

Second-order indirect response modelling of complex biomarker dynamics

A. Russu,^{1,*} E. Marostica,² G. De Nicolao,² I. Poggesi¹

¹ Model Based Drug Development, Janssen Research and Development, a Division of Janssen Pharmaceutica NV, Beerse Belgium

² Department of Industrial and Information Engineering, University of Pavia, Pavia, Italy

* E-mail: arussu@its.jnj.com

INTRODUCTION

Biomarker dynamics in response to drug action may not always be fully understood.

Redundant pathways, tolerance, feedback and counter-regulation may be such that the response to a drug stimulus can show complex patterns¹⁻³.

This motivates the present work, where a new pharmacokinetic/pharmacodynamic (PK/PD) approach inspired by indirect response modelling (IRM)⁴ and precursor-dependent IRM⁵ is investigated.

SECOND-ORDER INDIRECT RESPONSE MODEL

Model equations

$$\begin{cases} \dot{x}_1(t) = k_{in} \left(1 + \frac{S_{max} c(t)}{SC_{50} + c(t)} \right) - k \left(1 - \frac{c(t)}{IC_{50} + c(t)} \right) x_1(t) & x_1(0) = bas \\ \dot{x}_2(t) = k \left(1 - \frac{c(t)}{IC_{50} + c(t)} \right) x_1(t) - kx_2(t) & x_2(0) = bas \\ y(t) = x_2(t)(1 + \varepsilon) & \varepsilon \sim N(0, \sigma^2) \end{cases}$$

Figure 1

The new PK/PD model incorporates two equations (i.e. "second-order" model): precursor $x_1(t)$, and response $x_2(t)$. Measurements of the response, $y(t)$, are assumed to be available.

Model scheme

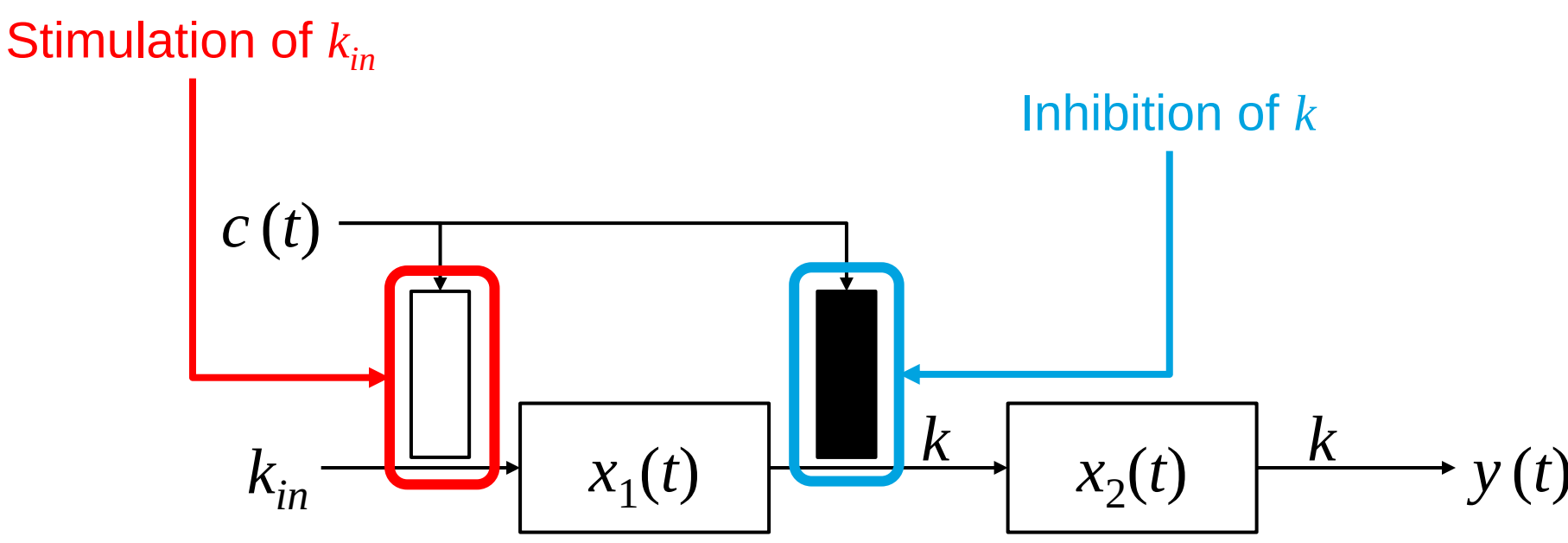


Figure 2

Drug concentration $c(t)$ stimulates precursor formation rate k_{in} (through SC_{50}) and inhibits the rate k of conversion to response (through IC_{50}).

