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Semi-mechanistic modelling of absorption from extended release formulations - linking *in vitro* to *in vivo*

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In vitro to *In vivo* Correlation (IVIVC) for extended release products

- Why
 - Surrogate for bioequivalence study “Biowaiver”
 - Product quality demands
- Level A IVIVC (FDA)
 - *“The model should predict the entire in vivo time course from the in vitro data”*
- Different methods used to establish IVIVC
 - Deconvolution
 - Convolution model / Differential equation model
 - Prospective predictions based on mechanistic models (bottom up)



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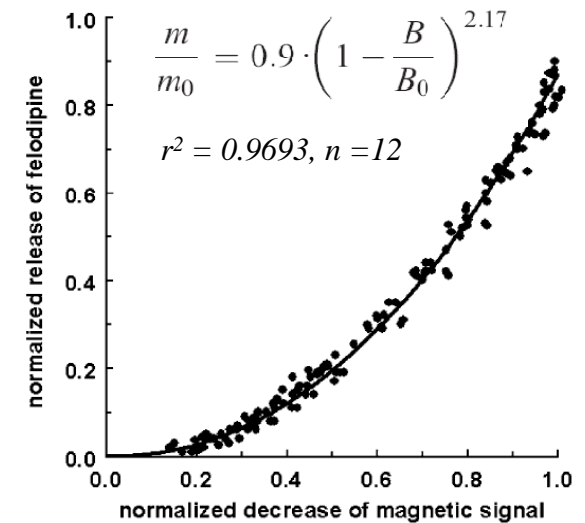
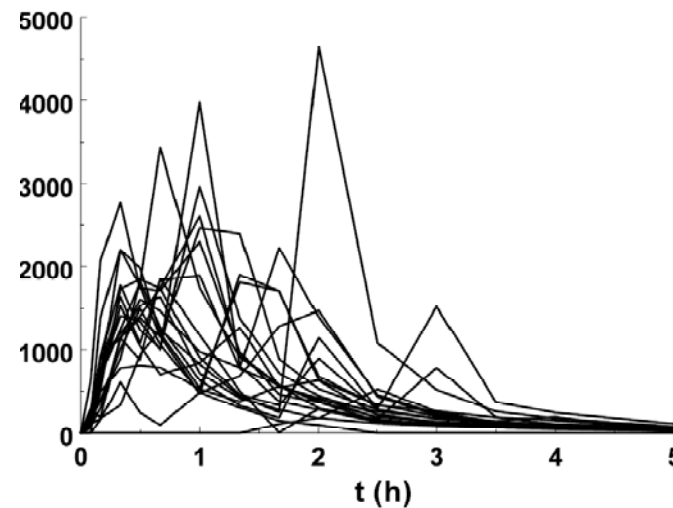
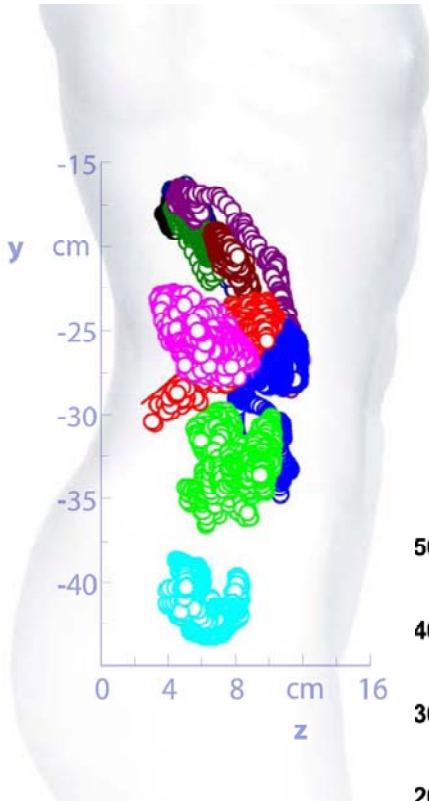
Aim

To outline and test a modelling framework capable of incorporating relevant clinical data and *in vitro* data to establish IVIVC by prospective simulations



Magnetic Marker Monitoring (MMM)

- Three types of observations:
 - GI position of solid dosage form
 - Plasma concentration
 - *In vivo* drug release





Mechanistic Modeling of a Magnetic Marker Monitoring Study, Linking Gastrointestinal Tablet Transit, *In Vivo* Drug Release, and Pharmacokinetics

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CLINICAL PHARMACOLOGY & THERAPEUTICS

1

Article describes:

- Differential equation based Markov-model to describe tablet GI transit
- Simultaneous modelling of *in vivo* drug release, regional absorption and disposition.
- Estimated effect of concomitant food intake and tablet GI position on absorption and drug release parameters
- Simulation of: tablet GI transit -> *in vivo* drug release -> plasma conc.



Suggested approach for pilot project (1/2)

1. Develop one or several models describing *in vitro* drug release as a function of environmental factors such as; pH, RPM etc. for the formulations of interest.
2. Apply *in vitro* model and physiological prior information about the GI tract environment to *in vivo* drug release data (assessed with MMM). Estimate the relationship between *in vitro* and *in vivo* conditions for different GI regions.
3. Utilize different sources of clinical plasma concentration data to build an integrated PK model
 - MMM study (using model from step 2 as input function)
 - Bioperm[®] capsule study (remote controlled local GI adm. in colon)
 - Study with administration of i.v. infusion and oral solution



Suggested approach for pilot project (2/2)

4. Model the tablet GI transit (MMM study)
5. Perform prospective simulations of clinical study with “new” formulations based on estimated *in vitro* drug release.
 - A. Tablet transit model \Rightarrow individual tablet transit profiles
 - B. Tablet transit + *in vitro* estimates + *in vivo* drug release model \Rightarrow individual drug release profiles
 - C. Drug release profiles + Integrated PK model \Rightarrow predicted individual PK profiles
 - D. Repeated step A-C N number of times, to simulate out N number of possible realizations of the clinical study ($N \geq 200$)
 - E. Calculate 95 % confidence interval for the simulated median plasma concentration vs. time profile and compare to the observed median.
 - F. Judge whether a satisfactory IVIVC can be concluded.



The data used for the pilot project, ***In vitro* drug release data**

(1/4)

- 6 different formulations (HPMC gel matrix)
 - Different fractions of active ingredient (API)
 - Different doses, size of tablets etc.
- Dissolution tests (USP 2) under different experimental conditions
 - pH: 1, 2, 3, 4.5, 5, 6, 6.8 and 7.4 (not all pH for all formulations)
 - RPM: 10, 50 and 100 (not all RPM for all formulations)
 - Ion strength: 0.05, 0.1, 0.2 and 0.3 M (not all ion strengths for all form)
 - In total 169 experiments
- Dissolution tests measure the composite of drug release and drug dissolution. Under the investigated conditions for the substance at hand the dissolution of released substance can be considered very fast in comparison to the drug release.



The data used for the pilot project, **MMM study data (*clinical*)**

(2/4)

- One of the investigated ER formulations (formulation X)
- Three way cross-over study with 6 healthy volunteers
 - Fasting administration
 - Food intake followed by dose
 - Dose followed by food intake

Measurements:

- *In vivo* drug release data
 - Magnetic signal correlated to drug release in *in vitro* experiments
- Tablet GI position, classified into;
 - Upper stomach, lower stomach, small intestine (incl. terminal ileum), ascending, transverse, descending and sigmoid colon (rectum)
- Plasma concentration of parent compound



The data used for the pilot project, **Additional clinical data for model building**

(3/4)

Plasma concentration data from two studies:

- Two way cross-over trial with administration of oral solution (17) and infusion (7) or bolus injection (5) in colon (ascending or transverse) via remote operated capsule Bioperm®.
- 10 healthy volunteers receiving both i.v. dosing and oral solution

Summary clinical data:

- Plasma concentration data from 33 individuals with 67 rich profiles
- 7 different ways of administration



