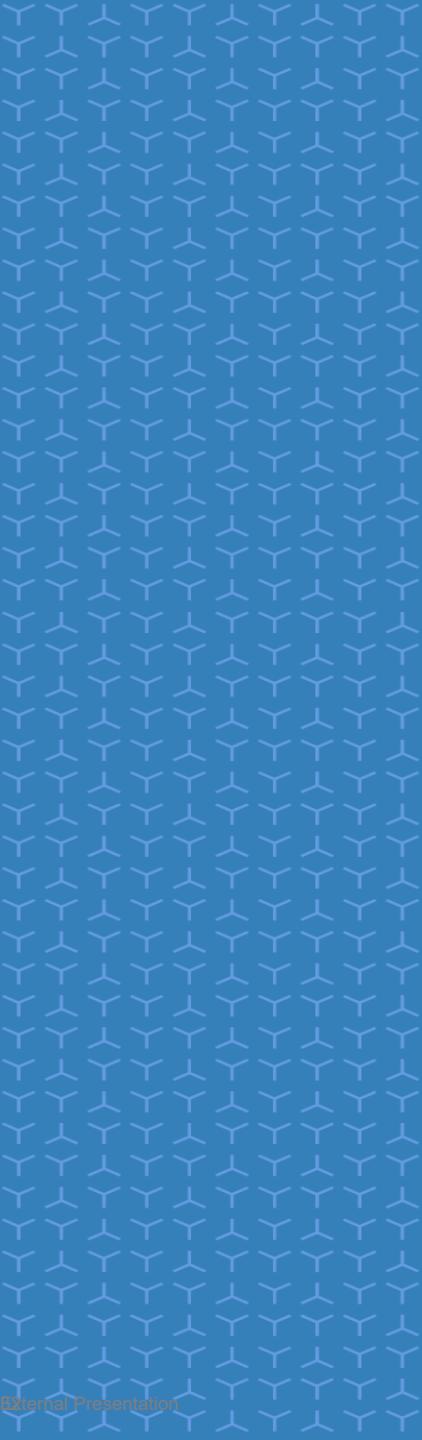
xgx\_annotate\_status(status)  
Adds watermark to figures indicating status (e.g. DRAFT)



# Conclusion

- We are developing a resource to encourage a structured approach to exploring PKPD data
- xGx website: <https://opensource.nibr.com/xgx/>
- xGx cheat sheet:
- xgxr package
  - GitHub: <https://github.com/Novartis/xgxr>
  - CRAN: <https://cran.r-project.org/web/packages/xgxr>
- Feedback is welcome!  
<https://github.com/Novartis/xgx/issues> (submit an issue)





# Your turn



# Instructions

- Pick a page from the website that you want to apply to your dataset
- Download the Rmd file from our website or GitHub
- Save the Rmd file and your dataset in a location where you can work
- Update the top sections of the Rmd file to:
  - Read in your dataset
  - Rename the variables as they are named in your dataset\*
  - Create any variables that are not in your dataset
- Run the different graphing sections, refining the data definitions at the top of the Rmd if necessary

\*Note that the Rmd files are designed for use with a nonmem/monolix modeling dataset, applying them to another data format may require additional effort



# Acknowledgements

## Core Team

Alison Margolskee  
Camille Vong

Andy Stein  
Fariba Khanshan

Theodoros Papathanasiou

## Extended Team

Matt Fidler

## Contributors

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Konstantin Krismer

Kostas Biliouris

Oliver Sander

Anwesha Chaudhury

Ivo Vranesic

Xinting Wang

Xinrui Zhang

Andrijana Radivojevic

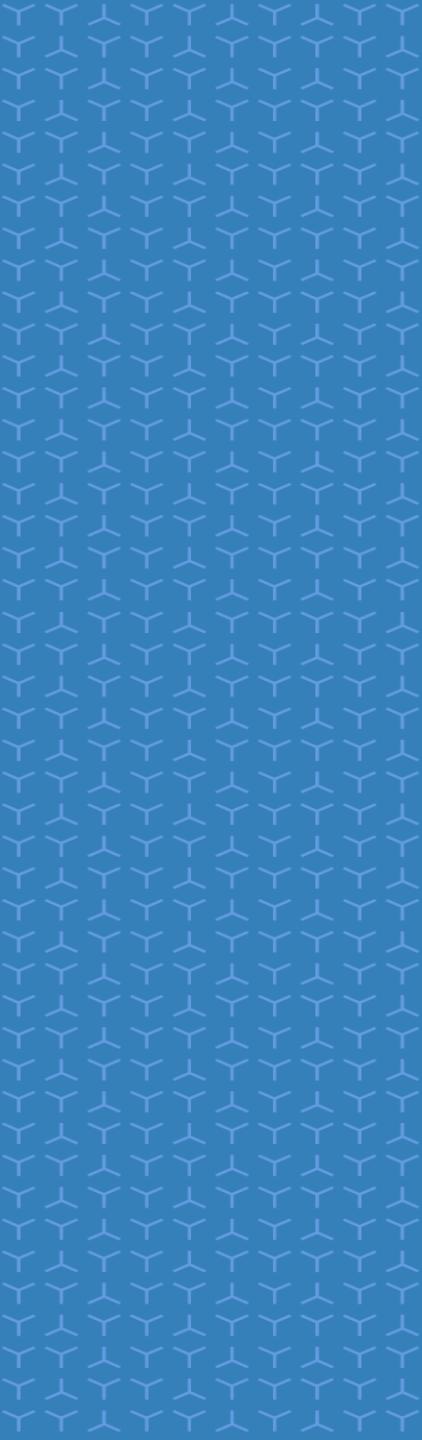
Joseph Kahn

## Leadership Team

Mick Looby

Yu-Yun Ho





**Thank you**

