

# Insel Basic Pharmacokinetic Modeling Workshop 2022

12<sup>th</sup> January 2022, KEMRI (virtual event)

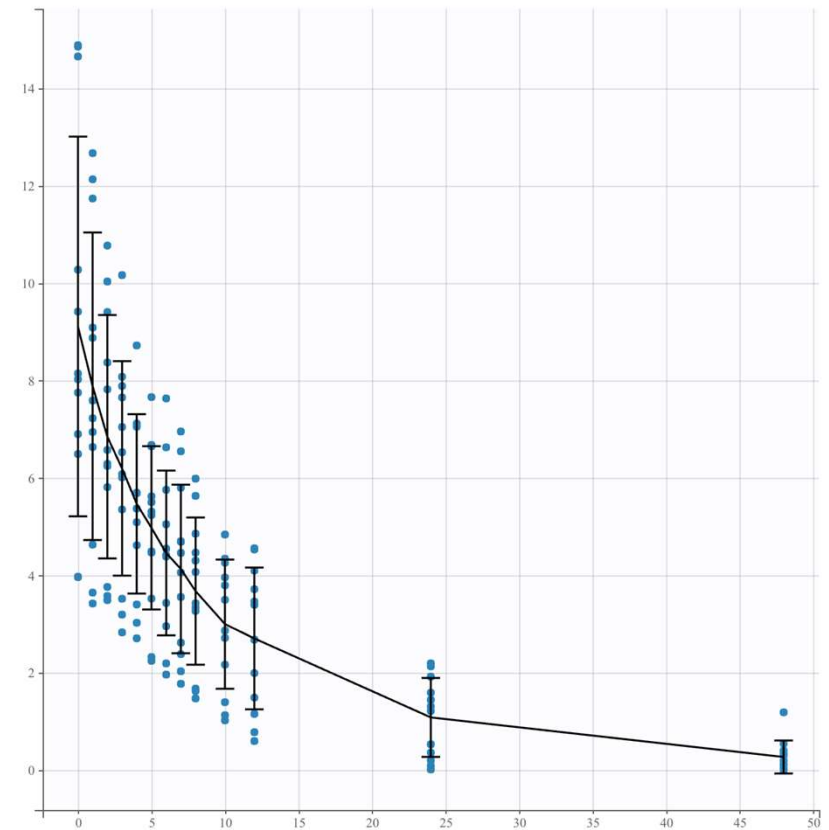


# CA hands-on exercises



## Dataset\_ee.csv

- Confirm dataset was imported properly
- Pick an appropriate structural model
- Check initial estimates
- Compare CA and NCA results