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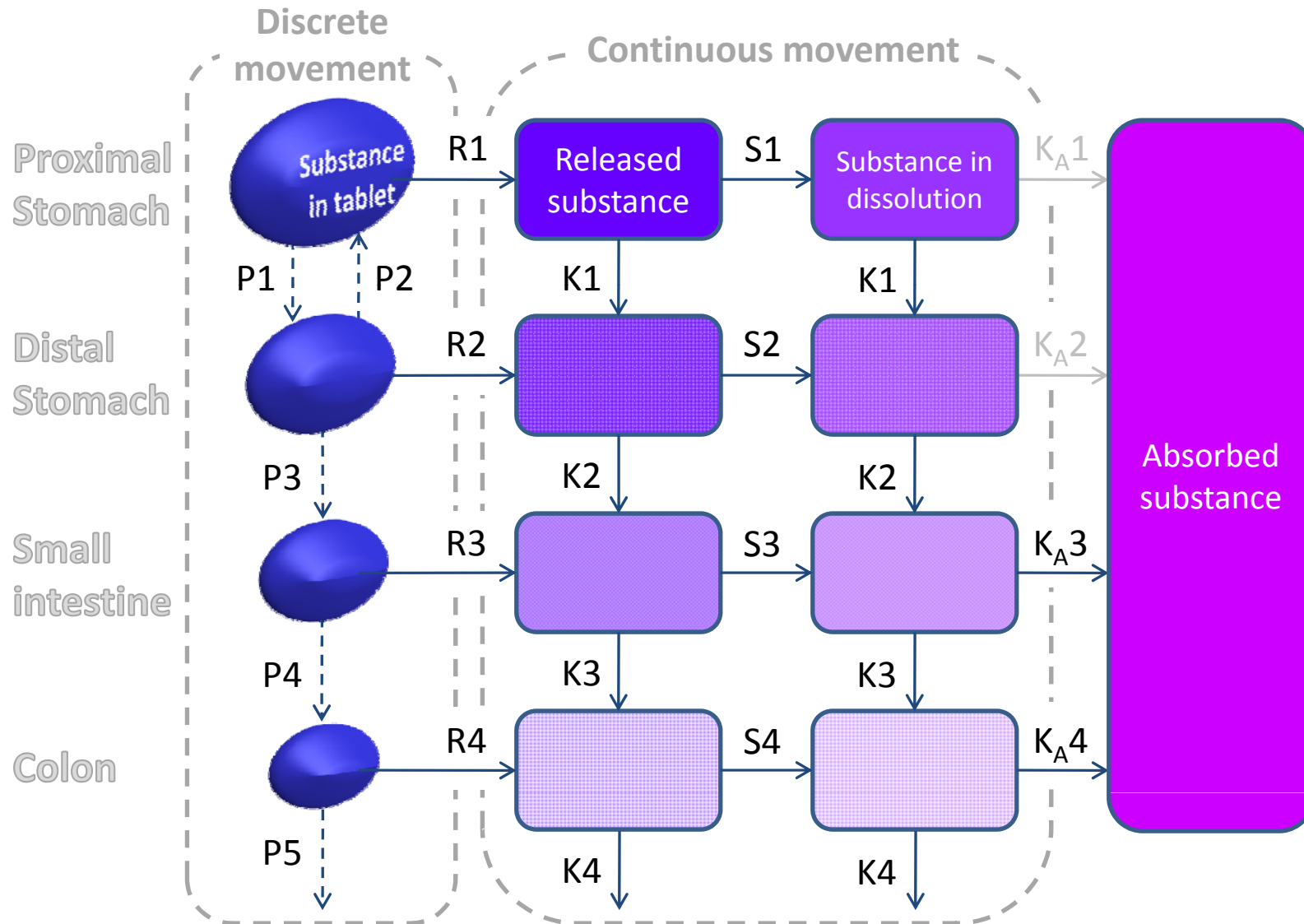
The data used for the pilot project, **Clinical data for model (IVIVC) validation**

(4/4)

- Study with three formulations A, B, C and oral solution.
- Formulation B both under fasting and fed conditions
- 6 individuals in each cohort (24 profiles)



Processes in oral absorption from gel matrix tablets





In vitro drug release model

- Drug release was found to be best explained as a power function of remaining tablet weight.
 - Probably corresponds to drug release as a function of surface area
 - Surface area of a perfect sphere \propto Volume^{2/3} \propto Weight^{2/3}

$$\frac{dA}{dt} = -R \times API \times \left(\frac{A}{\text{Nominal Dose}} \times \text{Tablet weight} \right)^x$$

(*A* = Amount of substance remaining in the tablet)

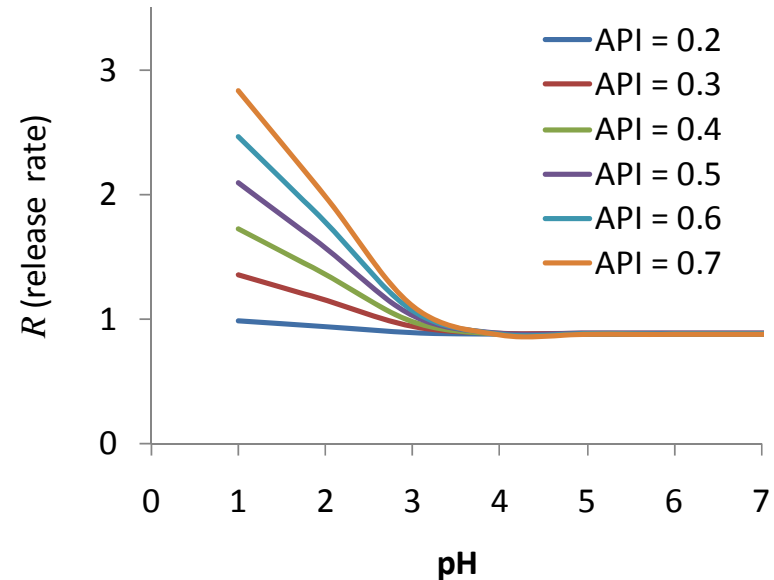
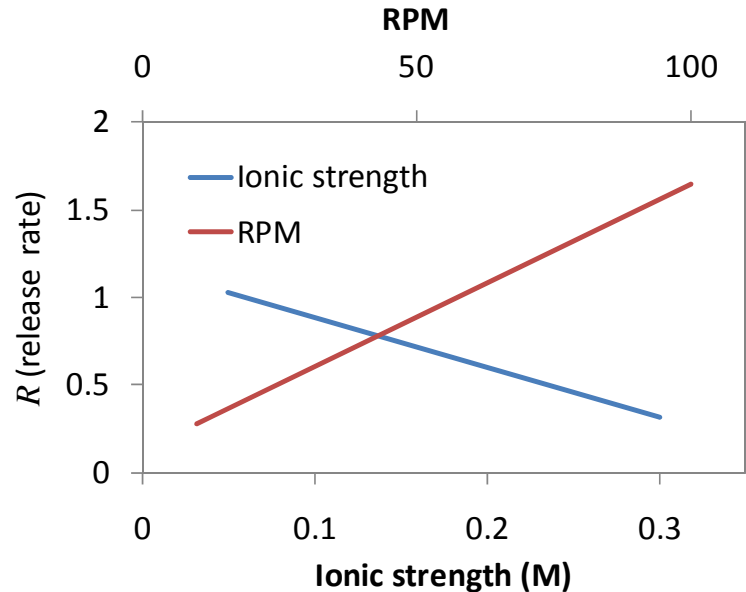
- Estimated X (95% CI) = 0.55 (0.52-0.60)

- Established covariate relationships on R for
 - RPM
 - Ionic strength
 - pH (and API)





Covariate relationships



$$R_{typ} \propto 1 - 3.23 \times (\text{Ionic strength} - 0.1)$$

$$R_{typ} \propto 1 + 0.0172 \times (\text{RPM} - 50)$$

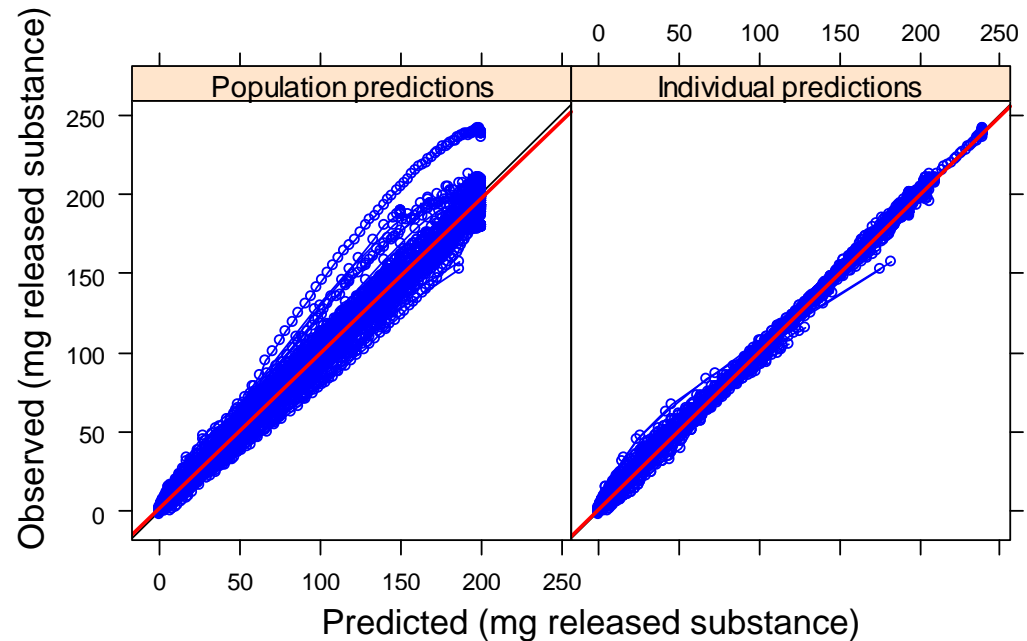
$$R_{typ} \propto 1 + \left(1 + 2.65 \times (\text{API} - 0.55)\right) \times -0.686 \times (\text{PH} - 3.27) \times \frac{1}{1 + \text{EXP}(7 \times (\text{PH} - 3.27))}$$

