UPPSALA UNIVERSITET

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

Martin Bergstrand[1], Erik Söderlind[2], Ulf Eriksson[2], Werner Weitschies[3], Mats O. Karlsson[1]

[1] *Department of Pharmaceutical Biosciences, Uppsala, Sweden.*

[2] *AstraZeneca R&D, Mölndal, Sweden.*

[3] *Institute of Pharmacy, University of Greifswald, Germany.*

UPPSALA UNIVERSITET

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

- Why
  - Surrogate for bioequivalence studies "Biowaiver"
  - Product quality demands
- Level A IVIVC (FDA)
  - *"The model should predict the entire in vivo time course from the in vitro data"*

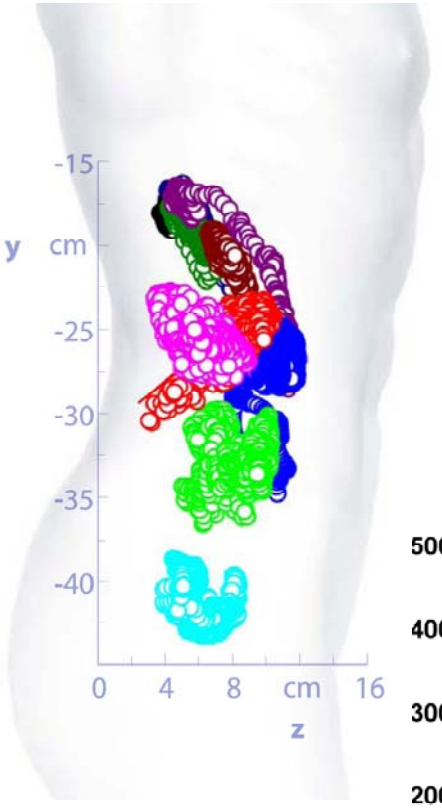
UPPSALA UNIVERSITET

Aim

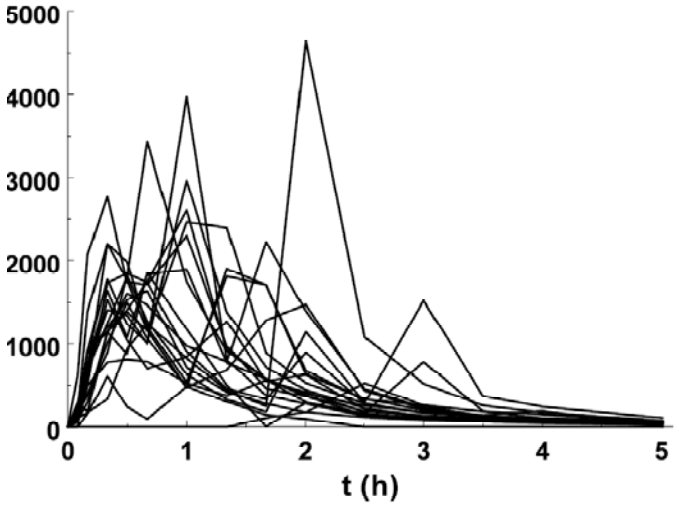
To outline and test a modelling framework capable of incorporating relevant clinical data and *in vitro* data to establish IVIVC by prospective simulations

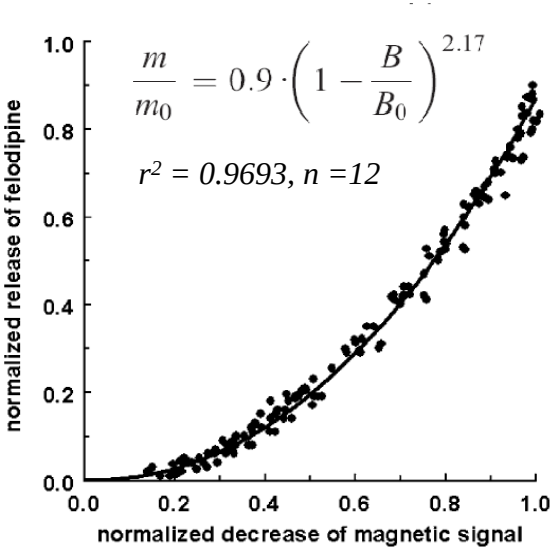
UPPSALA UNIVERSITET

Magnetic Marker Monitoring (MMM)



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





UPPSALA UNIVERSITET

nature publishing group ARTICLES

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

M Bergstrand[1], E Söderlind[2], W Weitschies[3] and MO Karlsson[1]

[1]Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; [2]Product Development, AstraZeneca R&D, Mölndal, Sweden; [3]Institute of Pharmacy, University of Greifswald, Greifswald, Germany. Correspondence: M Bergstrand (martin.bergstrand@farmbio.uu.se)

Received 18 November 2008; accepted 25 February 2009; advance online publication 22 April 2009. doi:10.1038/clpt.2009.43

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.

