Modelling a complex input process in a population pharmacokinetic analysis:

example of mavoglurant oral absorption in healthy subjects

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Mavoglurant

- **Mavoglurant** (MVG) is a structurally novel **antagonist at the metabotropic glutamate receptor 5**, currently under clinical development at Novartis Pharma AG for the treatment of CNS diseases.

- An **oral immediate-release** (IR) **formulation** was initially used in the Phase I clinical studies:
  - Most of the **adverse events** (*e.g.* dizziness, fatigue, hallucination *etc.*) were related to **peak plasma concentrations**

- An **oral modified-release** (MR) **formulation** was developed in order to **reduce peak concentrations** without substantial change in the systemic exposure.

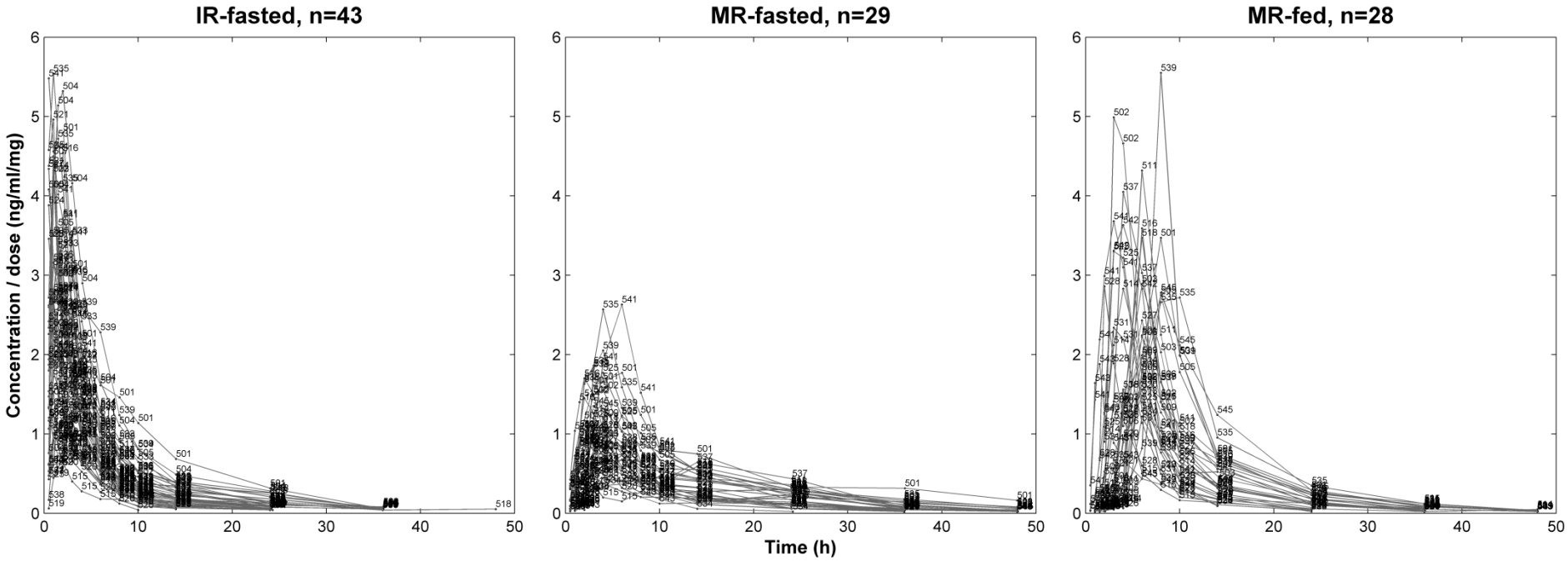
- The **pharmacokinetics** (PK) of the IR and MR formulations were compared in a cross-over study in healthy subjects (Study A2167, n=44).

- Since MVG is considered as a **BDDCS class II** compound, **food effect** was also investigated for the MR formulation.

- The PK of MVG following a brief **intravenous** (IV) **infusion** (10 min) was also evaluated in another study in healthy volunteers (Study A2121, n=120).

Plasma concentration-time profiles

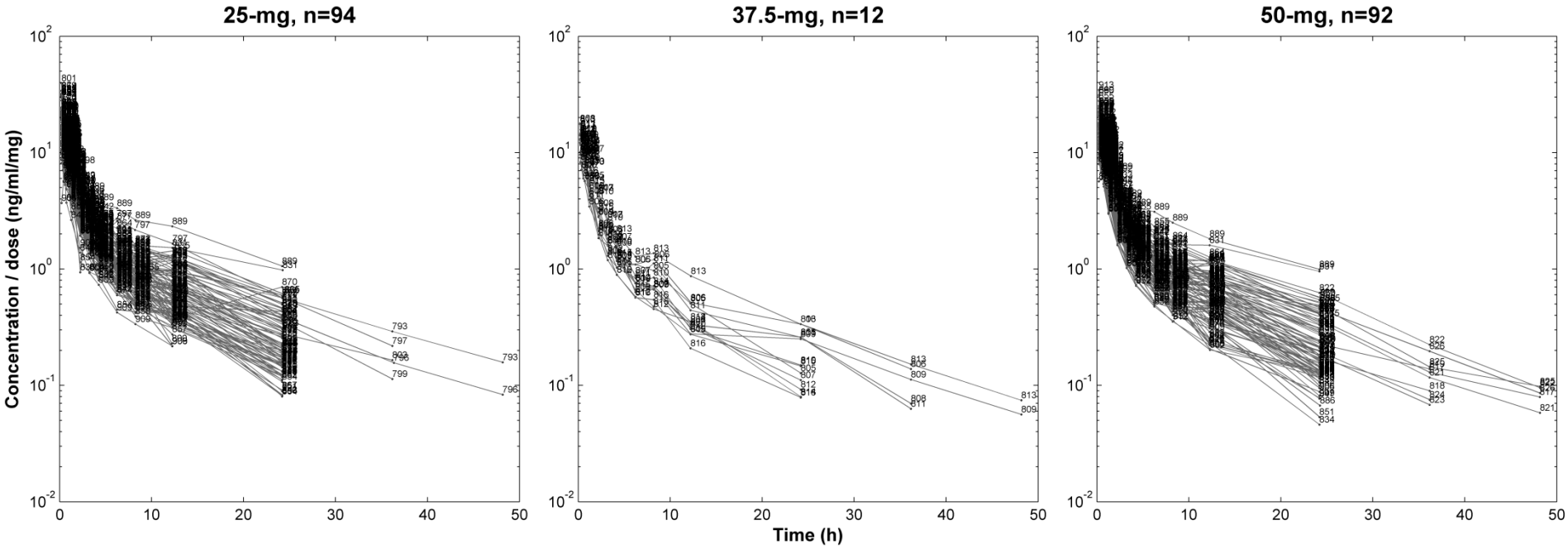
Oral administration ; cross-over design



- **Complex** and **highly variable** profiles
- **Food effect** on the MR formulation's PK

Plasma concentration-time profiles

IV administration



- **Bi-exponential decrease**
- **No sign of non-linearity with dose**

Motivation for a population PK analysis

- Describe **MVG disposition** in the population and identify any contributing **demographic covariates**.