- Covariate relationships the same across all 6 formulations



In vitro drug release model

Parameter	Typical (RSE)	% IIV (RSE)
R (release rate, FORM X)	0.883 (6)	11% (21)
Relative dose (fraction of nominal dose)	1 (FIX)	5% (18)
Form A on R	+15.4% (18)	
Form B on R	-15.9% (9)	
Form C on R	-36.6% (16)	
Form Q on R	-18.1% (11)	
Form Z on R	$\pm 0\%$	
ResErr (mg)	3.0 (3.5)	

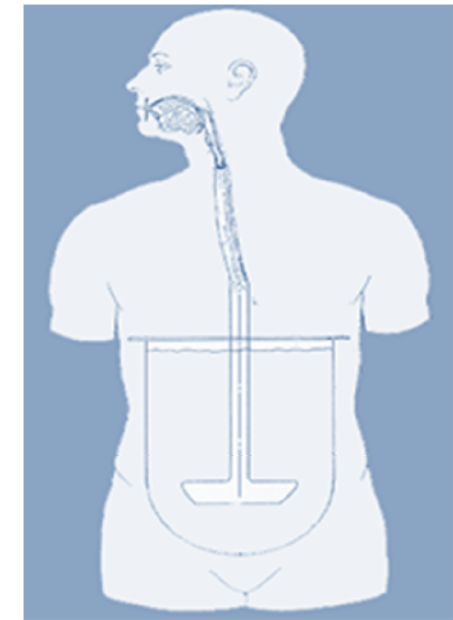
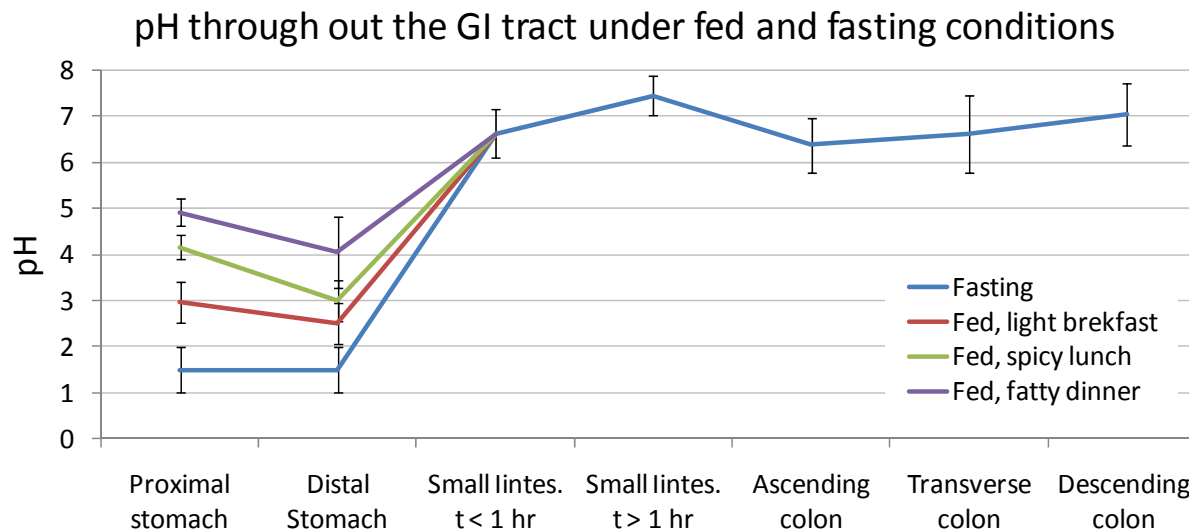




In vivo drug release model

Applied physiological prior knowledge:

- The MMM information about gastric location
- pH variability over the GI tract according to literature^[1,2]
- Ionic strength: 0.1 M (stomach/colon), 0.14 M (small intestine)^[3]



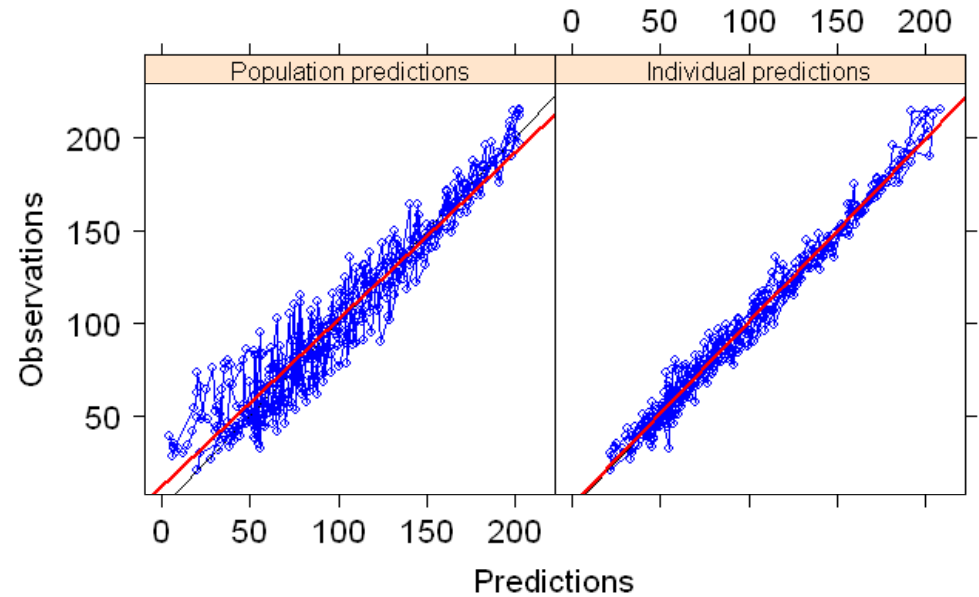
1. Evans DF et al. Measurement of gastrointestinal pH profiles in normal ambulant human subjects
2. Simonian HP et al. Regional postprandial differences in pH within the stomach and gastroesophageal Junction
3. Lindahl et al. Characterization of fluids from the stomach and proximal jejunum in men and women



In vivo drug release model

Estimation of the unknown

Parameter	Typical (RSE %)
Upper stomach (RPM)	93 (5.1)
Lower stomach (RPM)	129 (5.2)
Small intestine (RPM)	62 (3.2)
Colon (RPM)	44 (1.0)
Night effect on mixing (8 pm to 7 am)	-55% (6.1)
IOV Rel. dose (variability in fraction of nominal dose)	2.6% (120)

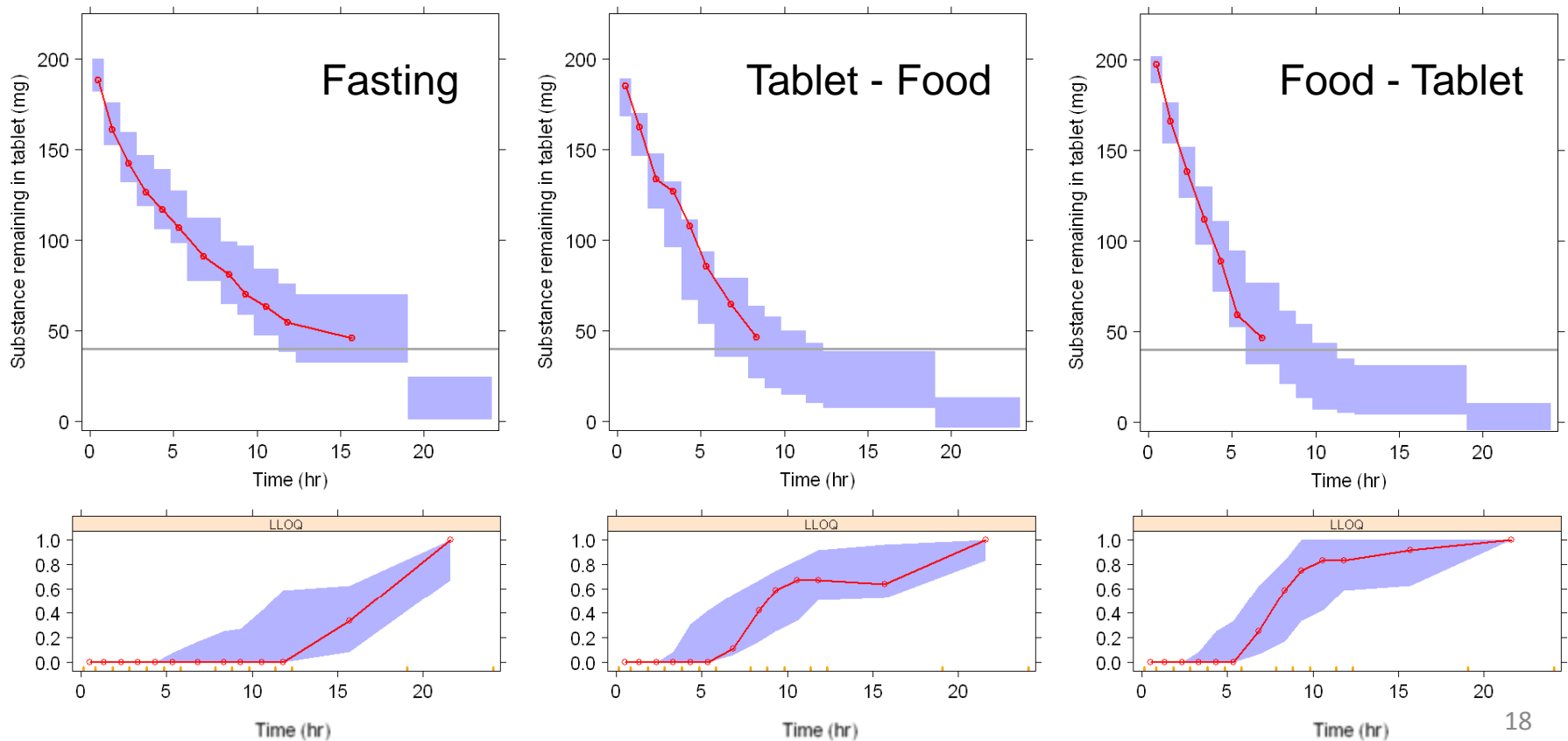


- Approximately in agreement with standard RPMs used to simulate stomach and intestinal environment.
- Significant night effect possibly related to lower GI motility during night. Uncertain estimate based on very limited information.
- Most observed variability explained by GI position and prior information about pH along the GI tract.