Example profiles

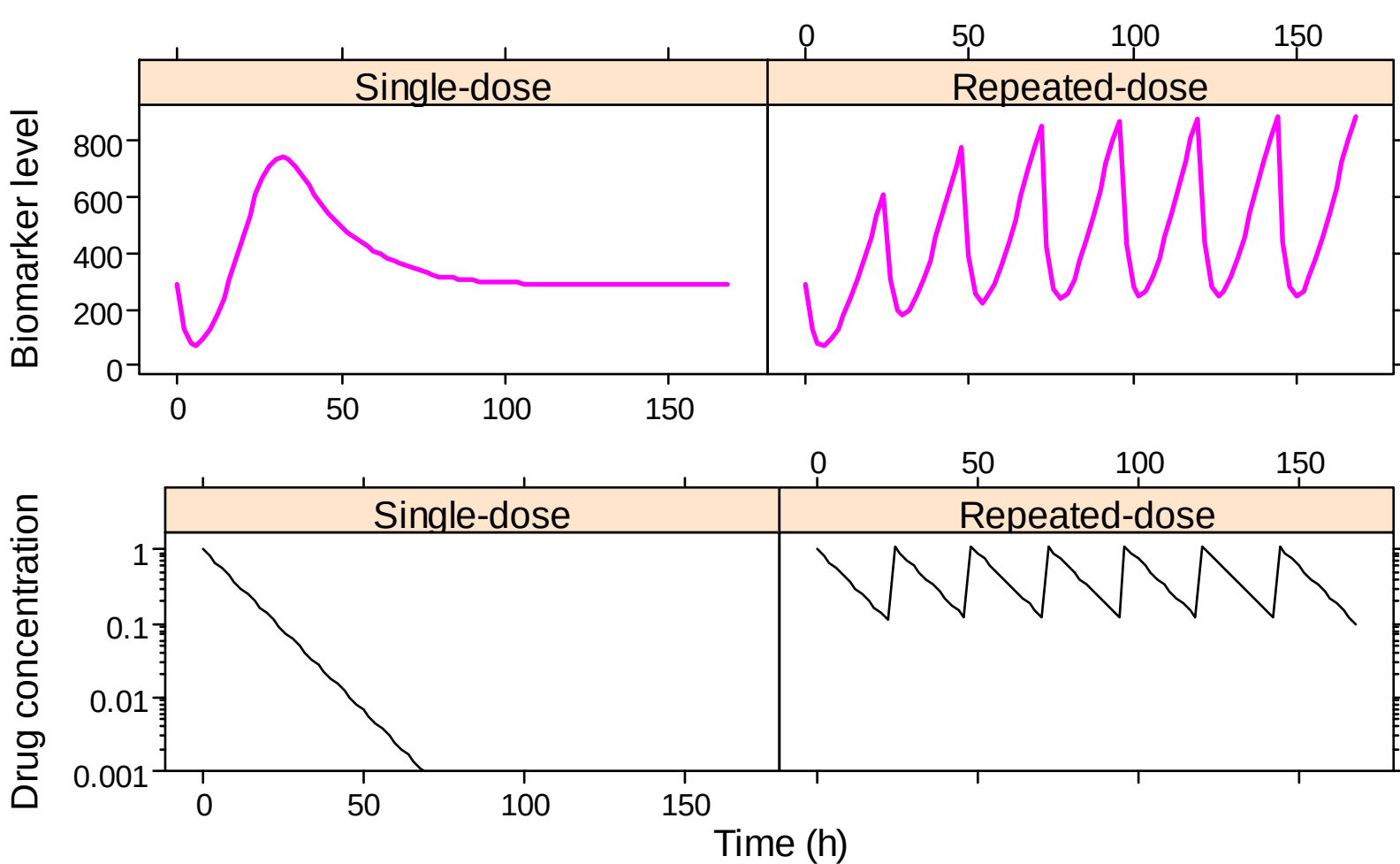


Figure 3

Simulated biomarker and PK profiles obtained from $bas = 291$, $k = 0.45$, $S_{max} = 0.71$, $SC_{50} = 0.0038$, $IC_{50} = 0.033$, and $c(t) = De^{-\alpha t}$ as PK profile ($D = 1$, $\alpha = 0.1$).