- Compare the **input characteristics** (rate and extent) of the IR and MR formulation.

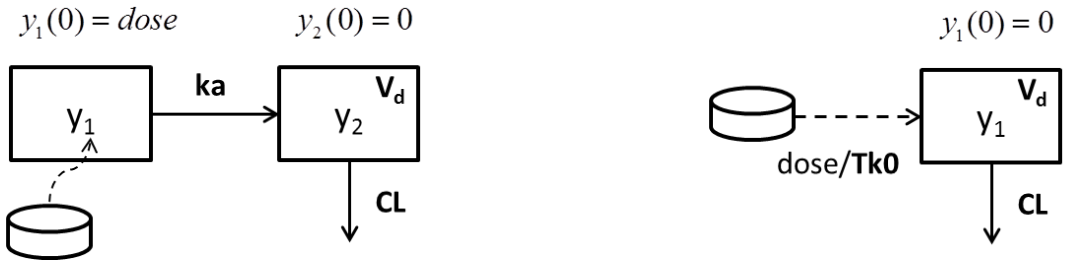
- Quantify the **effect of a high fat meal** on the bioavailability and input rate of the MR formulation.

- Predict the impact of MVG release-rate and of food intake on the **steady-state concentration range** provided by a twice-daily repeated administration of the oral formulations.

Adequate input model !

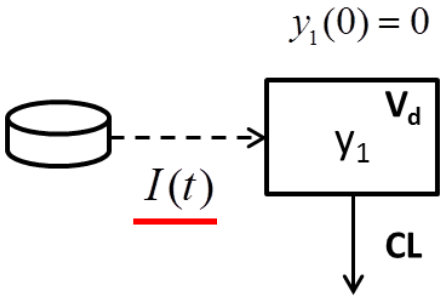
Modelling complex extravascular PK profiles

- **Conventional models** that assume a **first-order** or **zero-order input rate** for a fixed period are inadequate to model complex concentration-time profiles:



- Development of a more **mechanistic model** (incorporating drug dissolution, absorption, gut-wall metabolism *etc.*) can be time consuming and is challenging when only little **drug-** and **formulation-specific prior information** is available.

- Alternatively, a **flexible empirical function** can be used to model the **rate of input** into the system:
  - Polynomial *(Cutler, 1978)*
  - Cubic spline *(Fattinger and Verrota, 1995)*
  - Gamma distribution *(Weiss, 1983)*
  - Weibull distribution *(Bresolle et al, 1994)*
  - Inverse Gaussian distribution *(Weiss, 1996)*
  - *Etc.*



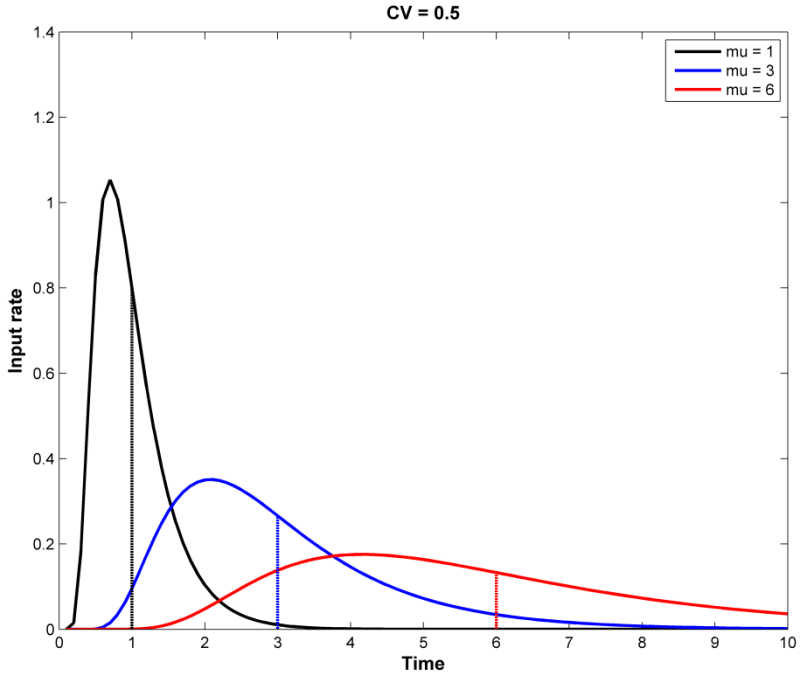
Inverse Gaussian (IG) distribution

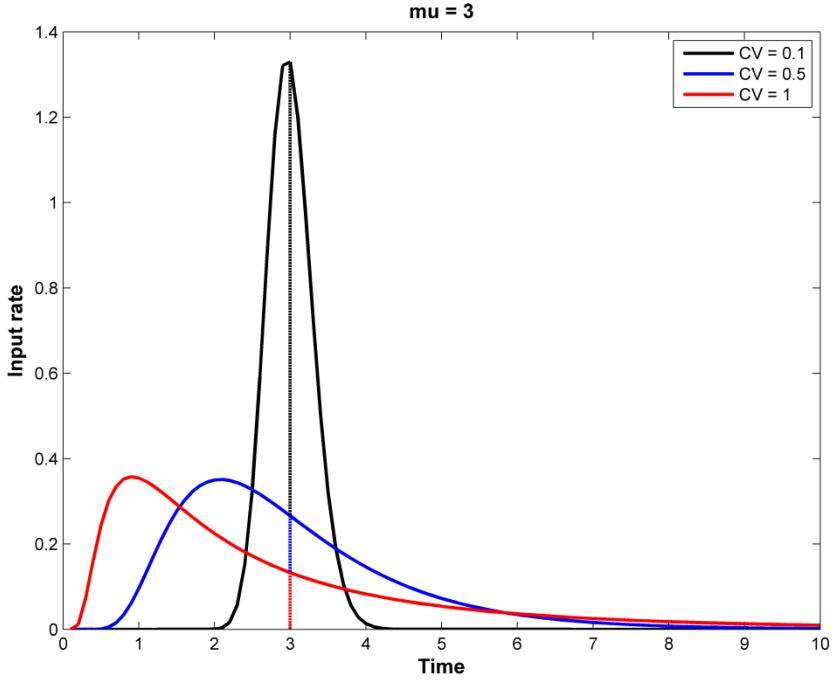
Density function

$$IG(t) = \sqrt{\frac{\mu}{2\pi CV^2 t^3}} \times \exp\left[-\frac{(t-\mu)^2}{2CV^2 \mu \cdot t} \right]$$

Two parameters:

- The mean of the distribution ***μ***
- The relative dispersion of the mean ***CV*** (skewness)