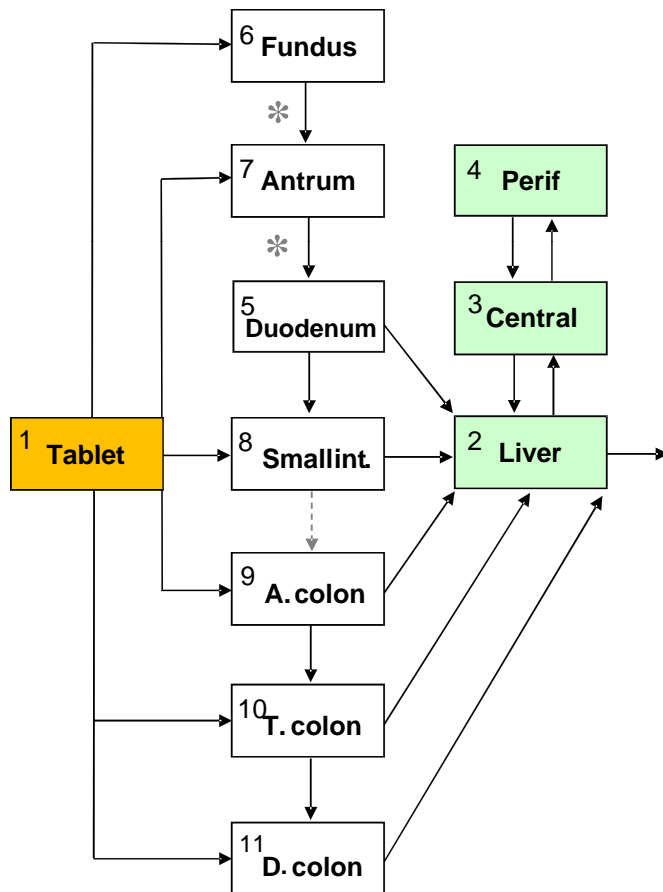
In vivo drug release model

- **Upper panel:** Substance remaining in tablet (mg) vs. time (hr)
- **Lower panel:** Fraction of observations below LLOQ vs. time (hr)
- Observed median (red line) and 95% CI for predicted median (blue)





PK model: *Structure and disposition*



- i.v. data well predicted with a two compartment model

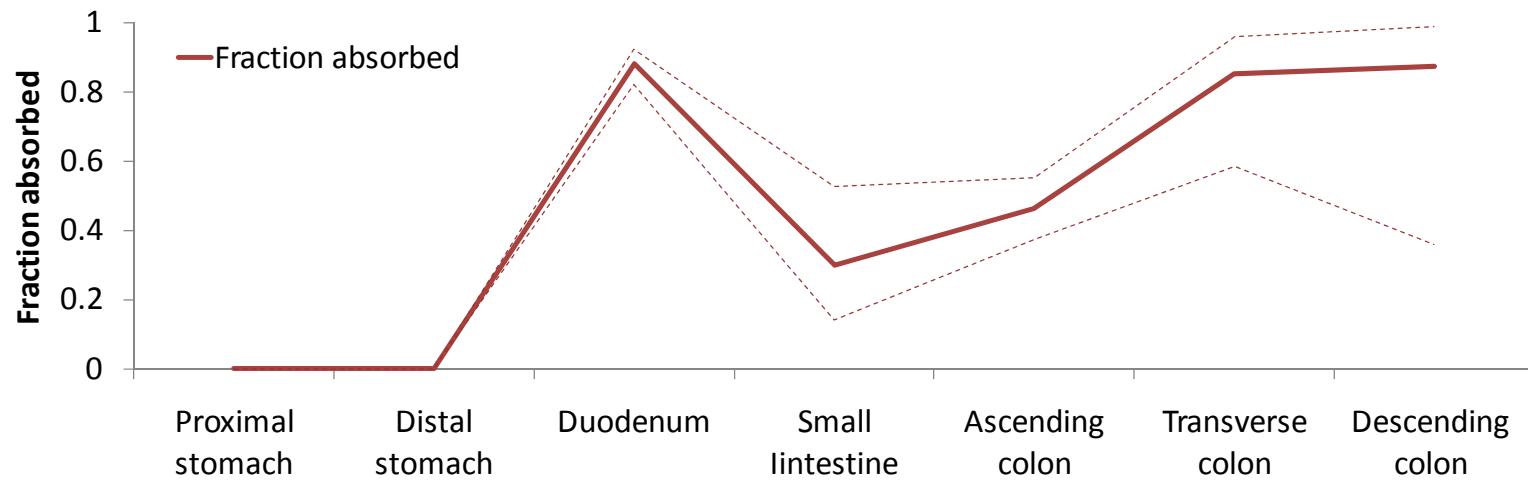
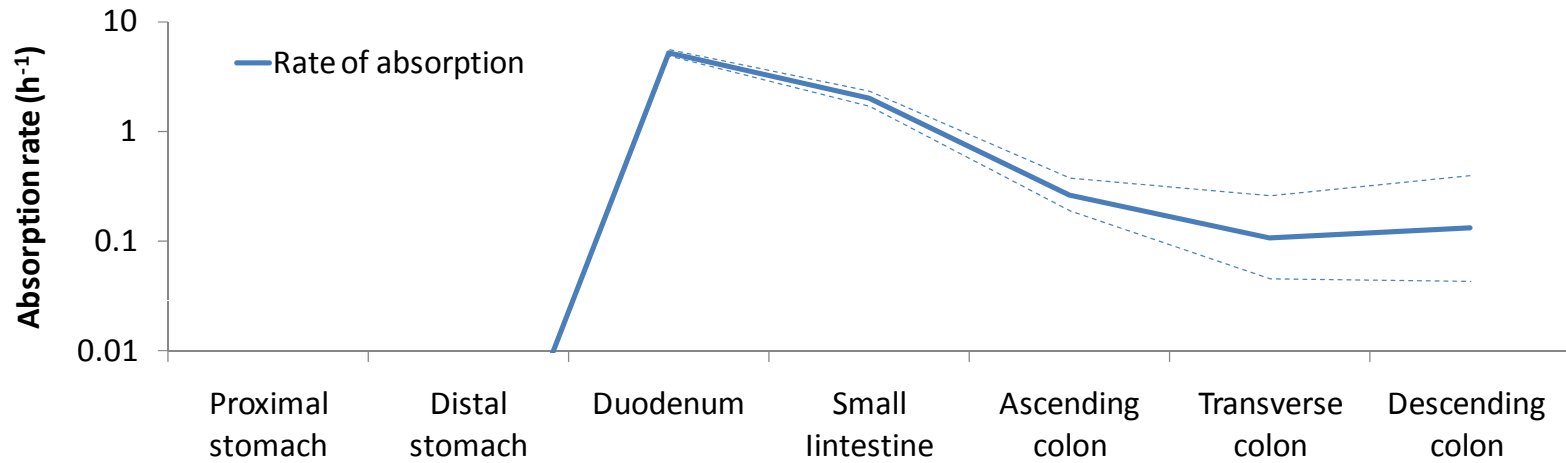
Disposition parameters	Typical	% IIV
E_H	0.17	19%
$V_{CENTRAL}$ (L)	6	7%
Q (L/hr)	20	12%
$V_{PERIPHERAL}$ (L)	10	26%

- Significant absorption from stomach ruled out
- Tablet passes the duodenum very fast
⇒ Approx. no drug release in duodenum
- Substance released in stomach to a large extent absorbed from duodenum



