# 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.

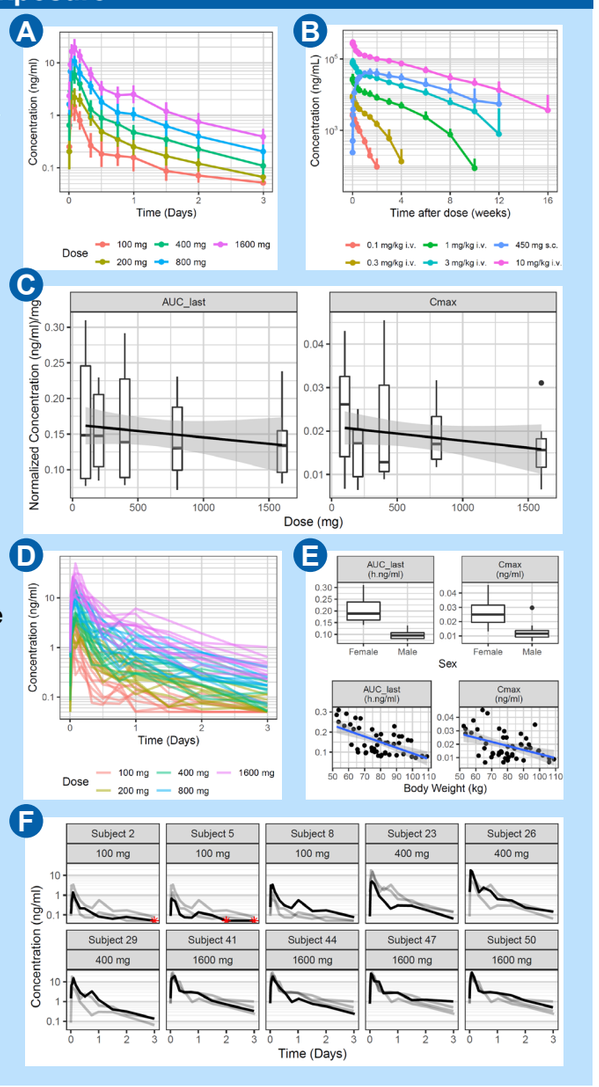
Assess PK linearity by looking for trends in the plot of dose vs dose normalized PK metric (e.g. AUC or Ctrough) (Figure C)

- 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)

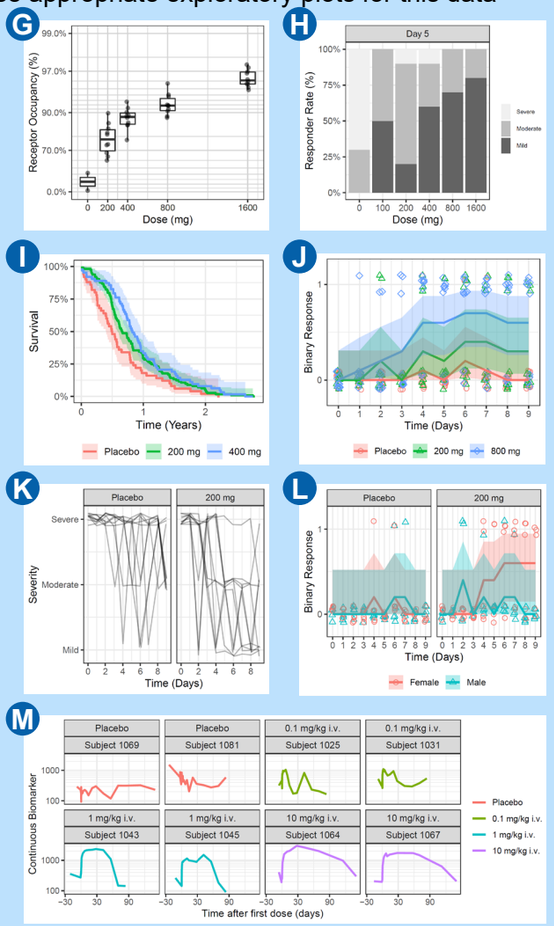
Assess trends over time by plotting summary plots of the endpoint against time (Figure I, J)

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)

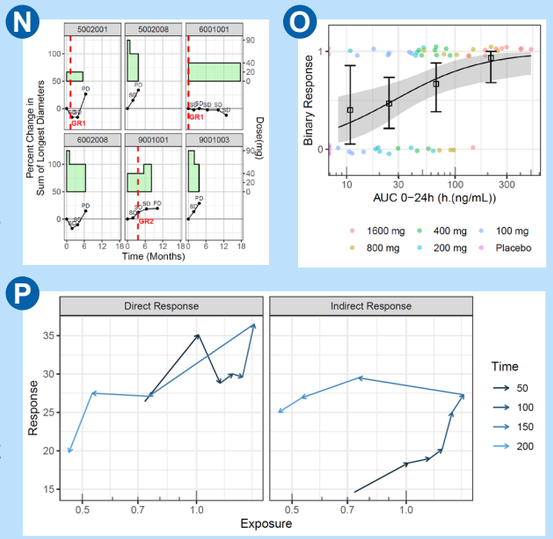
Q Is it a positive relationship?
Q How strong is the relationship?
Q Is there a lot of between subject variability?

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)

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# 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.<br>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:

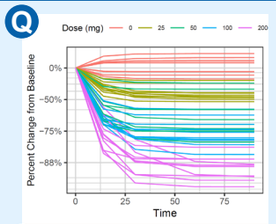
- Consider whether to use absolute difference (y - y*), ratio to reference (y/y*) or percent change from reference ([y-y*]/y*).
- Give special care to axis scales and confidence intervals for ratios and percent change from baseline (see section on Scales).
- Give special care when there is high within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

## Scales

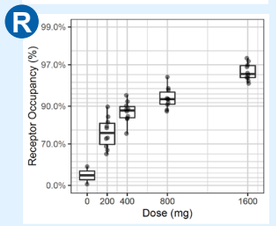
Axis scales should reflect the distribution of data and/or the question being answered

| | |
|---|---|
| PK | • Log scale helps identify # of compartments, linearity of elimination, & visualize wide range of doses on same plot.<br>• Linear scale focuses attention on Cmax, which may be important for drugs with narrow therapeutic window & Cmax-driven safety. |
| PD | • Log scale works well for PD markers that can change over several orders of magnitude.<br>• 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.<br>• For percent change from baseline, use the `xgx_scale_y_percentchangelog10()` function to increase the resolution around -100% (Figure Q)<br>• For receptor occupancy, use the `xgx_scale_y_reverselog10()` function to increase the resolution around 100% occupancy (Figure R) |

Q




R




# 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 -log10(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

**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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