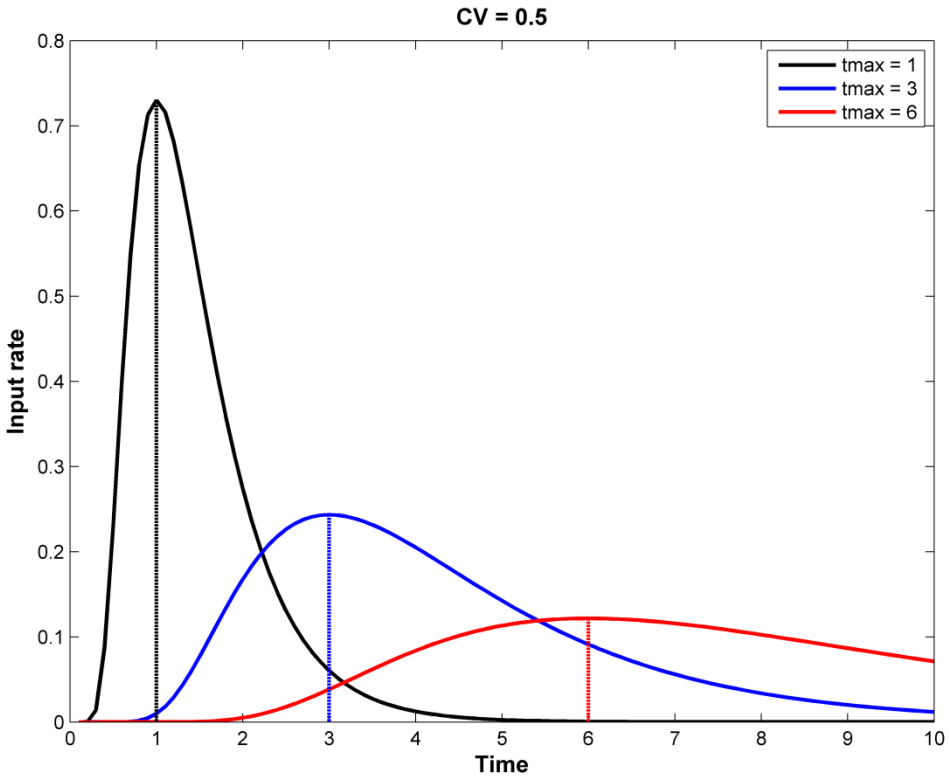




- When ***CV*** **tends to 0**, the IG distribution becomes a **Normal distribution** (symmetrical)
- More flexible than the log-normal distribution *(Chhikara and Folks, 1977)*

IG distribution

Mode



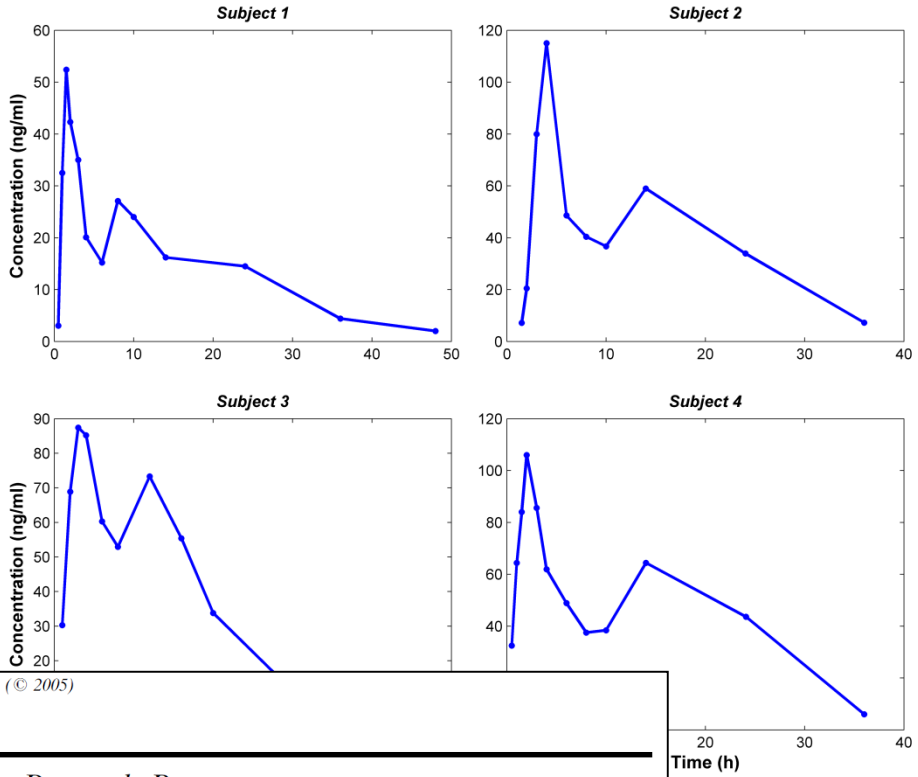
$$tmax = \mu \times \left[\sqrt{1 + \frac{9}{4} CV^4} - \frac{3}{2} CV^2 \right]$$

<u>The mode is more informative:</u> time at which the **input rate** reaches its **maximum**

- Convenient for initial parameter values
- Easier interpretation of results

How to capture multiple-peak profiles?

- The input func
- This can easily **functions** that **mode** (avoid fl



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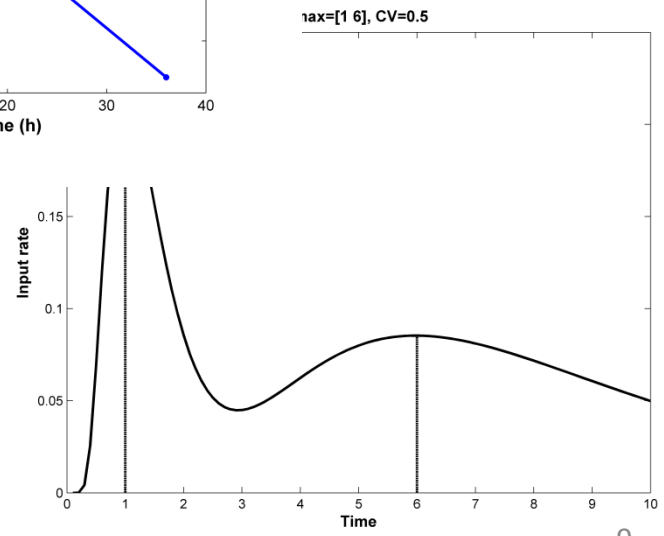
Research Paper

The Use of a Sum of Inverse Gaussian Functions to Describe the Absorption Profile of Drugs Exhibiting Complex Absorption

Chantal Csajka,[1] David Drover,[2] and Davide Verotta[1,3,4]

Received December 1, 2004; accepted March 23, 2005



A weighted sum of *n* IG functions as an input rate function

$$I(t) = F \cdot dose \cdot \sum_{j=1}^{n} f_j \cdot IG_j(t)$$

$tmax_j$

CV_j

- The **absolute bioavailability** ***F*** can be directly estimated if IV data are available.
- The parameters f_j are the **weights** for the IG functions (fraction of bioavailable-dose) such that:

$$\sum_{j=1}^{n} f_j = 1$$

- The number of structural parameters is ***n* x 3**:
  - $F, f_j, tmax_j, CV_j$ for j=1,..,n
  - f_n is derived from the f_j (j=1,…,n-1) rather than estimated, to constrain the sum

Stochastic model for a sum of IG functions as input function

$$I(t) = F \cdot dose \cdot \sum_{j=1}^{n} f_j \cdot IG_j(t)$$

$tmax_j$

CV_j

- Using a sum of IG functions as an input function, one approach to build the statistical model is to **assign a random-effect on each parameter of each IG function** *(Csajka et al, 2005)*, and assess the parameter estimates and precisions (deterministic identifiability).