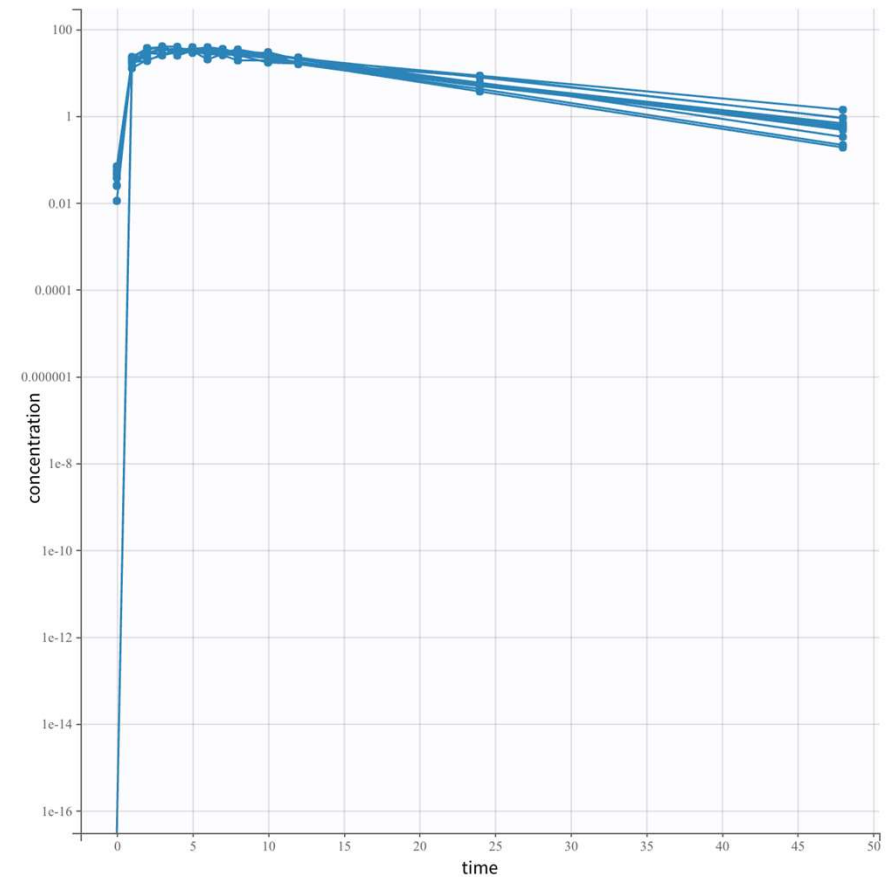
# Compare NCA and CA

|           | MIN  | Q1   | MEDIAN | Q3    | MAX   | MEAN  | SD   | SE   | CV    |
|-----------|------|------|--------|-------|-------|-------|------|------|-------|
| <b>V</b>  | 5.86 | 9.08 | 12.8   | 14.78 | 27.51 | 12.93 | 5.92 | 1.71 | 45.79 |
| <b>Cl</b> | 0.64 | 0.74 | 0.98   | 1.54  | 3.48  | 1.37  | 0.94 | 0.27 | 68.49 |

|                        | MIN   | Q1    | MEDIAN | Q3     | MAX   | MEAN  | SD    |
|------------------------|-------|-------|--------|--------|-------|-------|-------|
| <b>AUCINF_obs</b>      | 33.46 | 67.45 | 106.14 | 136.71 | 157.4 | 99.88 | 42.86 |
| <b>AUC_%Extrap_obs</b> | 0.2   | 1.32  | 3.29   | 5.89   | 32.84 | 5.77  | 8.93  |
| <b>AUClast</b>         | 33    | 66.18 | 101.61 | 121.97 | 145.3 | 92.66 | 37.45 |
| <b>Cl_obs</b>          | 0.64  | 0.73  | 0.95   | 1.51   | 2.99  | 1.28  | 0.77  |
| <b>Cmax</b>            | 3.96  | 6.69  | 8.08   | 12.46  | 14.89 | 9.11  | 3.9   |
| <b>HL_Lambda_z</b>     | 2.32  | 5.36  | 7.97   | 10.7   | 30.22 | 9.42  | 7.21  |
| <b>MRTlast</b>         | 3.91  | 6.47  | 10.62  | 13.33  | 19.65 | 10.5  | 4.53  |
| <b>Tmax</b>            | 0     | 0     | 0      | 0      | 0     | 0     | 0     |
| <b>Vz_obs</b>          | 5.77  | 8.69  | 11.76  | 16.34  | 27.7  | 13.8  | 7     |

## Dataset\_ca\_weight.csv

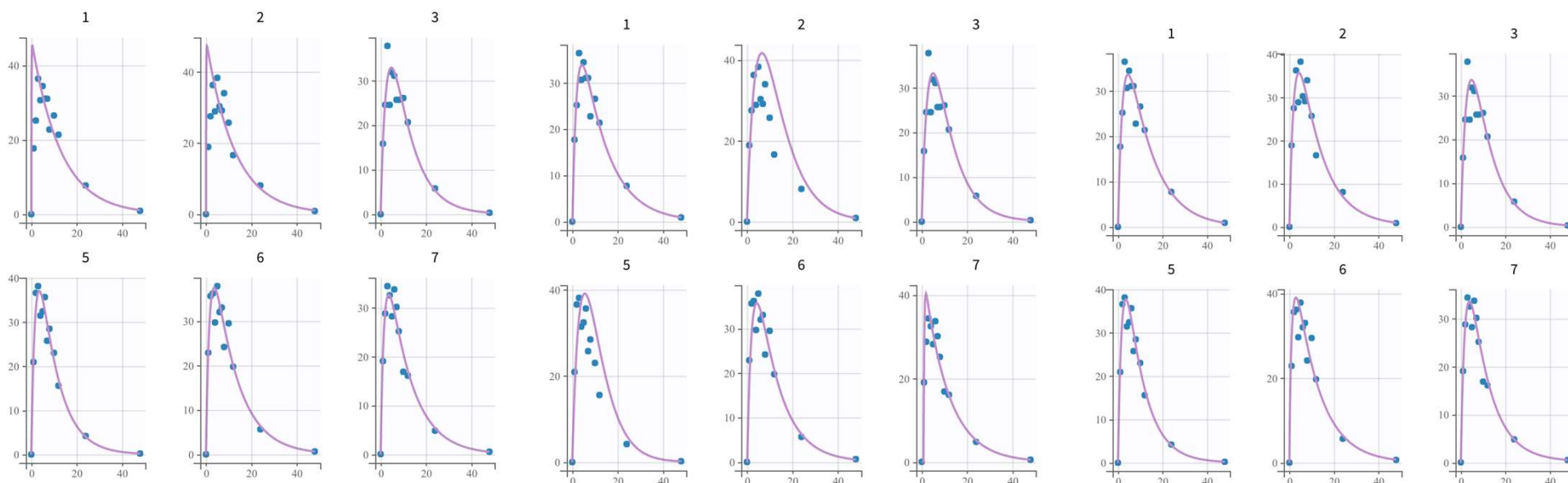
- Confirm dataset was imported properly
- Try different absorption models
- Change error weighting