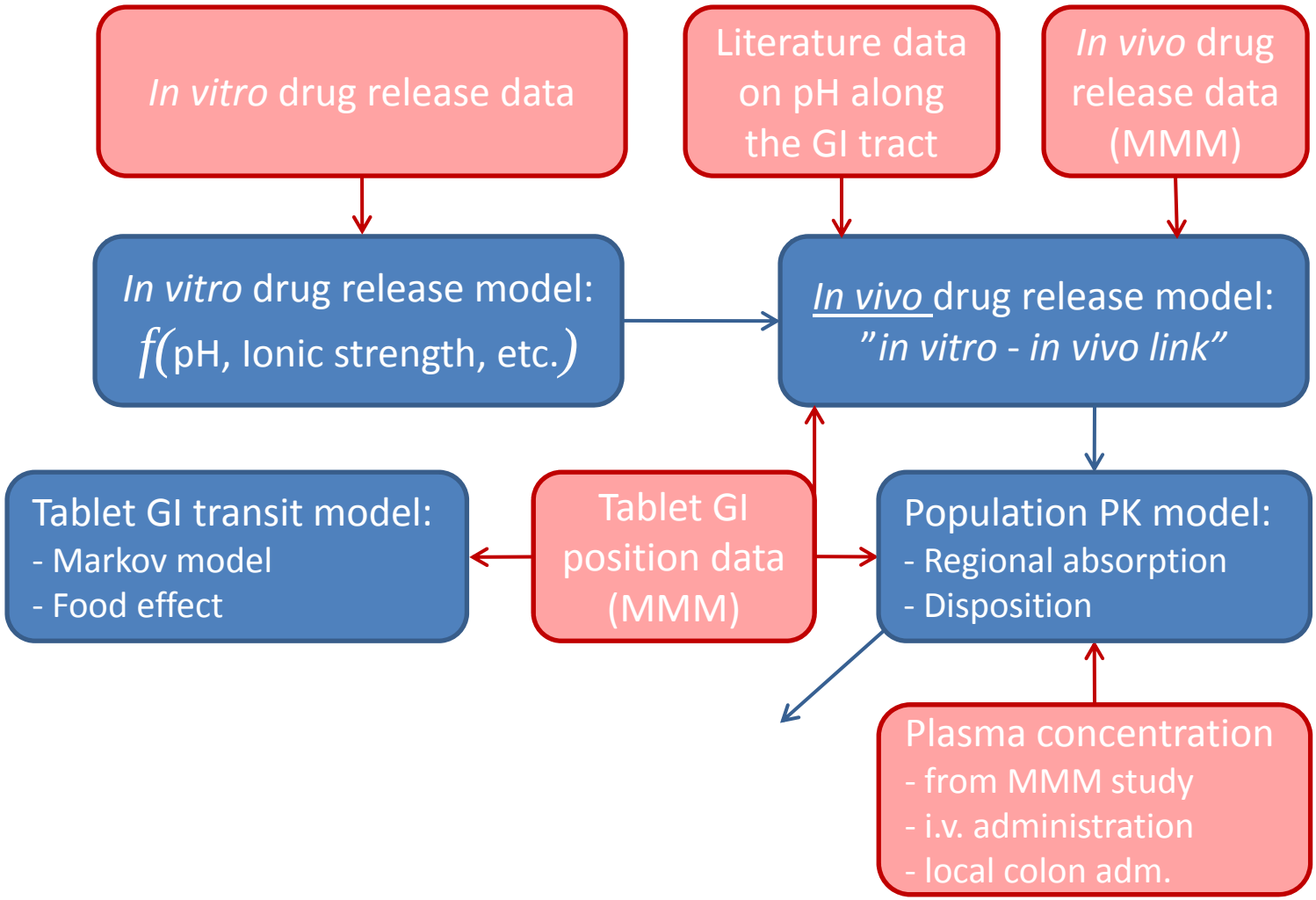
UPPSALA UNIVERSITET

Principal work flow

Observed data

Models

Simulated data



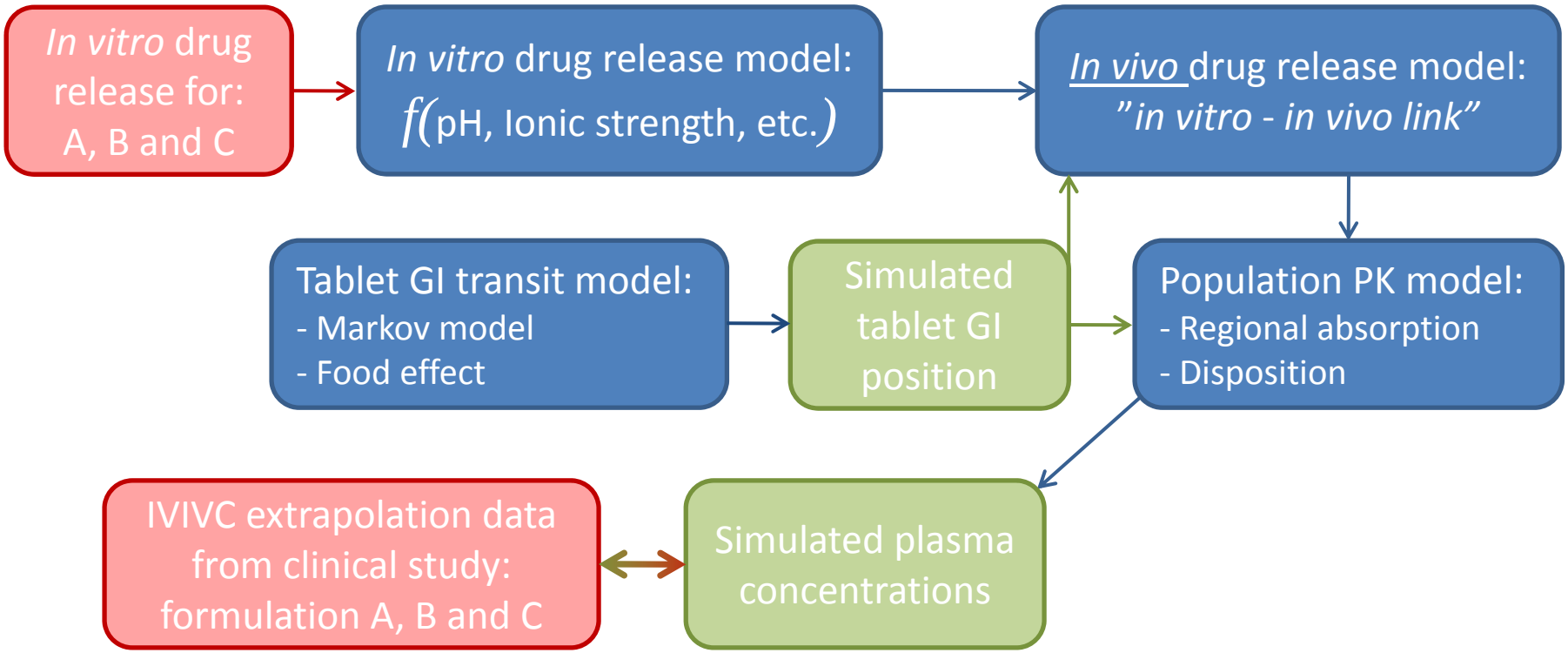
UPPSALA UNIVERSITET

Principal work flow

Observed data

Models

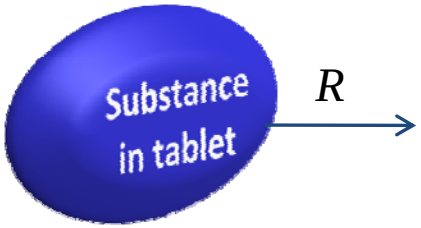
Simulated data

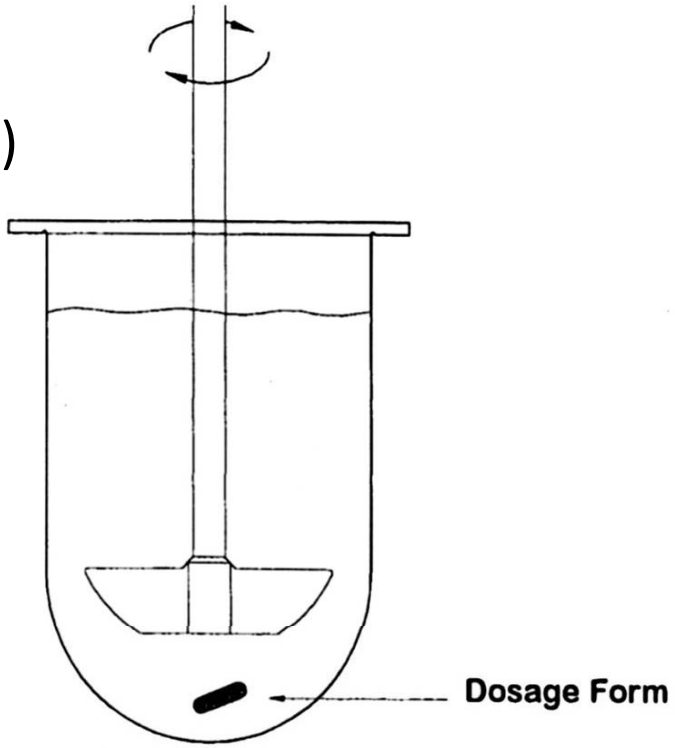


UPPSALA UNIVERSITET

In vitro drug release model

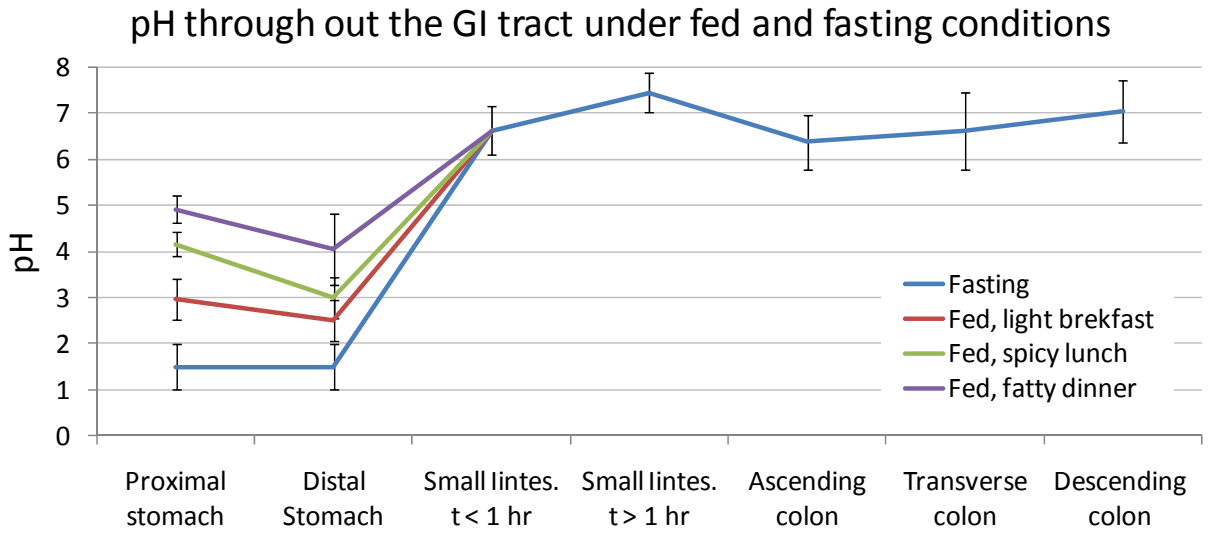
- Release rate (R) expressed as a function of:
  - Tablet characteristics
    e.g. size, API (fraction active ingredient)
  - pH
  - Ionic strength
  - RPM (rotations per minute)

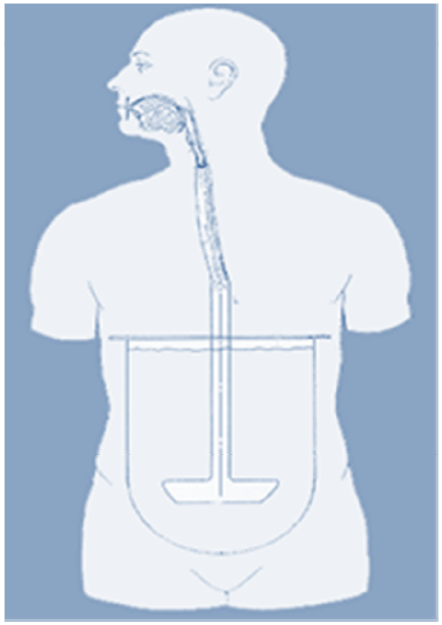




In vivo drug release model
Applied physiological prior knowledge:

- 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]