- However, it is more "reasonable" to estimate the same variance for the random-effects of the *n* ***tmax***, as well as for those of the *n* ***CV*** (*e.g.* option "SAME" in NONMEM®)
  - The number of parameters is reduced (more numerically stable)
  - The cost is a decrease in flexibility

- **Bootstrapping** can be applied to check that the estimated variance of a random-effect is statistically significantly different from zero and has a reasonable precision.

Constraining the subject-specific input parameters

- To ensure that the **IG densities** are **naturally ordered** (important for structural identifiability), the constraint $\boldsymbol{tmax_{j,i} \geq tmax_{j-1,i}}$ was imposed as follows:

$$tmax_{j,i} = tmax_{j-1,i} + \theta_{tmax_j} \cdot e^{\eta_{tmax_{j,i}}}$$, for the i^{th} subject and for $j=2,..,n$

- To be **consistent with physiology**, the constraint $0 \leq F_i \leq 1$ was imposed by defining ***F*** as **logit-normally distributed** within the population.

- Constraining the **joint distribution** of the f_j parameters such that:

$$\sum_{j=1}^{n} f_{j,i} = 1$$

while ensuring that $0 \leq f_{j,i} \leq 1$ (for $j=1,\ldots,n$), can be performed by use of a **multivariate logistic-normal distribution** *(Tsamandouras et al, 2014; in manuscript)*.

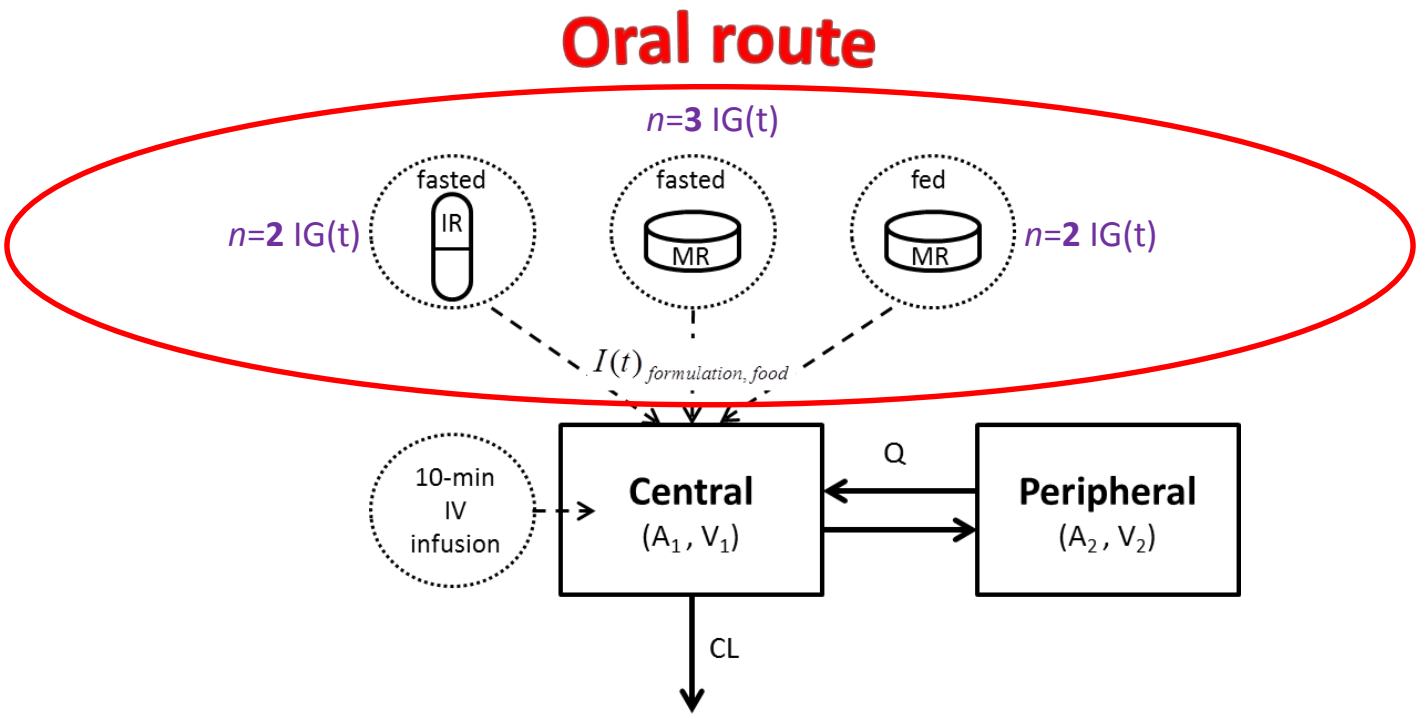
Impact of formulation and food intake on MVG input kinetics

- It was obvious from the raw data that MVG **input properties** depend on the **formulation** and **food conditions** at drug administration.
- Therefore, the **input rate function** was estimated **specifically for each formulation-food condition** rather than testing these factors as categorical covariates for the input parameters.
- **Each subset of data** was first analysed **together with IV data** to determine the **optimal number of IG terms** for each input function.
- Subsequently, all data were pooled and analysed using NONMEM®.
- The model was implemented as a system of two ODEs:

$$\frac{dA_1}{dt} = I_{formulation,\,food}(t) - A_1 \cdot (k_{10} + k_{12}) + A_2 \cdot k_{21}$$