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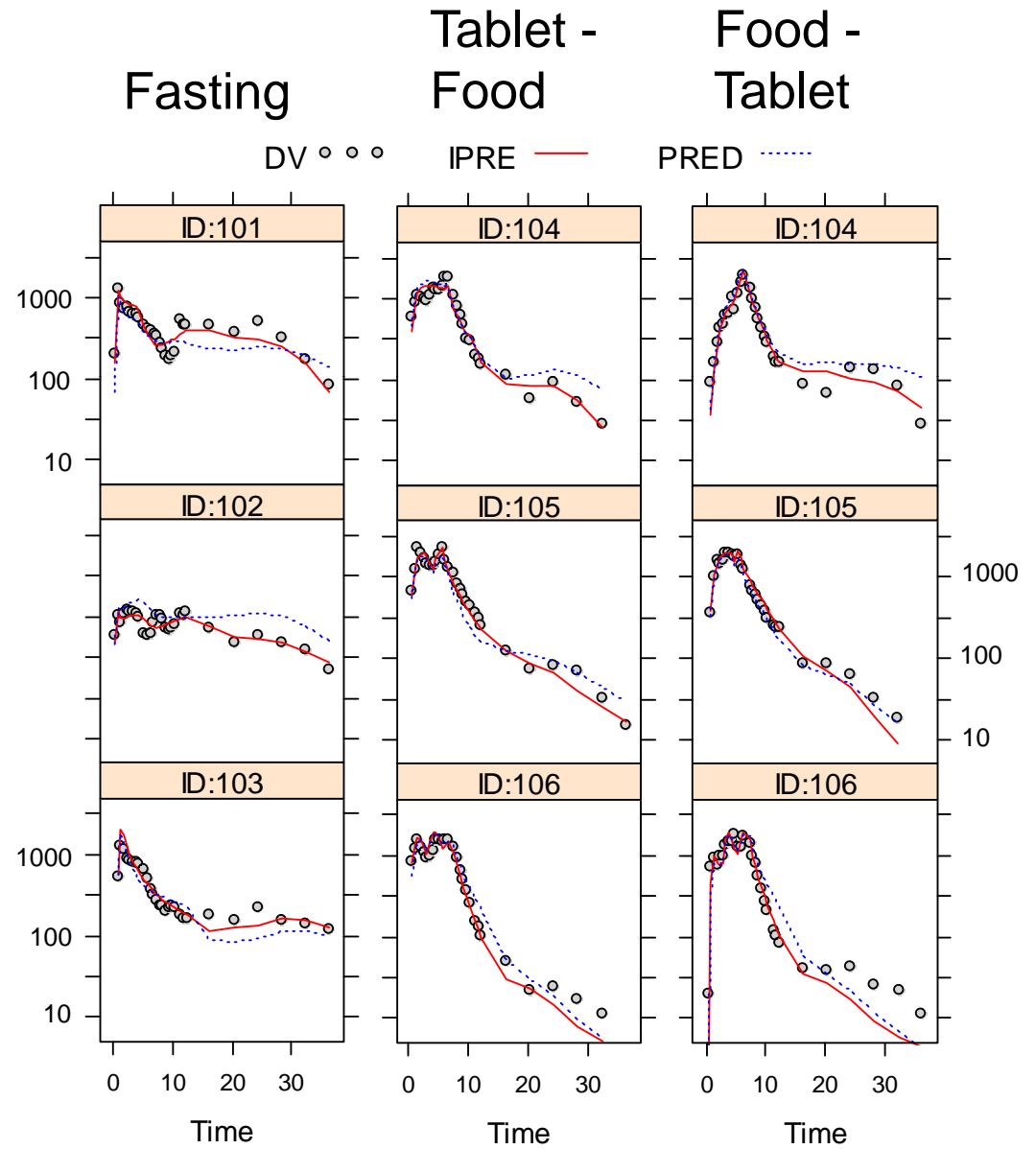
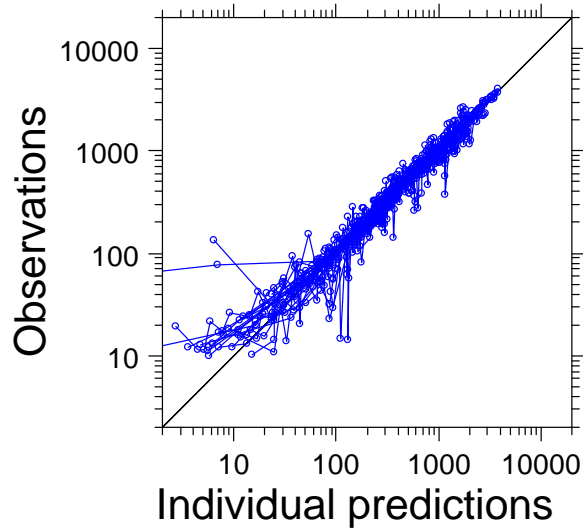
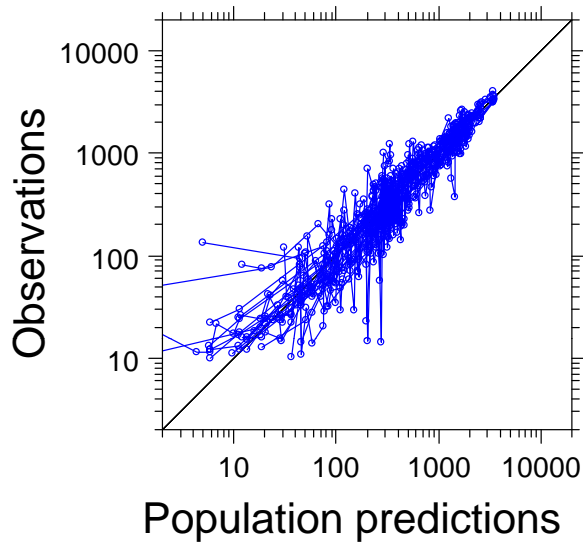
PK model: *Absorption and GI dist.*



