Dose-respone-time modelling
Second generation turnover model with integral feedback control

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Background

Dose-response-time data analysis

Dose-response-time (DRT) data analysis acts as a substitute to traditional PK/PD-modelling when pharmacokinetic data are sparse or absent. This is typically the case for locally administered drugs (e.g. ophthalmics) or when the pharmacological response precedes the plasma exposure (e.g. pulmonary administration). The technique is based on the assumption that the pharmacological response is driven by the presence of the drug in an intermediate *biophase* compartment.

Aim of this study

The present study was performed to demonstrate the utility of DRT data analysis. In order to do so, a large preclinical biomarker dataset on the interaction between nicotinic acid (NiAc) and free fatty acids (FFA) were analysed. Data were collected from studies that examined different rates, routes, and modes of NiAc provocations on the FFA time course. All exposure data of NiAc were intentionally excluded in this study.

Materials and Methods

Final biophase structure

Intravenous dose

$$\frac{dA_b}{dt} = \text{Inf} - k \cdot A_b \qquad A_b(0) = 0 \tag{1}$$

where A_b, k, and Inf are the drug amount, the elimination rate constant, and the intravenous infusion regime respectively.

Oral dose

$$\frac{dA_g}{dt} = -\frac{V_{max,g} \cdot A_g}{K_{m,g} + A_g} \qquad A_g(0) = D \tag{2}$$

$$\frac{dA_b}{dt} = \frac{V_{max,g} \cdot A_g}{K_{m,g} + A_g} - k \cdot A_b \qquad A_b(0) = 0 \tag{3}$$

where D, A_g, $V_{max,g}$, and $K_{m,g}$ are the drug dose, the gut drug amount, the maximal absorption rate, and the Michaelis constant.

Pharmacodynamic model

Turnover of FFA is described by

$$\frac{dR}{dt} = k_{in} \cdot (1 + u(t)) \cdot \left(\frac{R_0}{M_1}\right)^p \cdot I(A_b) - k_{out} \cdot R \cdot \left(\frac{M_8}{R_0}\right), \quad R(0) = R_0 \tag{4}$$

where k_{in}, k_{out}, R_0, p, and M_i, $i = 1,\ldots,8$ are the rate of production, the fractional turnover rate, the baseline of response, the amplification factor, and the moderators respectively and

$$I(A_b) = 1 - \frac{I_{max} \cdot A_b^\gamma}{ID_{50}^\gamma + A_b^\gamma} \tag{5}$$

where I_{max}, ID_{50}, and γ are the drug efficacy, drug potency, and Hill exponent respectively. The moderators $M_1,\ldots M_8$ are described by

$$\frac{dM_1}{dt} = k_{tol} \cdot (R - M_1) \tag{6}$$

$$\frac{dM_i}{dt} = k_{tol} \cdot (M_{i-1} - M_i), \quad i = 2,\ldots,8 \tag{7}$$

with $M_{1,0} = \ldots = M_{8,0} = R_0$. $u(t)$ is given by

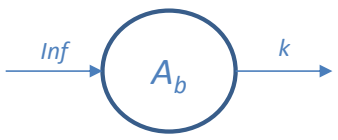
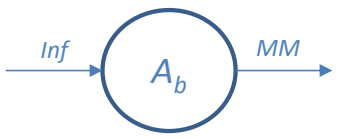
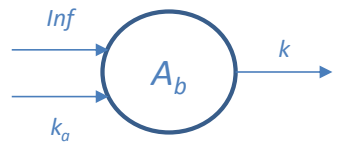
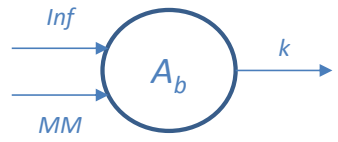
$$u(t) = K_i \int_0^t \left(1 - \frac{R(\tau)}{R_0}\right) d\tau, \quad u(0) = 0. \tag{8}$$

where K_i is the integral gain parameter.

Materials and Methods

Depending on the route of administration, the input is either directly into the biophase (intravenous administration) or absorbed into the biophase from the gut (oral administration). The biophase model structures were evolved through a series of steps were data of different routes and rates sequentially were included and the model complexity increased.

Table 1: Evolution of the Biophase Structure.

Step	Model	Description	Experimental data
I		Zero-order input First-order output	IV
II		Zero-order input Michaelis-Menten output	IV
III		Zero-order input (IV) First-order inout (PO) First-order output	IV + PO
IV		Zero-order input (IV) Michaelis-Menten input (PO) First-order output	IV + PO

Results

The model was successfully fitted on a population and individual level for all NEFA time courses.

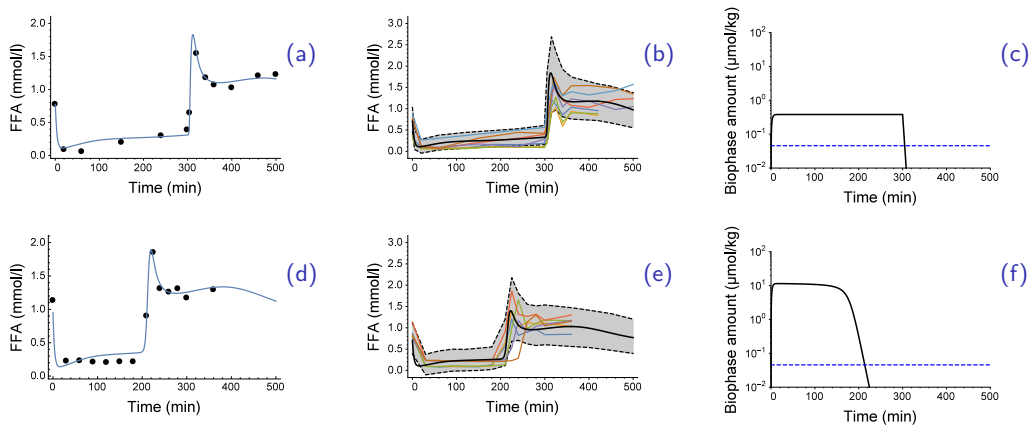


Figure 1: Individual fit, population fit with 90% Monte Carlo prediciton intervals, and estimated biophase kinetics with predicted ID_{50} (dashed blue line) for infusion of 51 µmol kg^{-1} min^{-1} (a-c) and oral dose of 812 µmol kg^{-1} (d-f).

Results

Half-lives for the three rate constants k_{out}, k_{tol}, and K_i with 90% bootstrap prediction intervals.

Table 2: Half-lives of System Rate Constants.

Parameter	Half-life	90% PI[a]
k_{out}	2.3	[1.3, 4.0]
k_{tol}	29	[15, 51]
K_{i}	400	[210, 710]

[a] 90% non-parametric bootstrap prediction interval

Conclusions

- Inhibitory Imax-model, driven by the biophase amount, controls turnover of FFA.
- Second generation NiAc/FFA model used encompassing integral control (slow) and moderator (rapid and oscillatory) feedback.
- Model successfully fitted to all time courses in normal rats.
- Dose-response-time data analysis can model non-linearities in the biophase.
- Slow integral control feedback allows 90% adaptation within 10 days.
- Half-life of the slow integral control feedback ranged between 3-12 hrs.
- New numerically algorithms, more efficient than conventional software like e.g. NONMEM, were successfully applied in the mixed-effect approach.

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