$$\frac{dA_2}{dt} = A_1 \cdot k_{12} - A_2 \cdot k_{21}$$

Structure of MVG population PK model



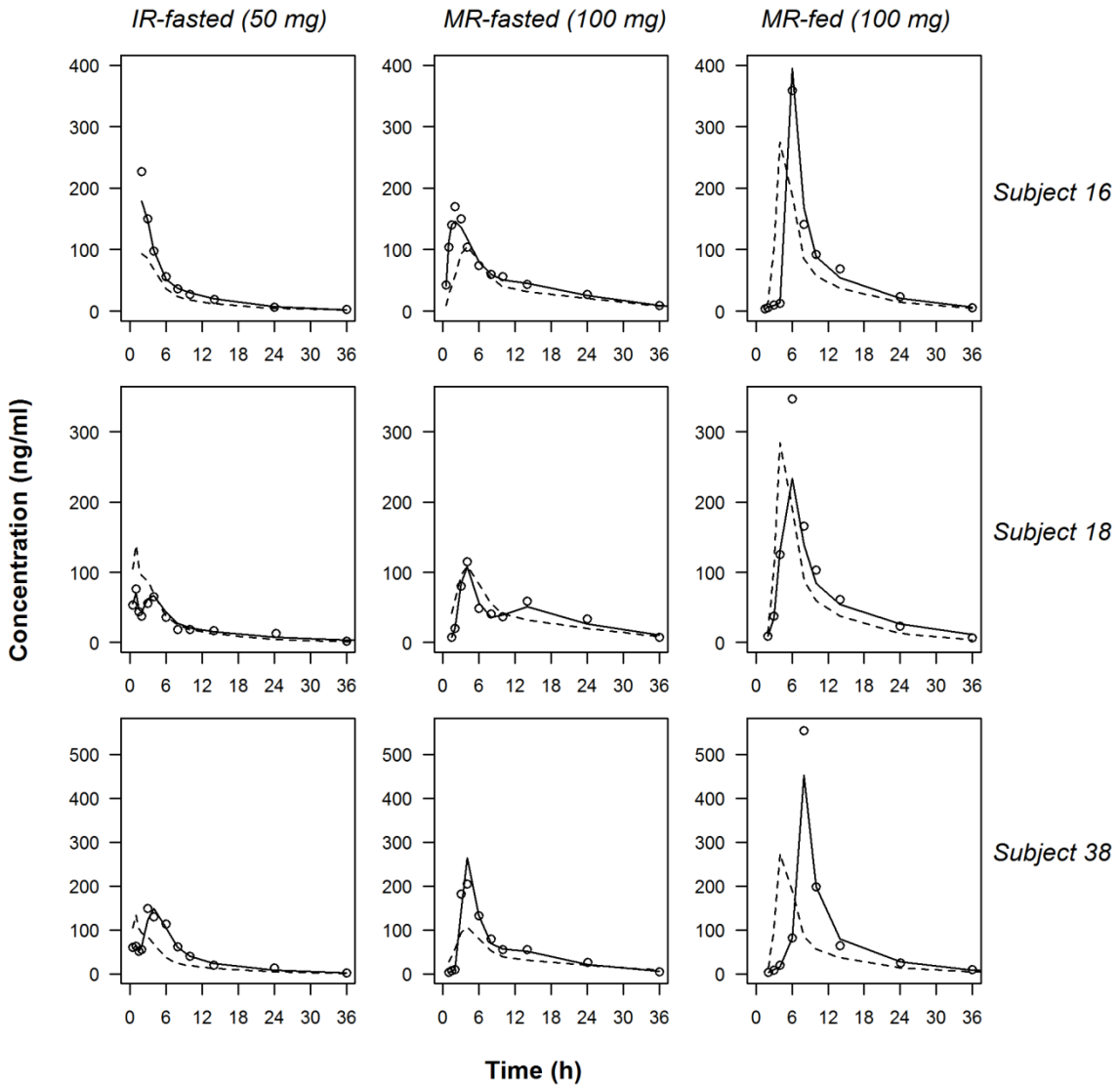
- The **volume terms** are functions a of subject's **bodyweight (BW)**:

$$V_{k,i} = \theta_{V_k} \left(\frac{BW_i}{BW_{med}} \right)^{\theta_{BW,V_k}} \cdot e^{\left(\eta_{V_{k,i}}\right)}$$

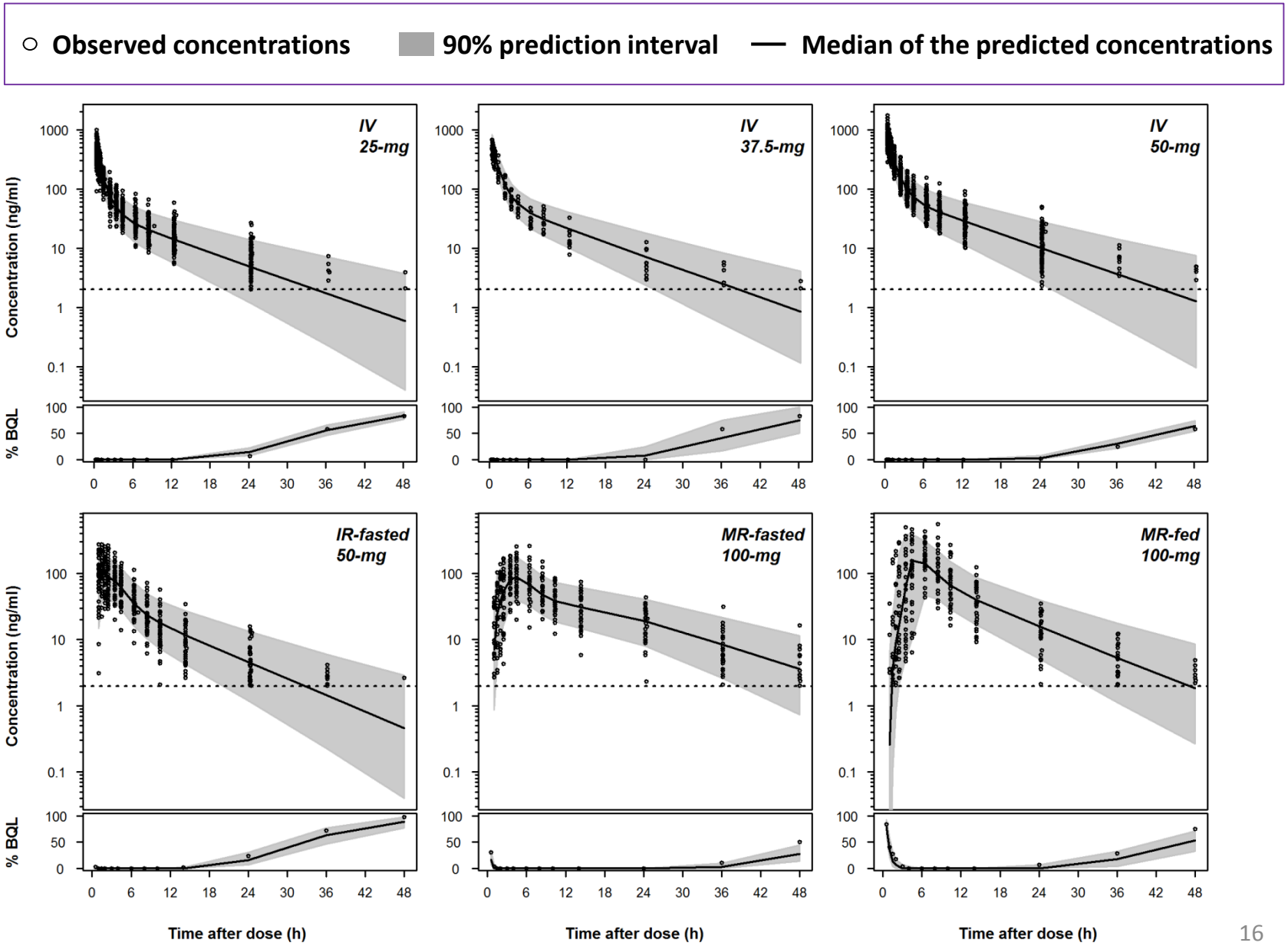
for *k=1,2* and the i^{th} individual

Goodness-of-fit

○ **Observed concentrations** — **Individual predictions** - - **Population predictions**



Visual predictive check of the model



Application of the input model

Simulation of the time course of the input rate and F

- The **derived input functions $I_{formulation,food}(t)$** can be used directly to simulate the **time course of the input rate** for each formulation-food condition.