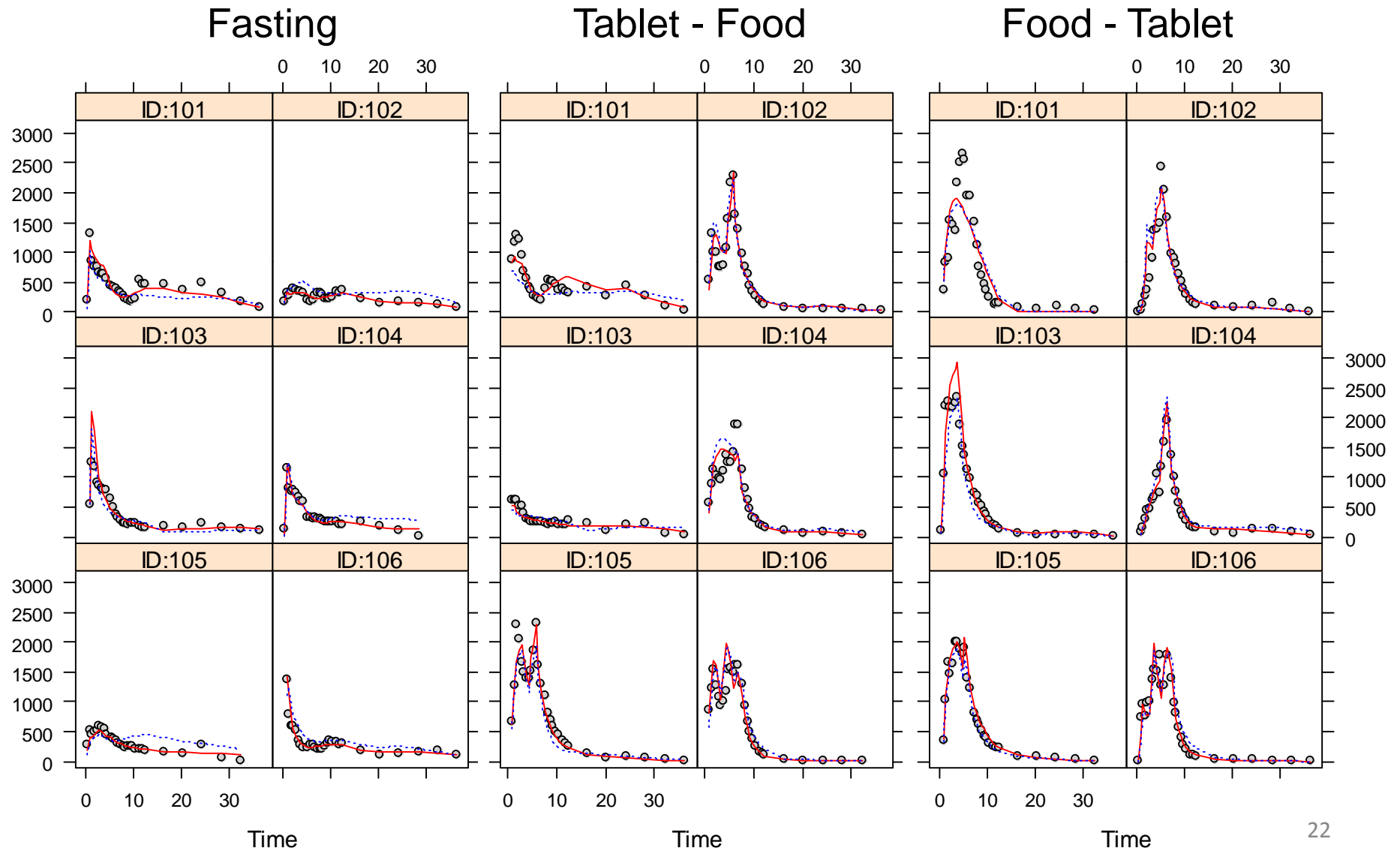


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PK model: *Model fit*



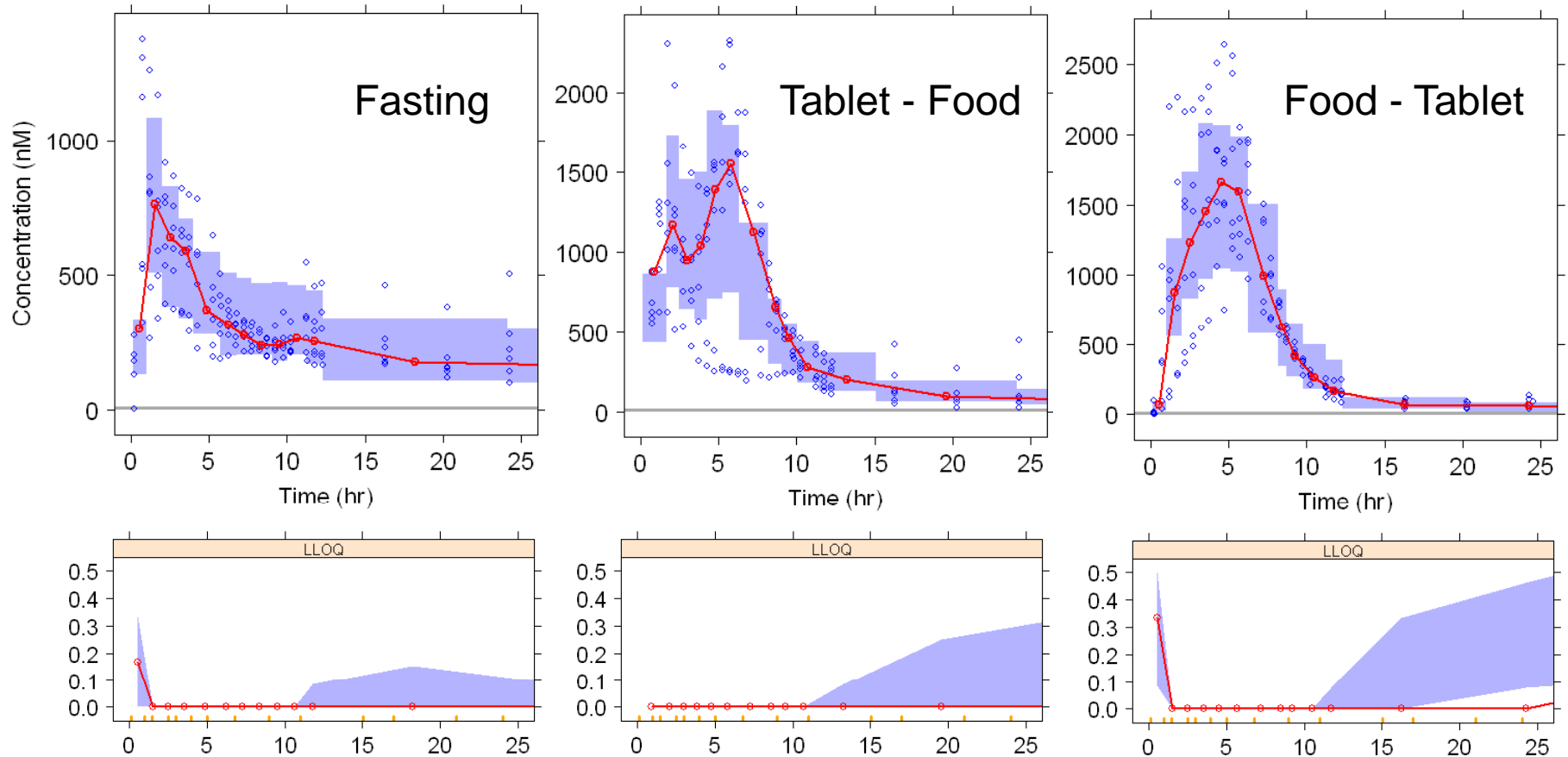
Individual Goodness of Fit





PK model: *VPCs*

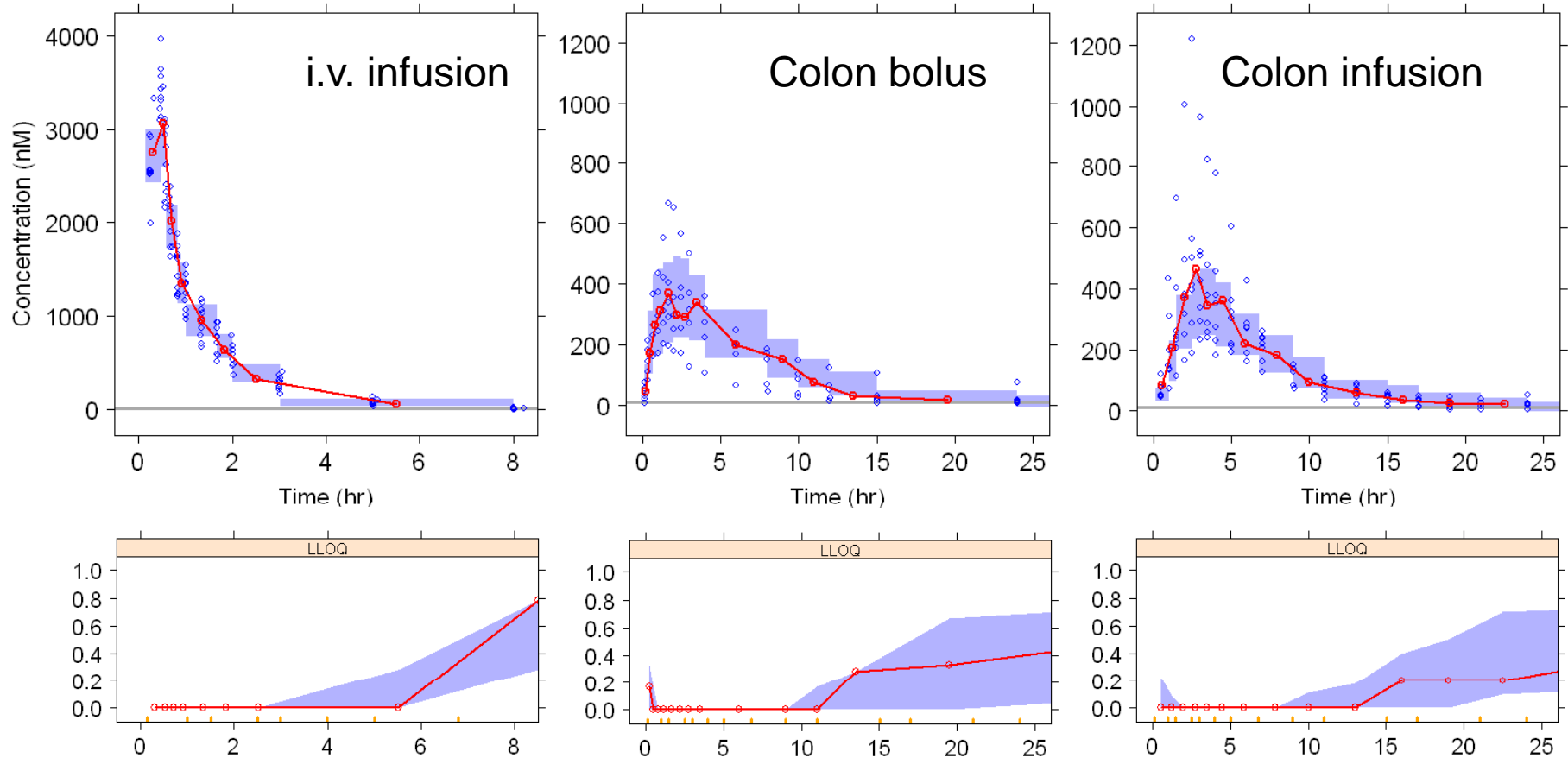
- Observed median plasma concentration / fraction BQL
- Model predicted 95% CI for median conc. / fraction BQL
- Observed plasma concentration samples





PK model: *VPCs*

- Observed median plasma concentration / fraction BQL
- Model predicted 95% CI for median conc. / fraction BQL
- Observed plasma concentration samples