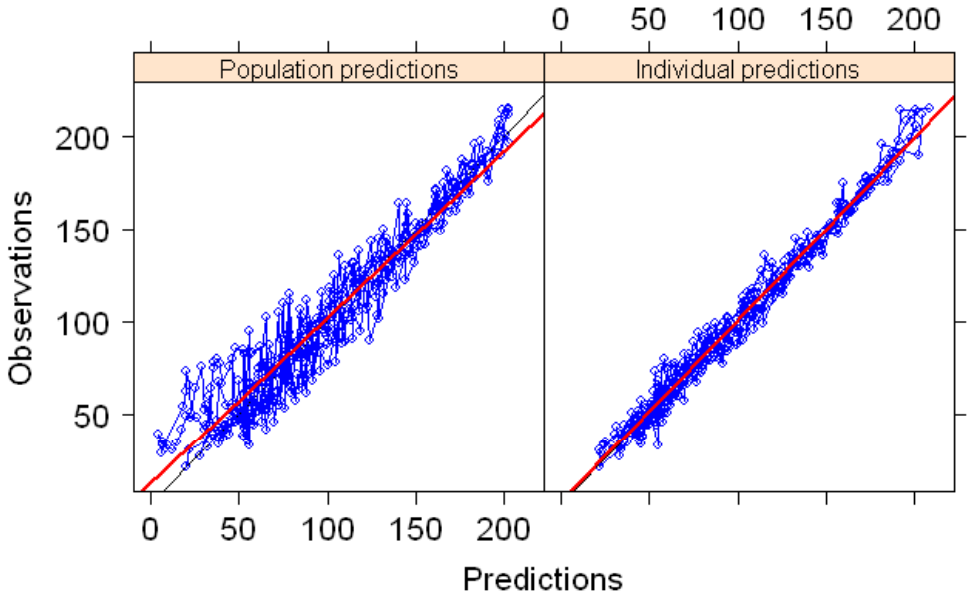


1. Evans DF et al. Measurement of gastrointestinal pH profiles in normal ambulant human subjects
2. Simonian HP et al. Regional postprandial differences in pH within the stomach and gastroesophageal Junction
3. Lindahl et al. Characterization of fluids from the stomach and proximal jejunum in men and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

UPPSALA UNIVERSITET

In vivo drug release model
Estimation of the unknown

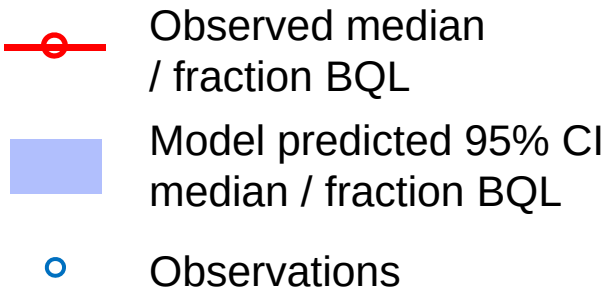
Parameter	Typical (RSE %)
Upper stomach (RPM)	93 (5.1)
Lower stomach (RPM)	129 (5.2)
Small intestine (RPM)	62 (3.2)
Colon (RPM)	44 (1.0)
Night effect on "RPM" (8 pm to 7 am)	-55% (6.1)
Dose variability (variability in fraction of nominal dose)	2.6% (120)