- The **time course of the bioavailability** can be simulated using the following function :

$$F_A(t) = F \cdot \sum_{j=1}^{n} f_j \cdot IGcdf_j(t) \qquad \text{with} \qquad F_{A,t\mapsto\infty}(t) = F$$

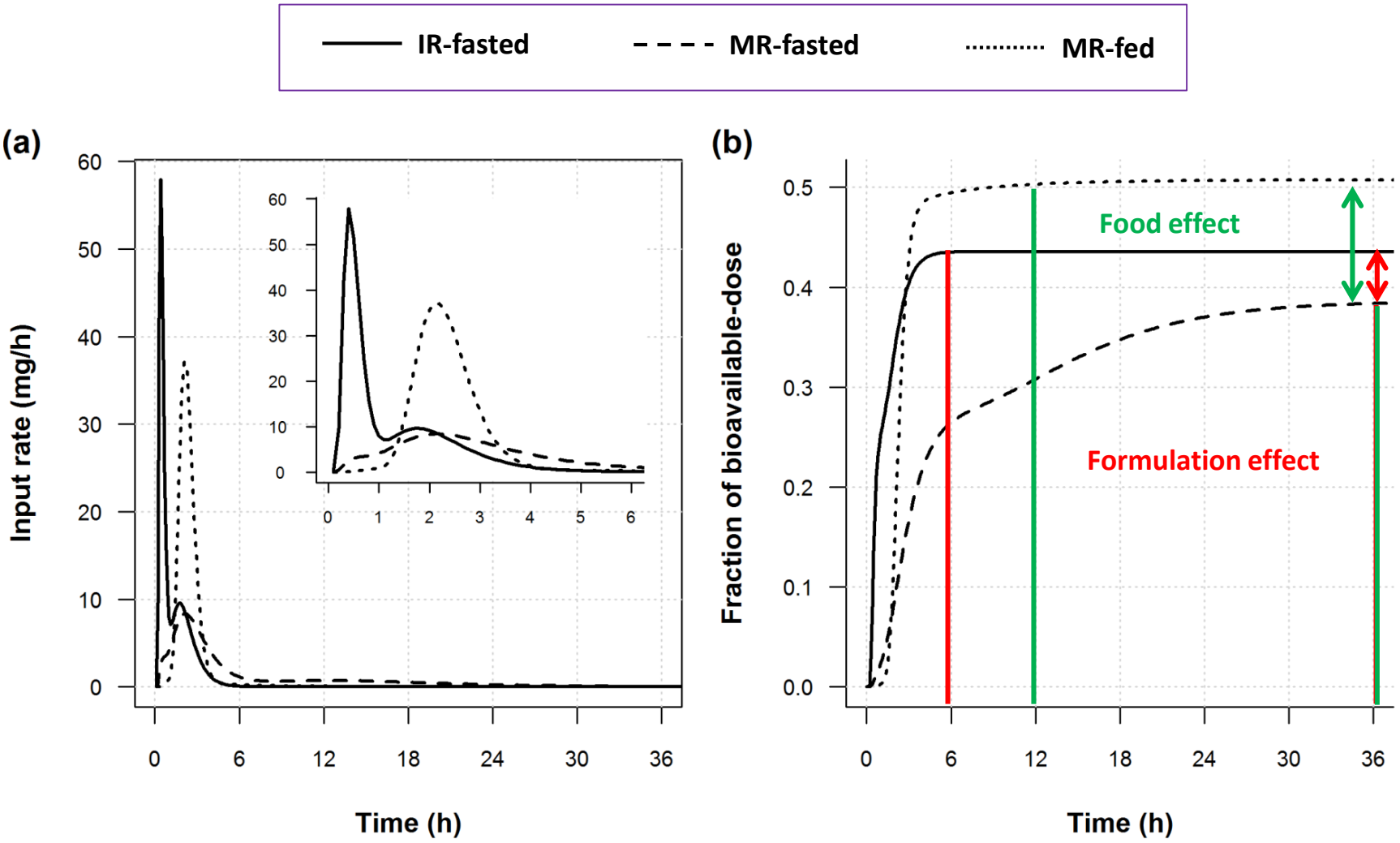
where $IGcdf_j(t)$ is the j^{th} IG cumulative distribution function (cdf).

- The **IG cdf** can be called in the software R for instance (*pinvgauss*) but is parameterized in terms of μ and λ:

$$\mu = tmax \Big/ \left[\sqrt{1 + \frac{9}{4} CV^4} - \frac{3}{2} CV^2 \right] \qquad \text{and} \qquad \lambda = \frac{\mu}{CV^2}$$

Input rate / bioavailability *versus* time profiles

Standard individual in the population

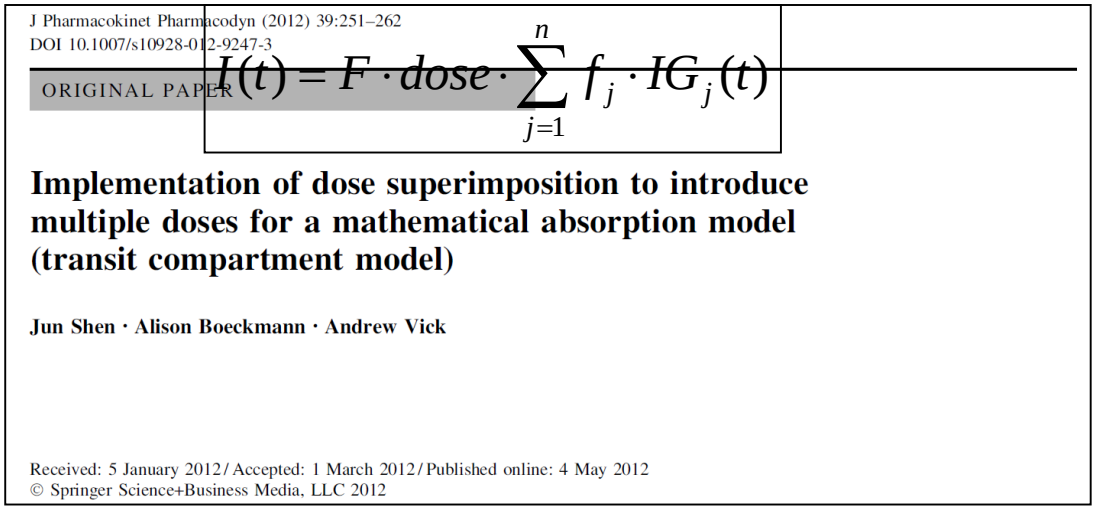


Using an empirical input model for multiple doses

- To eliminate the assumption that a dose has been completely absorbed prior to the next dosing event, **dose superimposition** should be implemented when using the **analytical solution** of the input model for a **repeated dose design**.