# Absorption models

Weighting

$1/Y_{pred}^2$  ▼



| Administration                        | Delay                | Absorption  |
|---------------------------------------|----------------------|-------------|
| bolus                                 | no delay             | zero order  |
| infusion                              | lag time             | first order |
| oral/extravascular                    | transit compartments |             |
| oral/extravascular and bolus/infusion |                      |             |

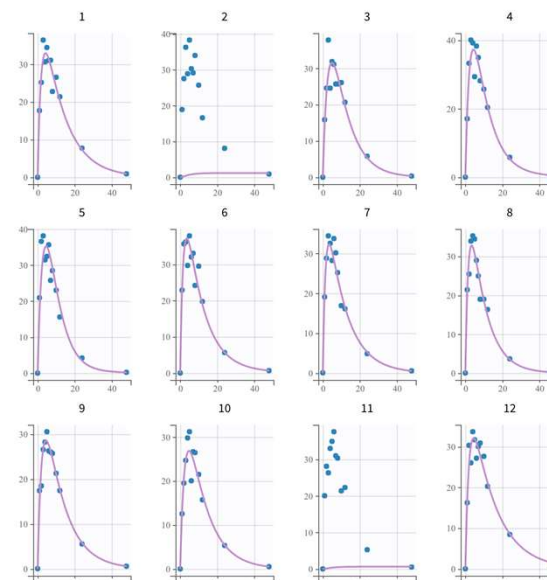
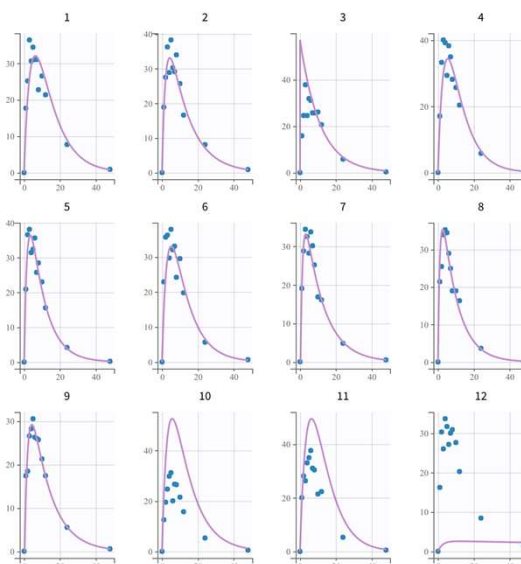
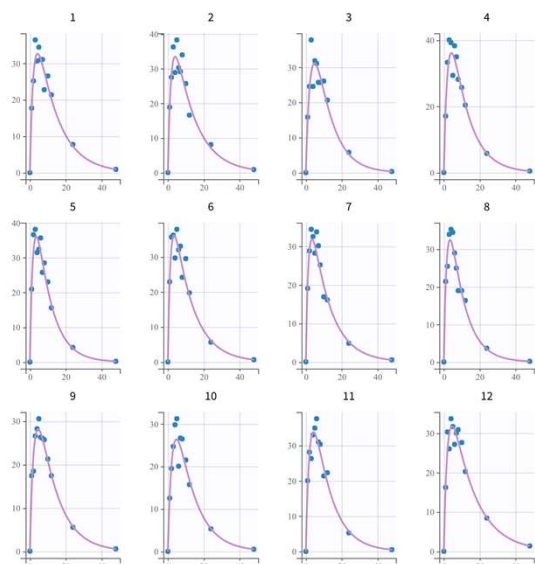
| Administration                        | Delay                | Absorption  |
|---------------------------------------|----------------------|-------------|
| bolus                                 | no delay             | zero order  |
| infusion                              | lag time             | first order |
| oral/extravascular                    | transit compartments |             |
| oral/extravascular and bolus/infusion |                      |             |