RESULTS: SENSITIVITY ANALYSIS

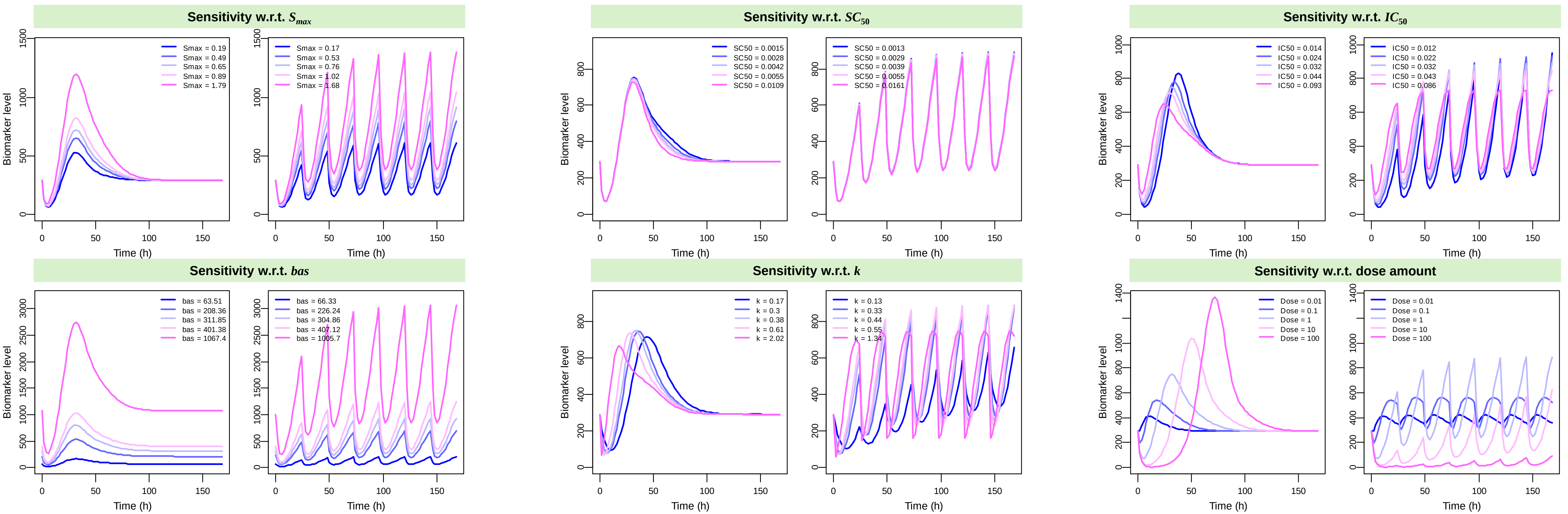


Figure 4

Different real-life patterns of response were simulated by varying in turn the 5 model parameters (S_{max} , SC_{50} , IC_{50} , bas , k) and the dose amount. PK was simulated as in Figure 3. Within each panel, colors ranging from blue to pink denote increasing values of a given parameter or the dose amount. The new model could describe a wide range of response profiles, generated from both single and repeated dose administration.