- Using NONMEM®, dose superposition can be implemented in a **user-defined FORTRAN subroutine**.

- The method was adapted to the use of **a sum of IG functions** as input function.



J Pharmacokinet Pharmacodyn (2012) 39:251–262
DOI 10.1007/s10928-012-9247-3

ORIGINAL PAPER

$$I(t) = F \cdot dose \cdot \sum_{j=1}^{n} f_j \cdot IG_j(t)$$

Implementation of dose superimposition to introduce multiple doses for a mathematical absorption model (transit compartment model)

Jun Shen · Alison Boeckmann · Andrew Vick

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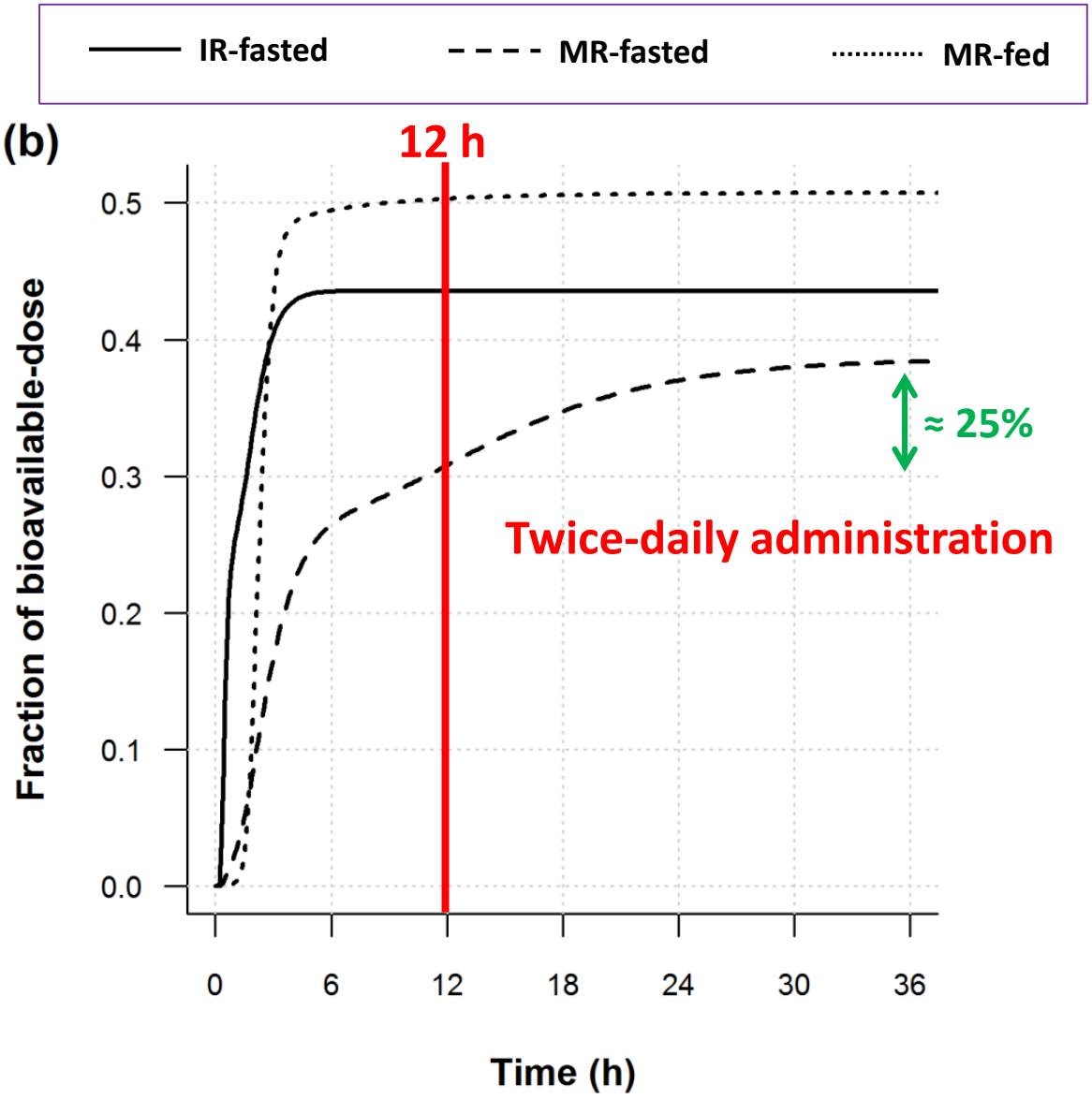
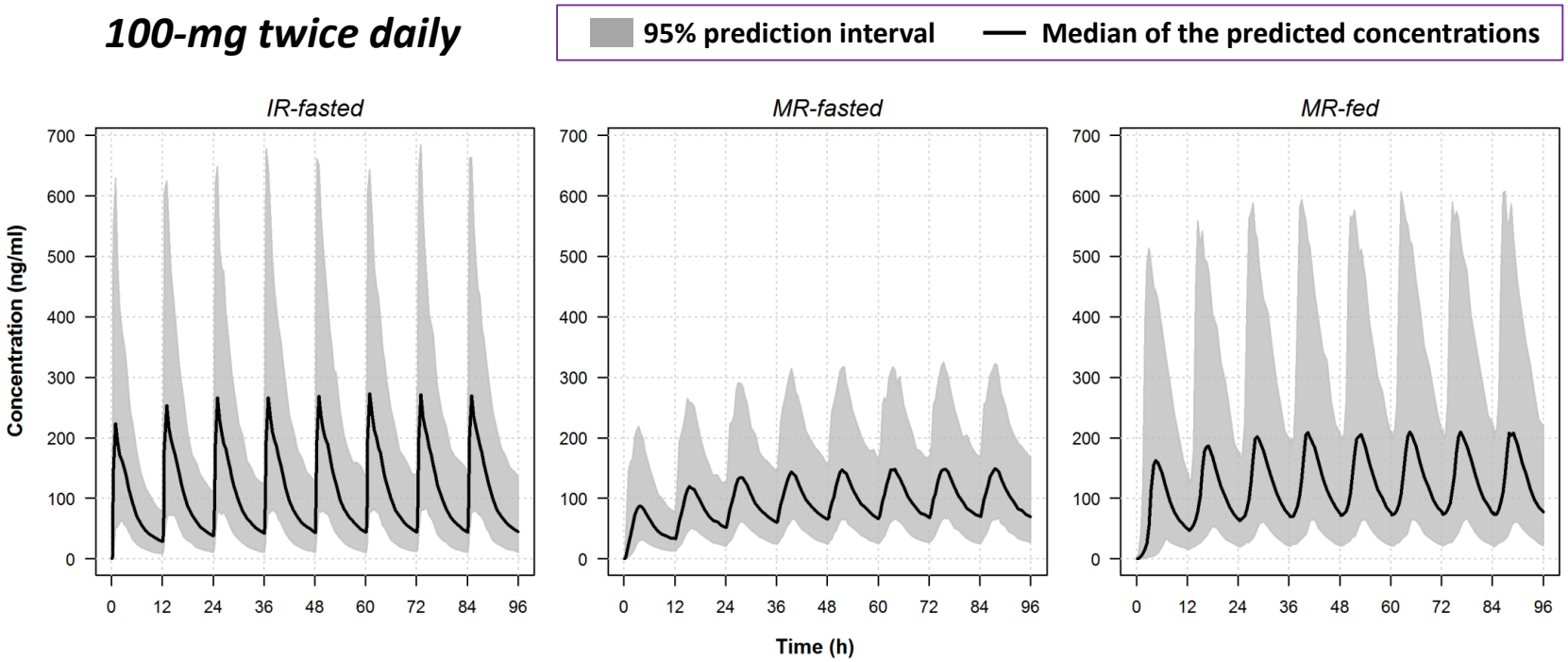
Does dose superimposition need to be implemented?