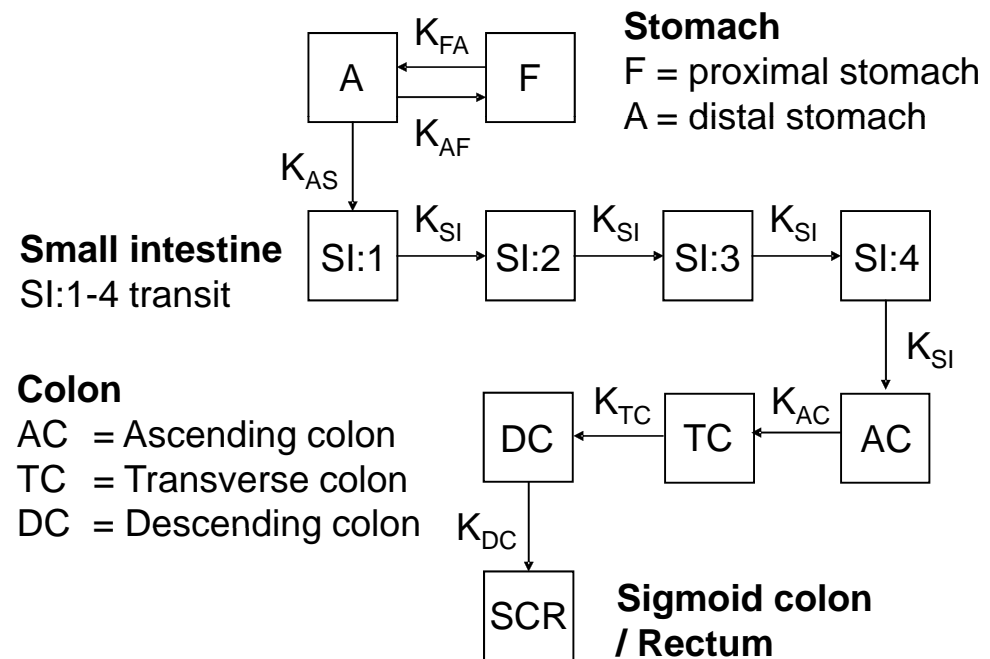


Tablet GI transit model

Estimates (min)

Parameter	Drug X
$MTT_{FA,FASTING}$	12
$MTT_{FA,FED}$	69
MTT_{AF}	262
$MTT_{AS,FASTING}$	16
$MTT_{AS,FED}$	232
MTT_{SI}	290
MTT_{AC}	327
MTT_{TC}	185
MTT_{DC}	240

Markov Model



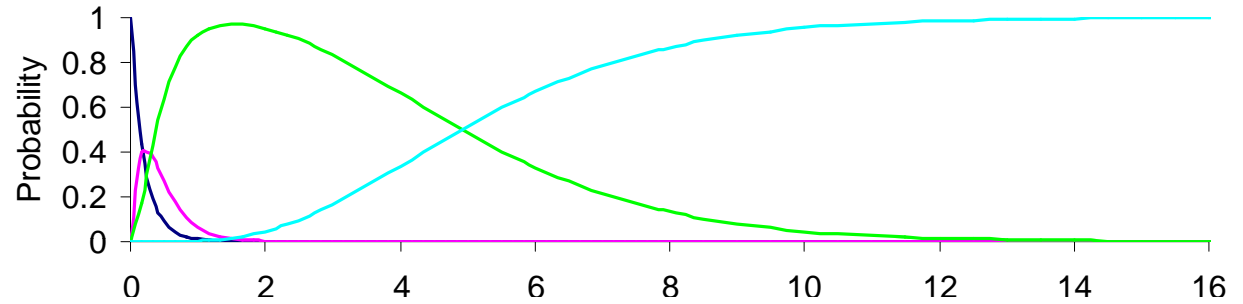


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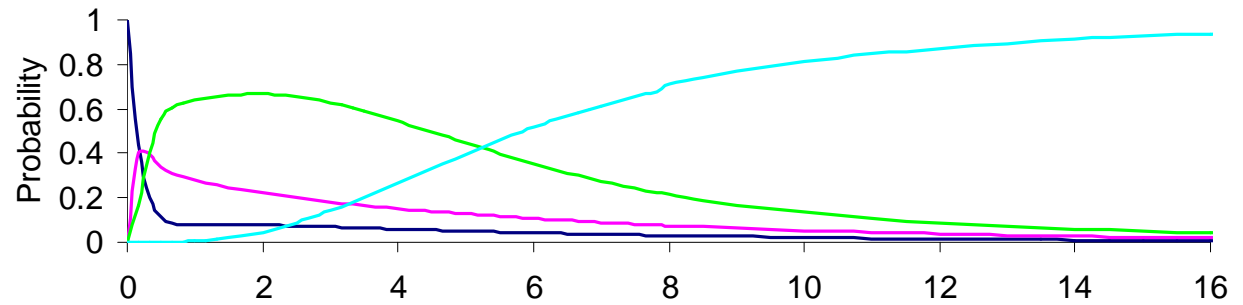
Probability of GI position

- Proximal stomach
- Distal stomach
- Small intestine
- Colon

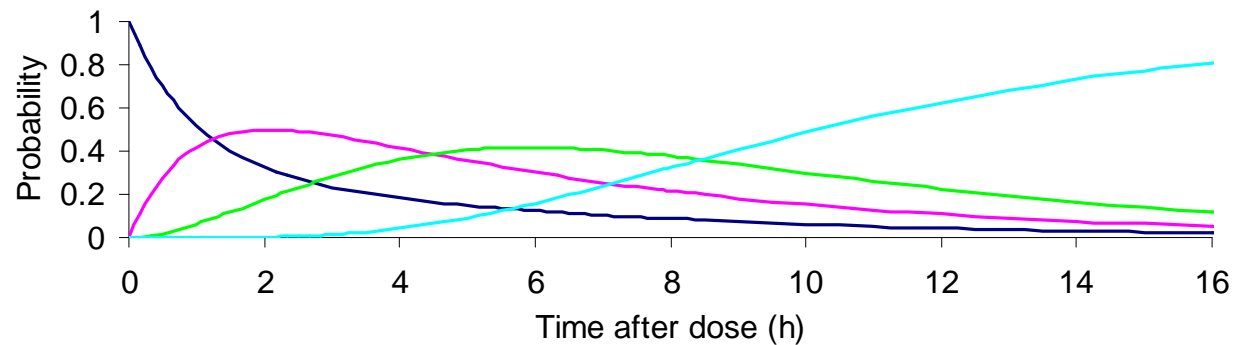
Fasting



Dose → Food

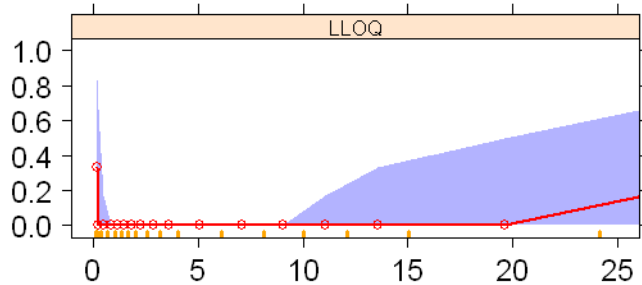
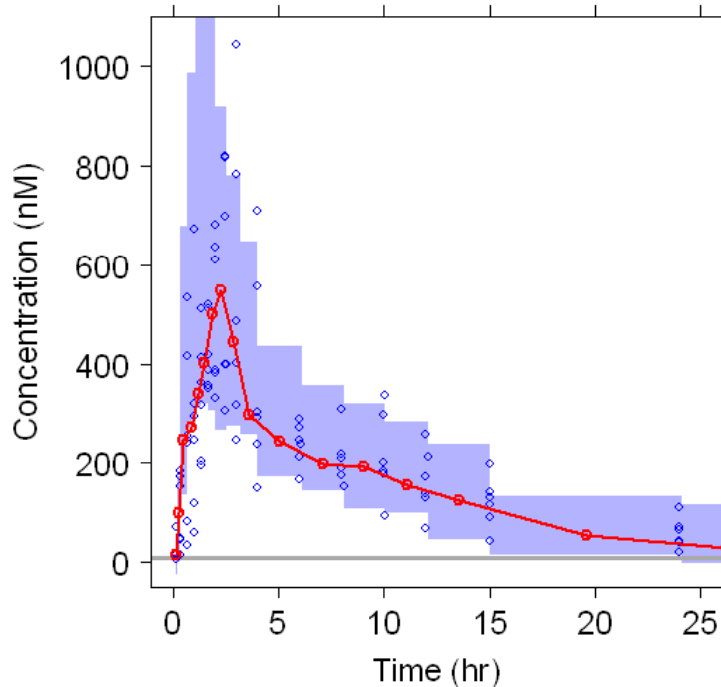