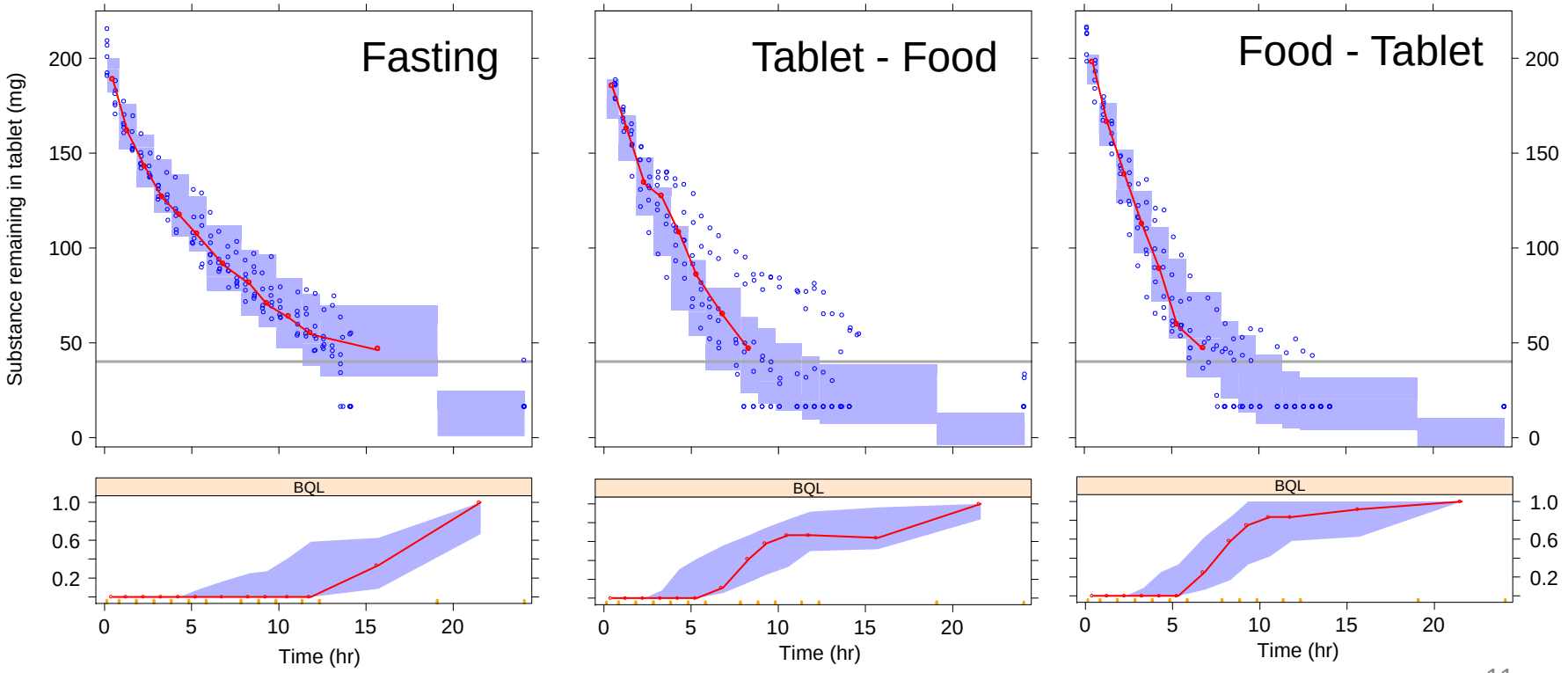
- Approximately in agreement with standard RPMs used to simulate stomach and intestinal environment.
- Significant night effect possibly related to lower GI motility during night.

UPPSALA UNIVERSITET

In vivo drug release

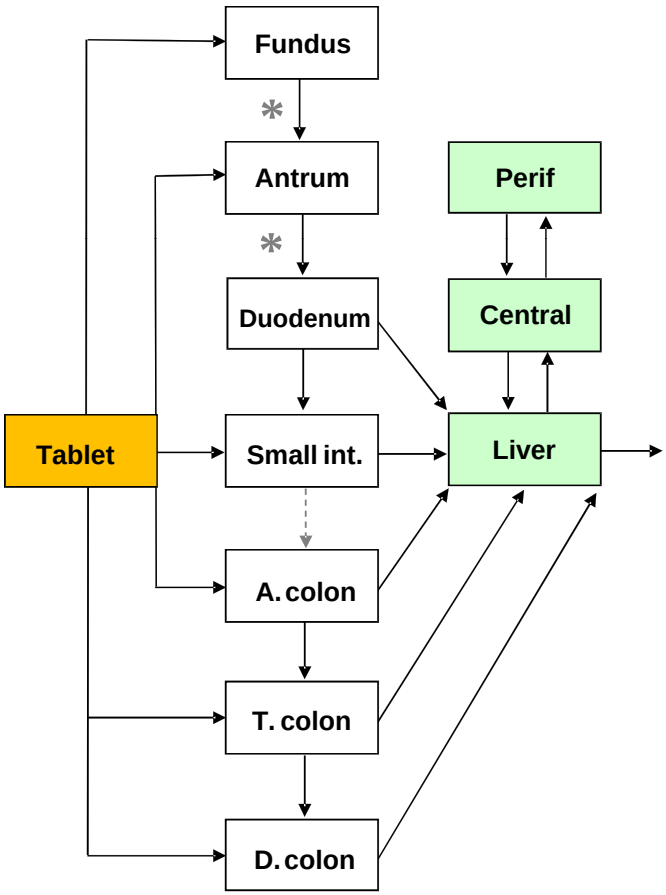


- ***Upper panel:*** Substance remaining in tablet (mg) vs. time (hr)
- ***Lower panel:*** Fraction of observations <40 mg vs. time (hr)



UPPSALA UNIVERSITET

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%

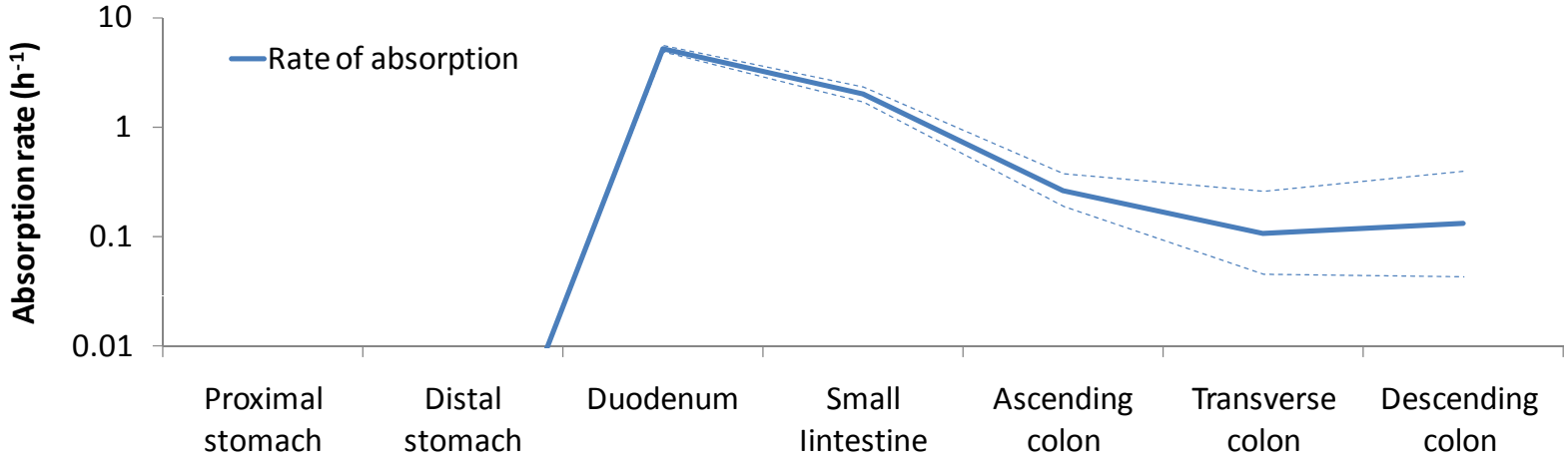
- Absorption from stomach ruled out
- Tablet passes the duodenum very fast