Application of the PK model

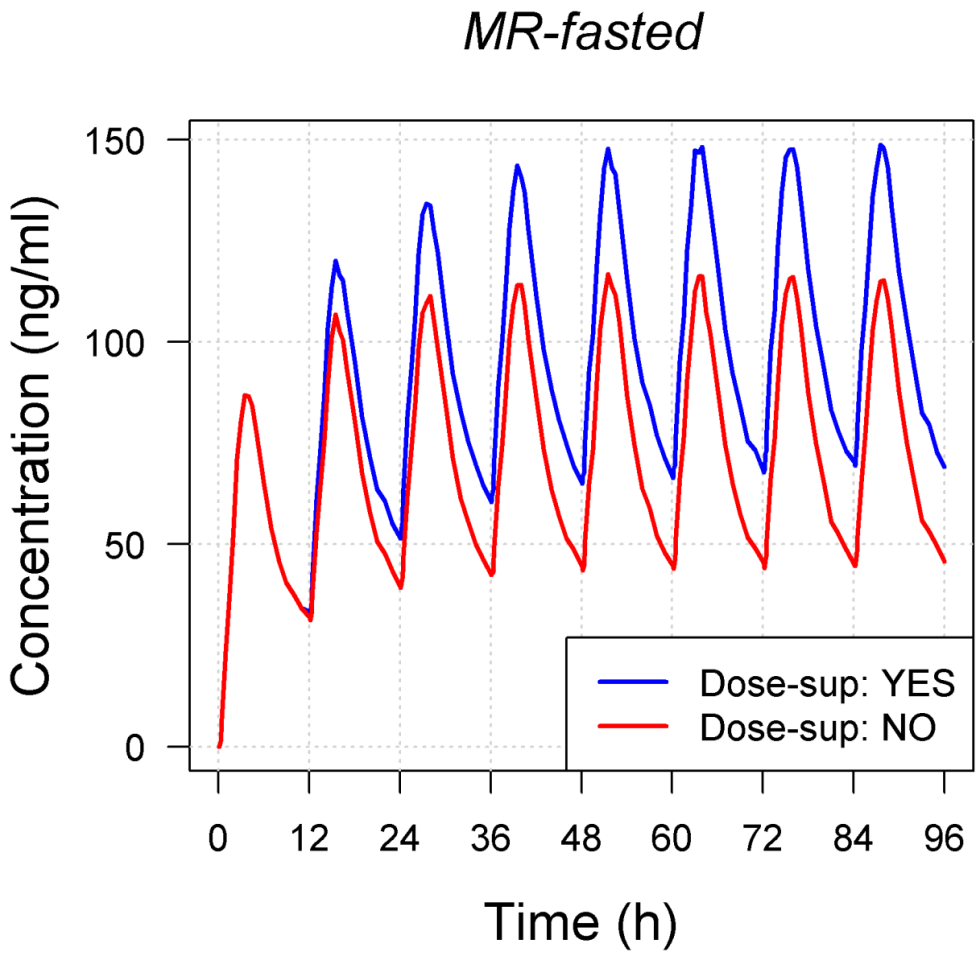
Simulation of the steady-state concentration range



- The MR formulation provides a **slightly lower steady-state concentration range** than the IR formulation, with **lower peaks** (possibly better drug tolerance).

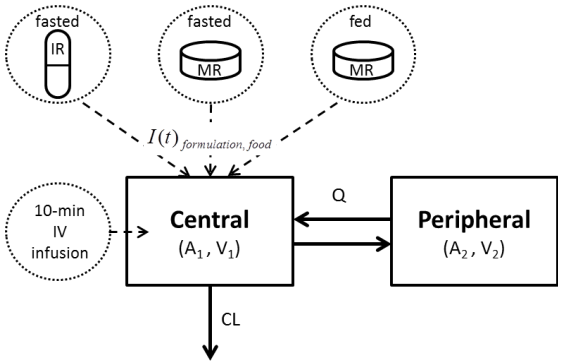
- The **steady-state exposure** to MVG strongly depends on the **food state** at each administration of the MR formulation.

Neglecting dose superimposition



The difference depends on the duration of the input process !

Conclusions on MVG population PK model



- **Advantages:**
  - **Easy implementation** and **fast** analysis runs
  - **Disposition model mechanistic enough** to evaluate the impact of covariates (*e.g.* demographics)
  - **Very flexible input model** that can capture complex profiles with multiple peaks
  - Although empirical, the derived input function helps to gain **insight into the input process** (*e.g.* comparison of the time course of bioavailability between formulations)

- **Disadvantages :**
  - **Can't extrapolate beyond the studied population and experimental conditions** (*e.g.* other disease states or age/weight range) due to its descriptive/empirical nature
  - Doesn't provide much information about the **absorption process** itself and the **first-pass effect**
  - Predicting concentrations in **clinically relevant tissues** is not possible (*i.e.* target sites and tissues exposed to drug toxicity)

Perspectives

- Develop a **physiologically-based PK model** for MVG in order to:
  - Gain insight into the underlying mechanisms of absorption, distribution and elimination
  - Predict concentrations in clinically relevant tissues (*e.g.* brain)
  - Extrapolate outside the studied population such as in a paediatric population

- Reduce the model using **proper lumping** technics and keeping clinically relevant tissues in the model *(Dokoumetzidis and Aarons, 2009)*.

- Optimise the model based on clinical data using a **Bayesian approach** *(Gueorguieva et al, 2006)*
  - Integrate the preclinical knowledge
  - Circumvent structural identifiability issues

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Back up

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RESEARCH PAPER

Model-Based Evaluation of the Impact of Formulation and Food Intake on the Complex Oral Absorption of Mavoglurant in Healthy Subjects

Thierry Wendling • Kayode Ogungbenro • Etienne Pigeolet • Swati Dumitras • Ralph Woessner • Leon Aarons

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Flexibility of the input model

9/1000 simulated profiles