RESULTS: PREDICTION BENCHMARK

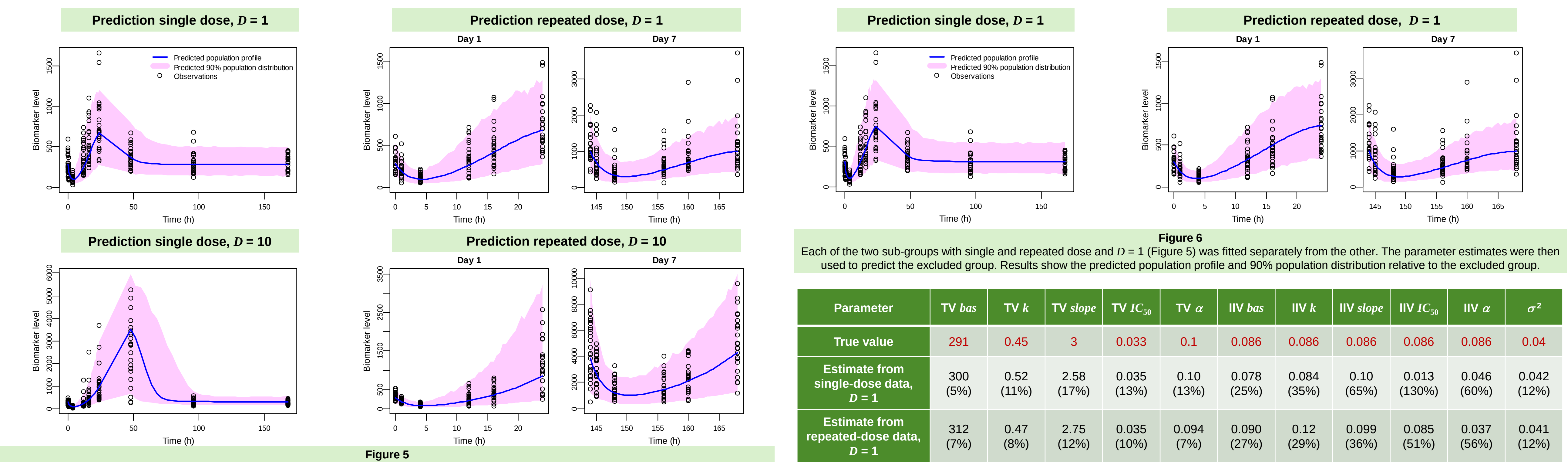


Figure 5

Four sub-groups of 1000 subjects each were simulated by varying dose level ($D = 1$ or 10) and dosing scheme (single or repeated dose), using parameters described in Figure 3 (except that a linear stimulus on k_{in} with $slope = 3$ was used). Log-normal inter-individual variability of 30% was adopted for all parameters, and a proportional error with 20% coefficient of variation was used for intra-individual variability. Each sub-group was set aside while the other 3 were fitted with the PK/PD model. Parameter estimates so obtained were then used to predict the excluded sub-group. Results show the predicted population profile and 90% population distribution relative to the sub-group excluded from model fitting.

Figure 6

Each of the two sub-groups with single and repeated dose and $D = 1$ (Figure 5) was fitted separately from the other. The parameter estimates were then used to predict the excluded group. Results show the predicted population profile and 90% population distribution relative to the excluded group.

Parameter	TV bas	TV k	TV $slope$	TV IC_{50}	TV α	IIV bas	IIV k	IIV $slope$	IIV IC_{50}	IIV α	σ^2
True value	291	0.45	3	0.033	0.1	0.086	0.086	0.086	0.086	0.086	0.04
Estimate from single-dose data, $D = 1$	300 (5%)	0.52 (11%)	2.58 (17%)	0.035 (13%)	0.10 (13%)	0.078 (25%)	0.084 (35%)	0.10 (65%)	0.013 (130%)	0.046 (60%)	0.042 (12%)
Estimate from repeated-dose data, $D = 1$	312 (7%)	0.47 (8%)	2.75 (12%)	0.035 (10%)	0.094 (7%)	0.090 (27%)	0.12 (29%)	0.099 (36%)	0.085 (51%)	0.037 (56%)	0.041 (12%)

Table 1

Parameter estimates and percentage relative standard error (in parentheses) obtained from the simulation benchmark described in Figure 6. NONMEM 7.1 with Importance Sampling was used to perform model fitting. TV: typical value (THETA). IIV: inter-individual variability (OMEGA). The true value of IIV (0.086) amounts to 30% inter-individual variation (log-normal IIV model). The value of σ^2 (0.04) amounts to 20% proportional error.

CONCLUSIONS

- These results confirm feasibility of a modeling approach for longitudinal data characterized by complex features.
- This approach extends and complements the well-known methodology of IRM^{2,5}, and is especially appealing when the mechanism of action of a drug is known (or assumed) to impact both the response itself and a precursor of response.
- Additionally, the proposed approach can be used effectively to describe inhibition of clearance for both a parent drug and its metabolite, in presence of a second drug that inhibits certain metabolic pathways (e.g. CYP3A4).

REFERENCES

- C. van Kesteren, A.S. Zandvliet, M.O. Karlsson et al. (2005). Semi-physiological model describing the hematological toxicity of the anti-cancer agent indinavir. *Invest. New Drugs* 23:225-234.
- A. Russu, E. Marostica, S. Zamuner et al. (2012). A new, second-order indirect model of depression time course. Population Approach Group in Europe 21st Meeting, Abstract 2516.
- I. Ortega Azpitarte, A. Vermeulen, V. Piotrovsky (2006). Concentration-response analysis of antipsychotic drug effects using an indirect response model. Population Approach Group in Europe 15th Meeting, Abstract 995.
- N.L. Dayneka, V. Garg, W.J. Jusko (1993). Comparison of four basic models of indirect pharmacodynamic responses. *J. Pharmacokinet. Biopharm.* 21:457-478.
- D.E. Mager, E. Wyska, W.J. Jusko (2003). Diversity of mechanism-based pharmacodynamic models. *Drug Metab. Dispos.* 31:510-519.
- S.L. Beal, L.B. Sheiner, A.J. Boeckmann (Eds.), 1989-2006. NONMEM Users Guides. Icon Development Solutions, Ellicott City, Maryland, USA.