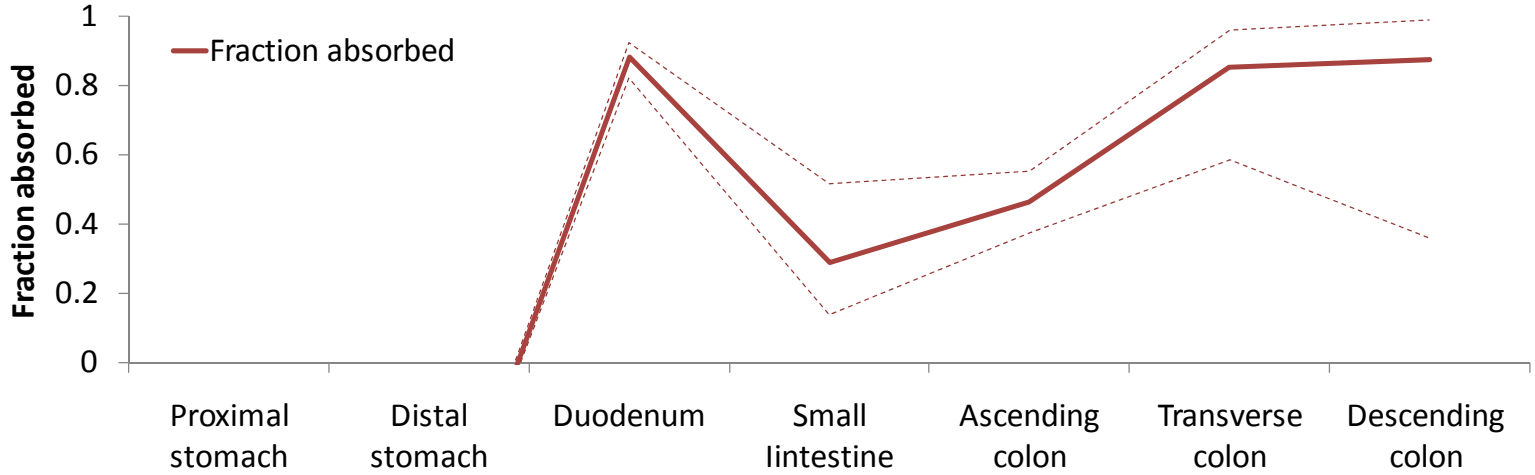
$\Rightarrow$ Approx. no drug release in duodenum

- Substance released in stomach to a large extent absorbed from duodenum

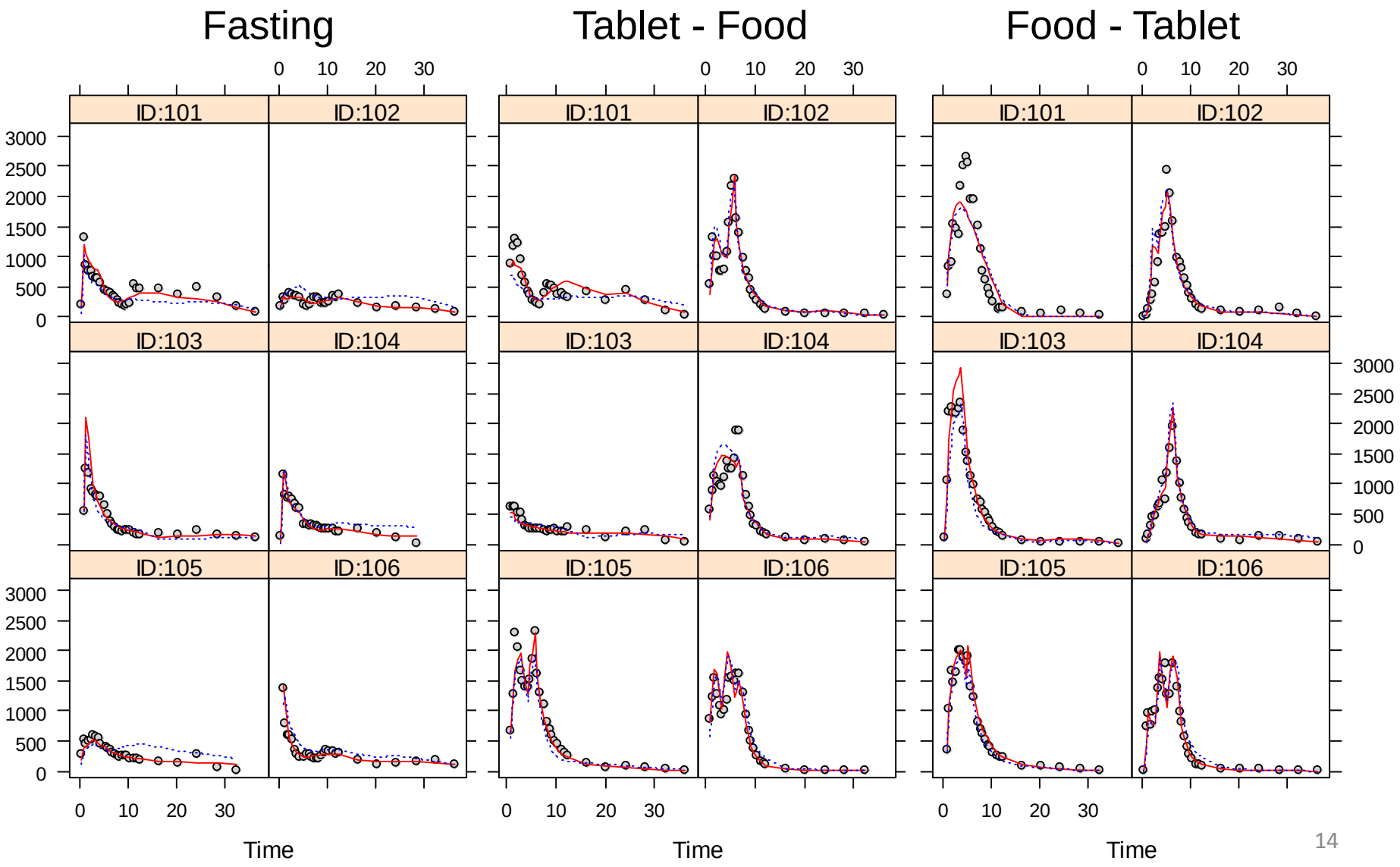
UPPSALA UNIVERSITET

PK model: *Rate & Extent of absorption along the GI tract* *(mean, 90% prediction interval)*