Food → Dose

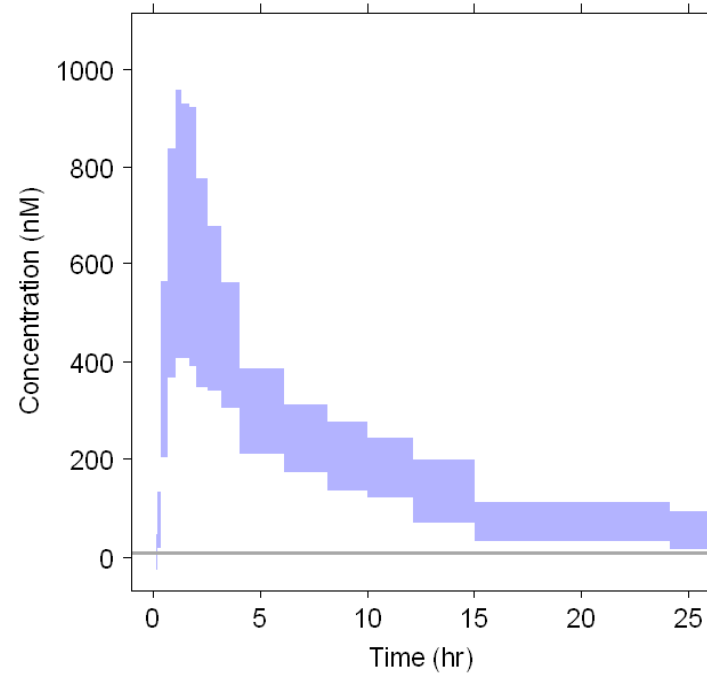




IVIVC: *Prediction of Formulation A*



If cohort included 12 subjects instead of 6

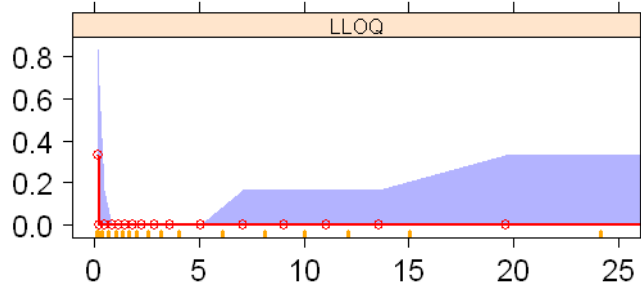
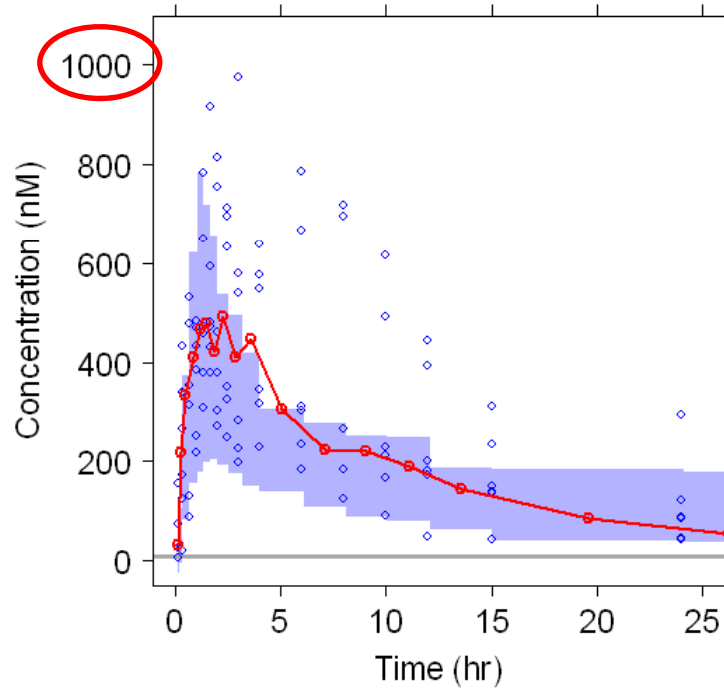




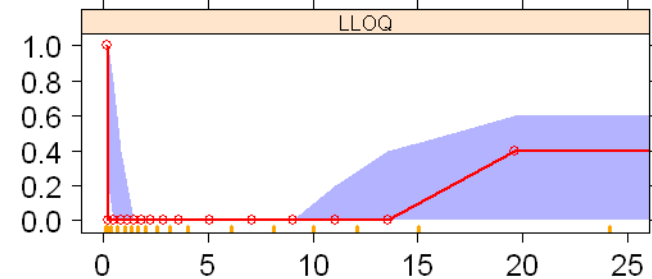
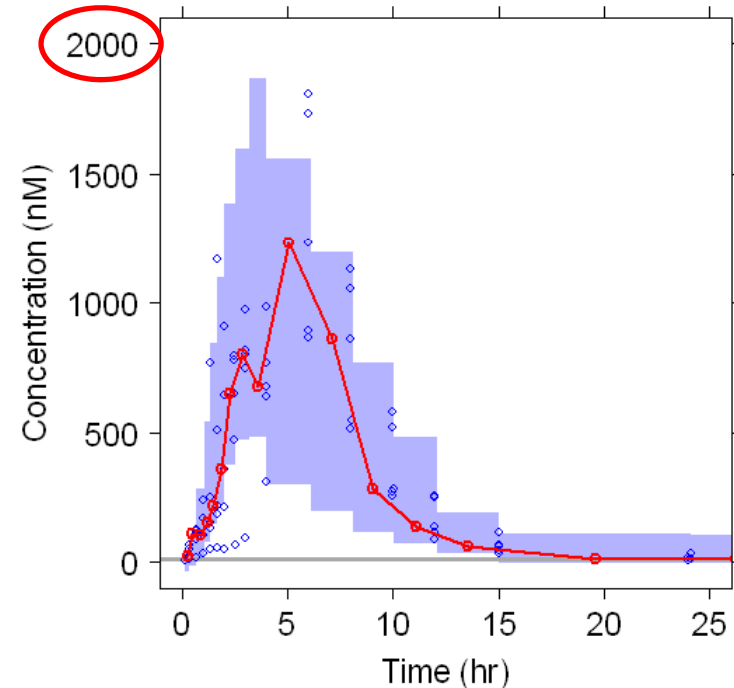
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IVIVC: *Prediction of Formulation B*

Fasting



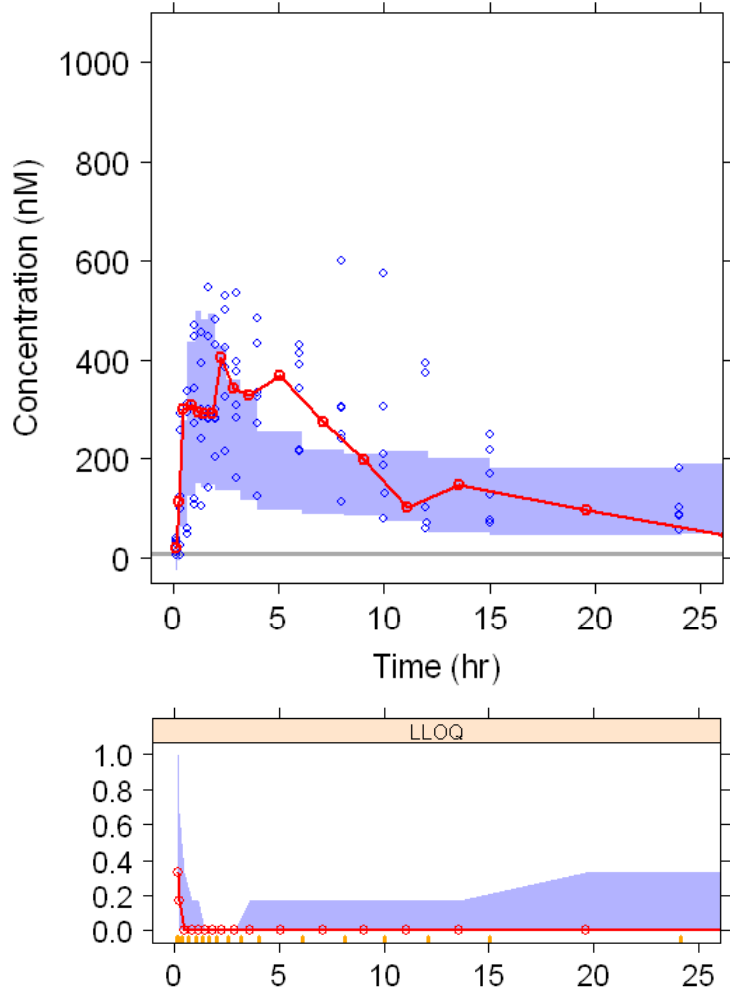
Fed





IVIVC: *Prediction of Formulation C*

Formulation C



Possible origin of the indicated model misspecification:

- Underestimated time in stomach
 - Lower stomach MTT than for felodipine
 - For formulation B and C there are 2 resp. 3 PK profiles that more resembles what was expected together with food (i.e. after longer stomach residence)
- Biased estimate of FA in small intestine and/or A. Colon (too low)
- Unexpected drug release behaviour for formulation C



Discussion

- A more robust model for tablet transit
 - Meta analysis across several MMM studies etc.
- Better prior on drug dissolution (now part of absorption rate)
 - Models and biological priors available for instance in SimCyp
- Estimation of disposition parameters for subjects in validation dataset and simulation based could reduce uncertainty (CI ↓)
 - Estimation of disposition parameters based on data from administration of oral solution or i.v. Dose



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Conclusions

- The suggested way to establish IVIVC for extended release formulations shows promising preliminary results
- To demonstrate a truly convincing case of IVIVC predictions of a larger dataset is needed



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Thanks to

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