| Administration                        | Delay                | Absorption  |
|---------------------------------------|----------------------|-------------|
| bolus                                 | no delay             | zero order  |
| infusion                              | lag time             | first order |
| oral/extravascular                    | transit compartments |             |
| oral/extravascular and bolus/infusion |                      |             |

# Error weighting

Weighting

$1/Y_{obs}^2$  ▼



| Administration                        | Delay                | Absorption  |
|---------------------------------------|----------------------|-------------|
| bolus                                 | no delay             | zero order  |
| infusion                              | lag time             | first order |
| oral/extravascular                    | transit compartments |             |
| oral/extravascular and bolus/infusion |                      |             |

| Administration                        | Delay                | Absorption  |
|---------------------------------------|----------------------|-------------|
| bolus                                 | no delay             | zero order  |
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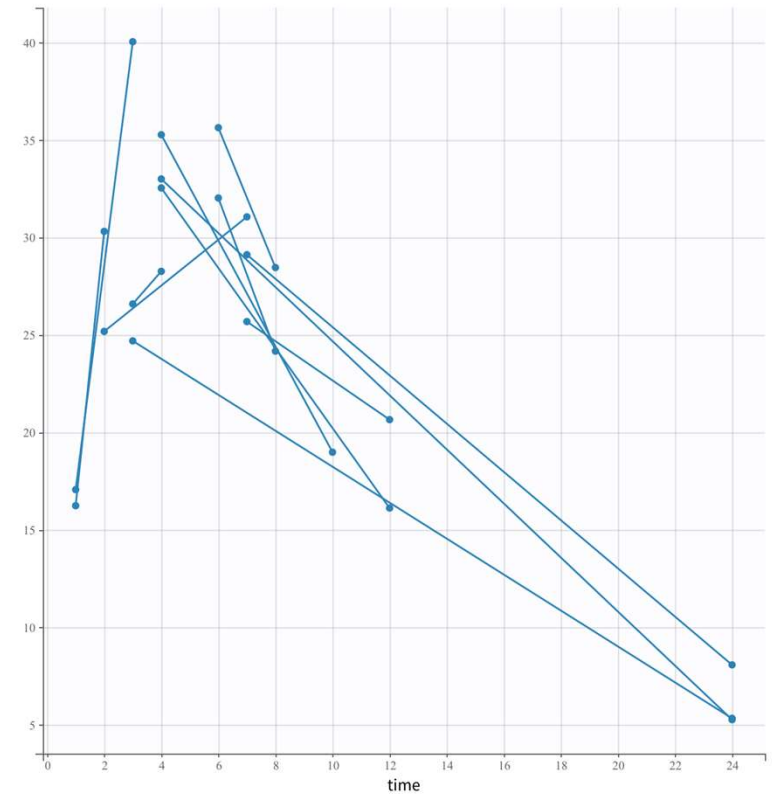
| Administration                        | Delay                | Absorption  |
|---------------------------------------|----------------------|-------------|
| bolus                                 | no delay             | zero order  |
| infusion                              | lag time             | first order |
| oral/extravascular                    | transit compartments |             |
| oral/extravascular and bolus/infusion |                      |             |

## Dataset\_ca\_weight\_sparse.csv

- Subset of Dataset\_ca\_weight.csv (2 samples per individual)
- Try the following approaches
  - NCA analysis
  - Individual CA analysis
  - Pooled fit

☒ Pooled fit

Fit with individual parameters or with the same parameters for all individuals





# Pooled fit

- Naïve pooled data analysis (NPD)
- Can be done when data was sparsely sampled
- One set of parameters estimated on the entire dataset
- Heavily biased and unsuitable for covariate analyses
- Careful with overparameterization
- Better approach: population PK