Individual Goodness of Fit



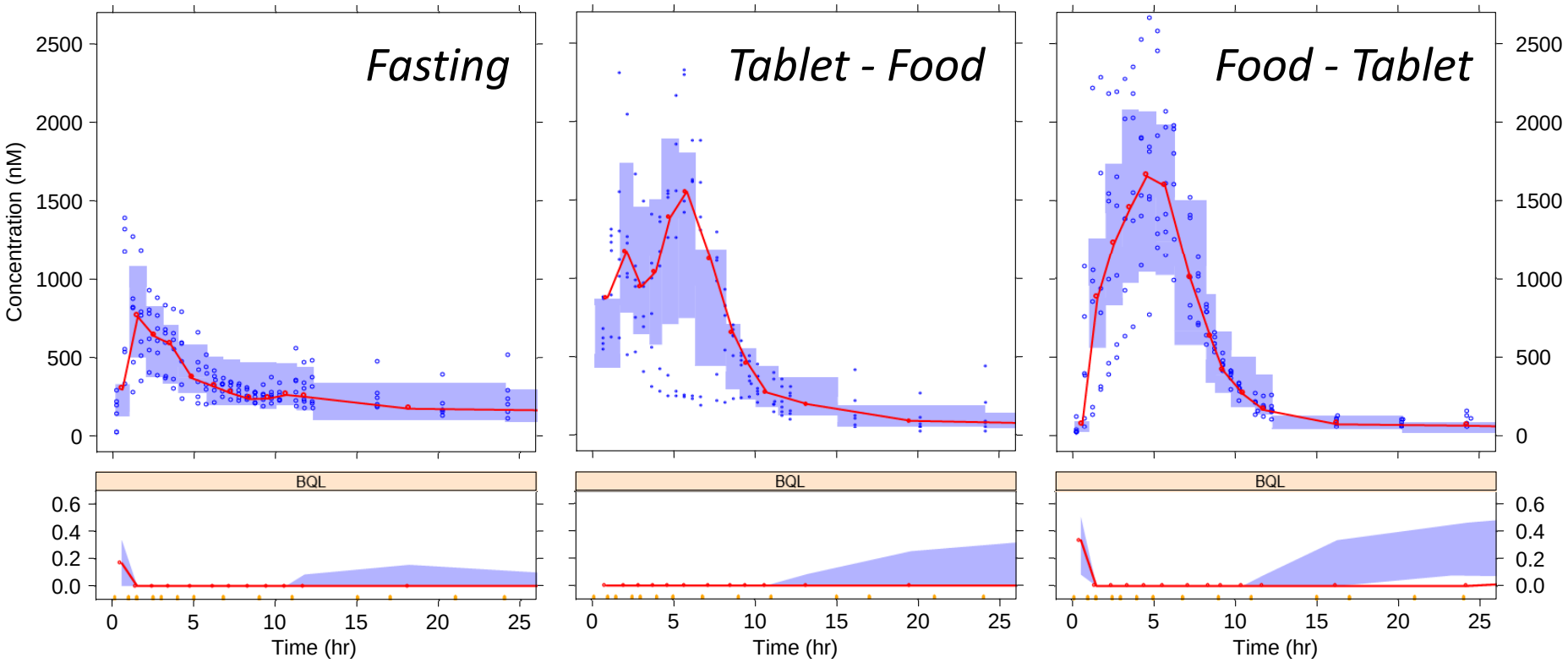
UPPSALA UNIVERSITET

PK model: *VPCs*

Observed median plasma concentration / fraction BQL

Model predicted 95% CI for median conc. / fraction BQL

Observed plasma concentration samples



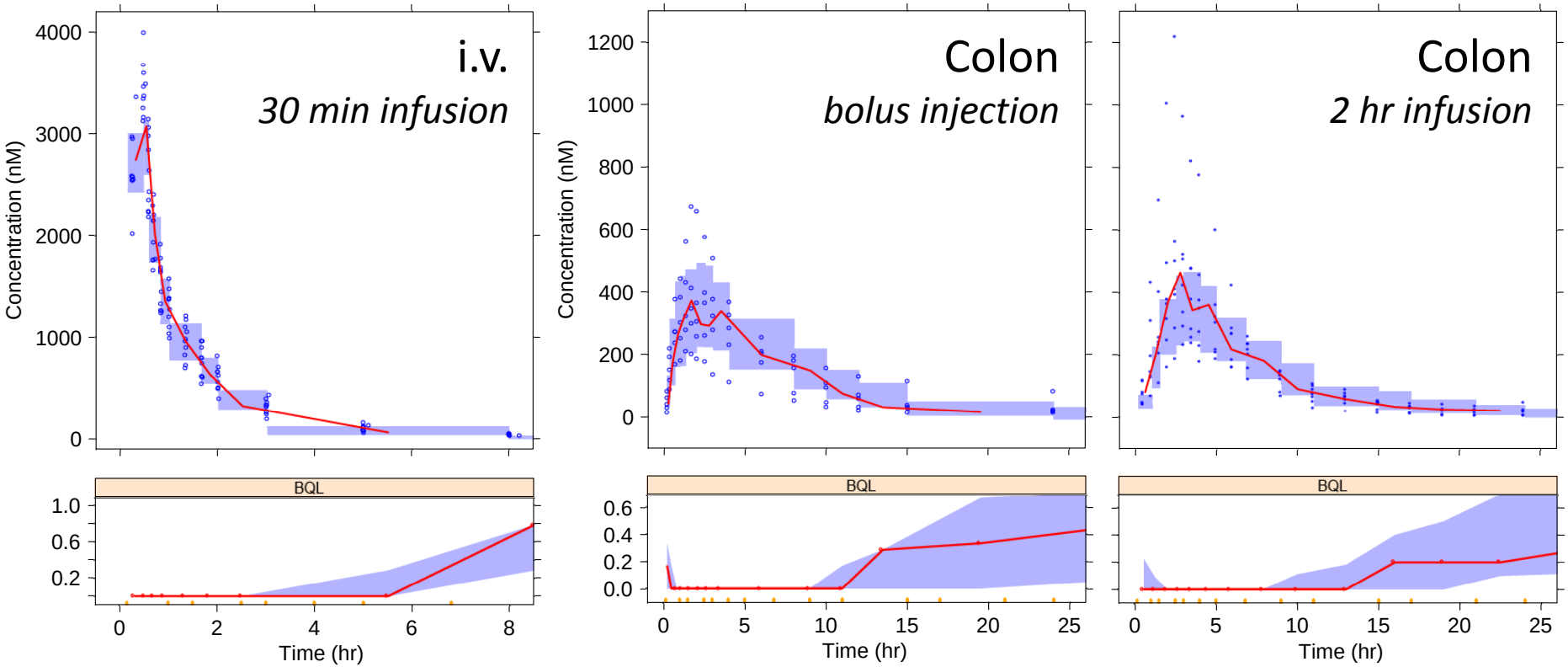
UPPSALA UNIVERSITET

PK model: *VPCs*

Observed median plasma concentration / fraction BQL

Model predicted 95% CI for median conc. / fraction BQL

Observed plasma concentration samples



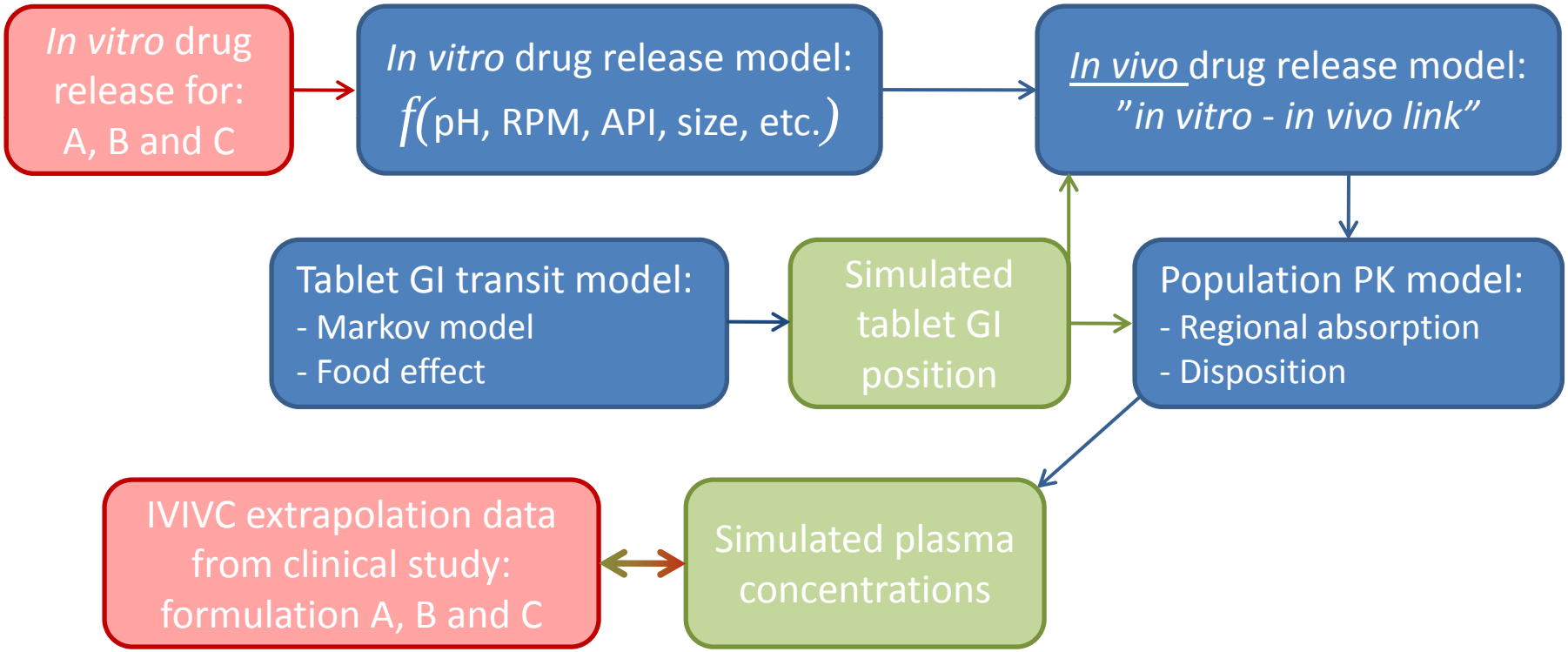
UPPSALA UNIVERSITET

Principal work flow

Observed data

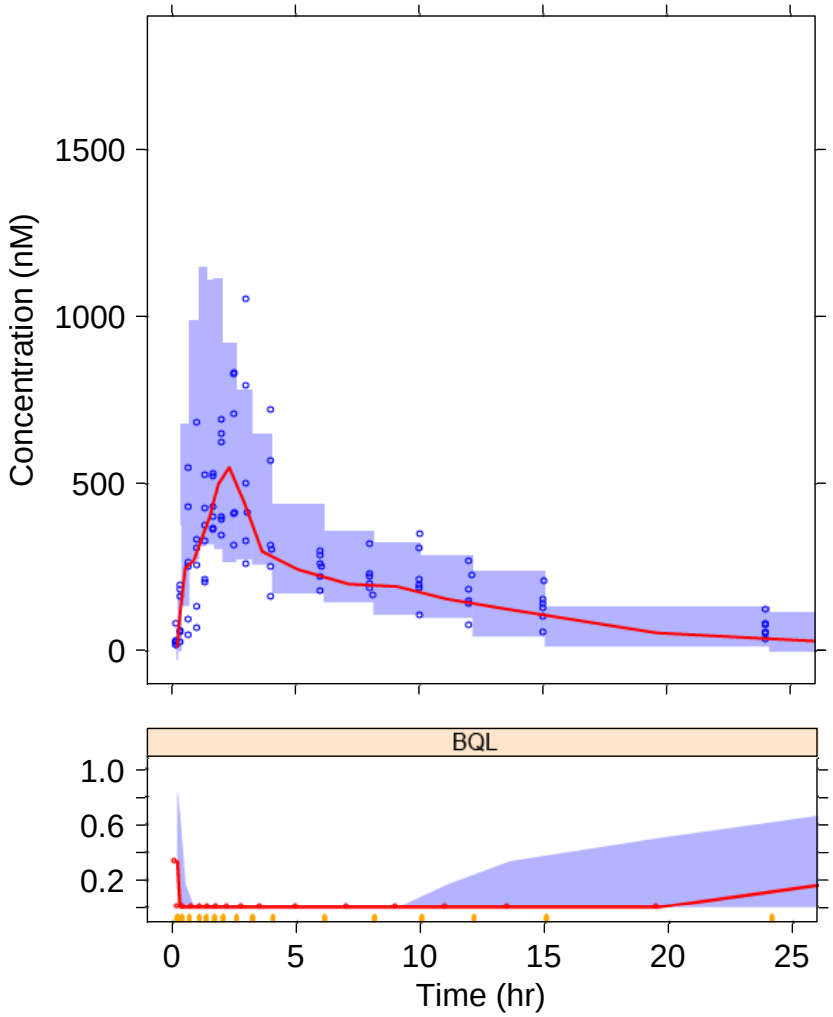
Models

Simulated data



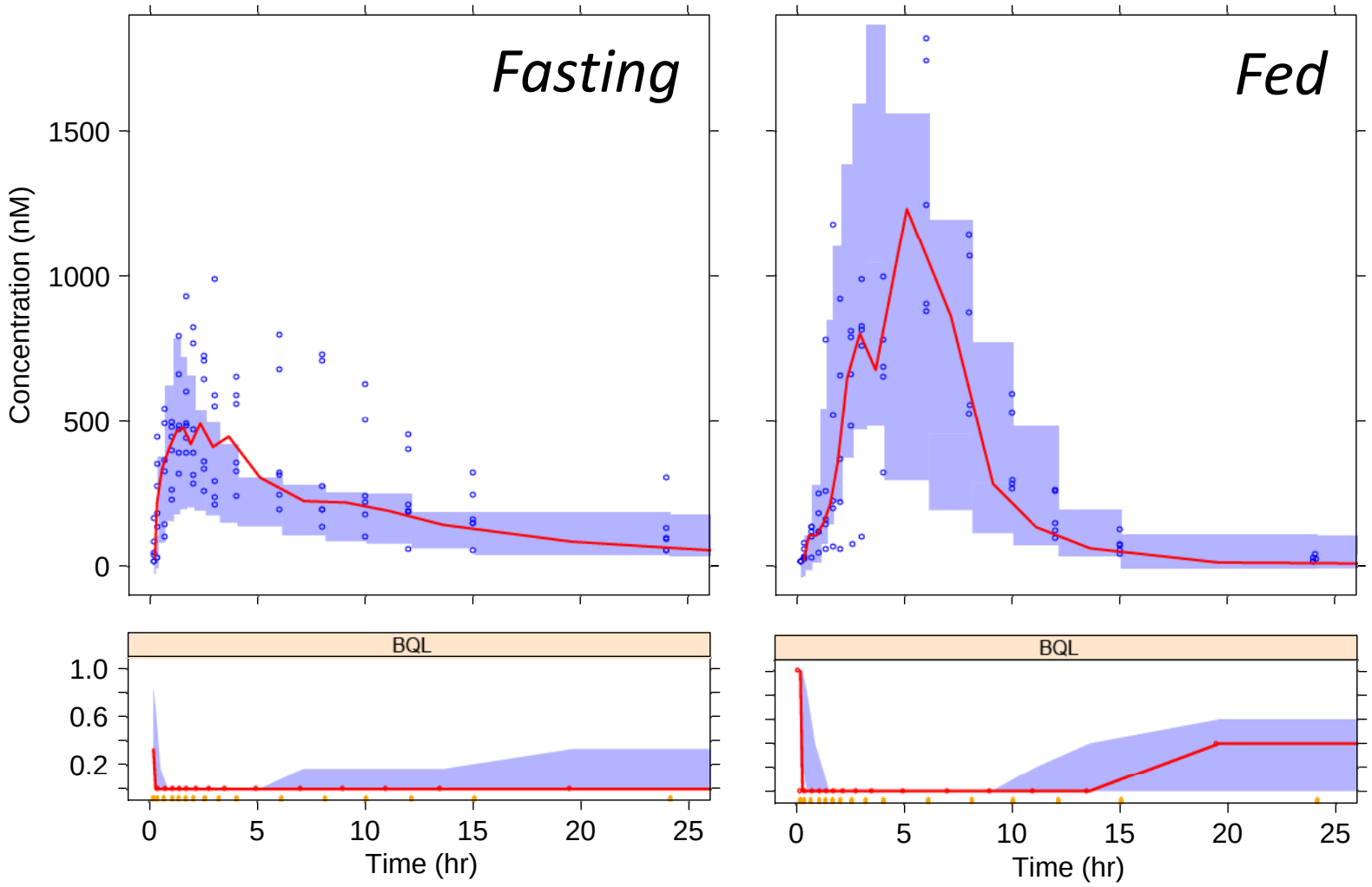
UPPSALA UNIVERSITET

IVIVC: *Prediction of Formulation A*



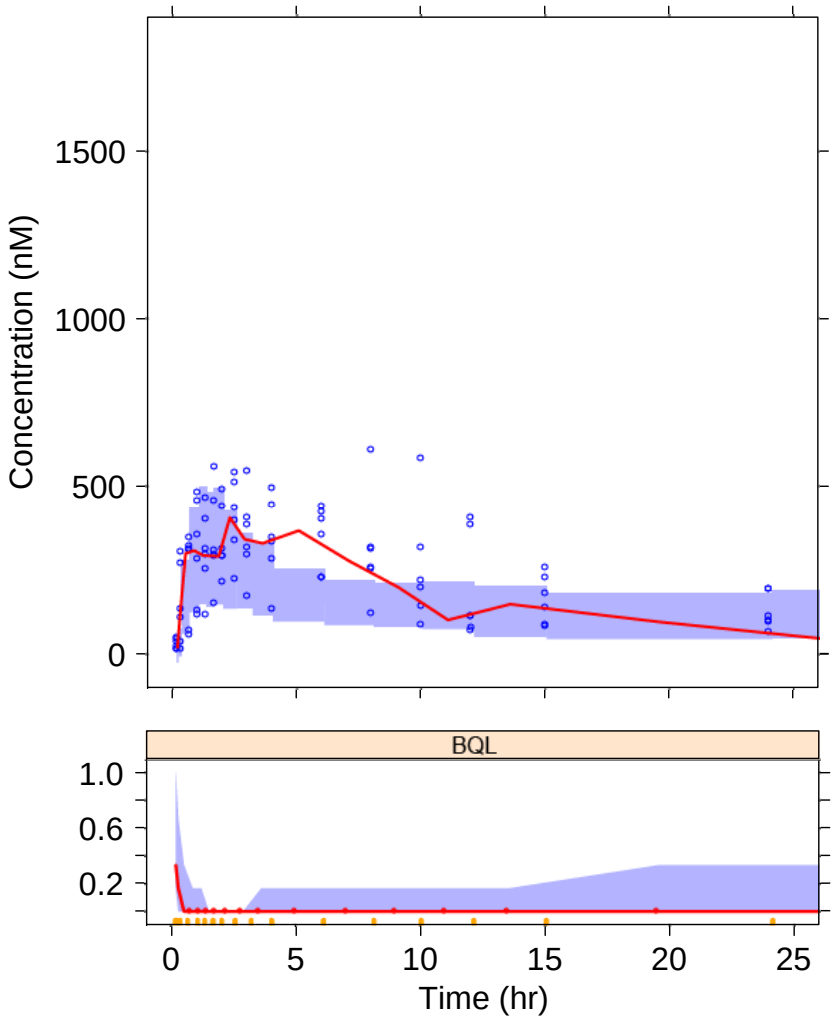
UPPSALA UNIVERSITET

IVIVC: *Prediction of Formulation B*



UPPSALA UNIVERSITET

IVIVC: *Prediction of Formulation C*



Possible origin of the indicated model misspecification:

- Underestimated time in stomach
  - 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

UPPSALA UNIVERSITET

Conclusions

- Complex absorption properties giving rise to erratic and highly variable plasma concentration profiles was successfully characterized with a semi-mechanistic population PK model
- Prospective simulations to establish IVIVC resulted in overall encouraging results with only a minor indication of under predicted concentrations for formulation C

UPPSALA UNIVERSITET

Thanks to

- **Colleagues for valuable input**
- **Sponsor:** AstraZeneca
- **All of You for listening!**