Frequency-domain response analysis for quantitative systems pharmacology models

Pascal Schulthess[1], Teun Post[1,2], James Yates[3], and Piet Hein van der Graaf[1,4]

Cluster Systems Pharmacology

INTRODUCTION

It was recently demonstrated that key biological control systems (such as the MAPK pathway) are highly sensitive to the frequency of external stimuli in a non-intuitive manner which cannot be predicted by conventional pharmacometrics approaches [1]. This suggests that quantitative systems pharmacology (QSP) can provide novel insights into optimal dosing regimens which could add a new dimension to the design of novel treatments. However, methods for such an approach are currently lacking. We therefore apply frequency-domain response analysis (FdRA), a method widely used in engineering [2,3] and already employed for systems biology models in S. cerivisae [1,4,5], to optimise drug treatment regimen of drug tolerance QSP models.

METHODS

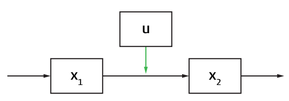

Figure 1: Pool/precursor model

A simple pool/precursor model is depicted in Fig. 1 and defined by

$$\dot{\boldsymbol{x}} = \begin{bmatrix} \beta - \gamma x_1 \delta(u) \\ \gamma x_1 \delta(u) - \gamma x_2 \end{bmatrix}$$

wherein $\delta(u) = 1 + \frac{\alpha_1 u}{\alpha_2 + u}$ is the drug effect. The unforced system has $\bar{x}_1 = \bar{x}_2 = \frac{\beta}{\gamma}$ as steady-state from which the Jacobian matrix with respect to the model states $\boldsymbol{x}$ follows to:

$$\boldsymbol{A} = \begin{bmatrix} -\gamma & 0 \\ \gamma & -\gamma \end{bmatrix}$$

Since all eigenvalues of $\boldsymbol{A}$ have negative real parts the steady-state is stable [6]. Thus, we can linearise the model around this stable steady-state and express it in state-space respresentation as

$$\dot{\boldsymbol{x}} = \boldsymbol{A}\boldsymbol{x} + \boldsymbol{b}u$$
$$y = \boldsymbol{c}^T\boldsymbol{x} + du$$

with

$$\boldsymbol{b} = \frac{\alpha_1}{\alpha_2}\begin{bmatrix} -\beta \\ \beta \end{bmatrix}$$

depicting the Jacobian matrix with respect to the model inputs u. Here, we defined the output y of the model to be x_2, i.e. $\boldsymbol{c}^T = \begin{bmatrix} 0 & 1 \end{bmatrix}$ and $d = 0$. Exciting the linearised model with three sinusoidal inputs of different periods and results in the time courses shown in Fig. 2.

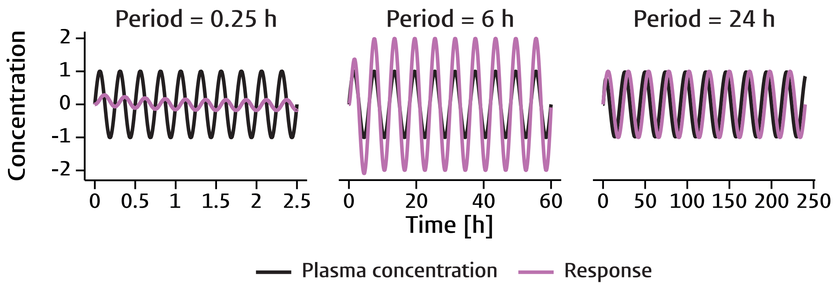

Figure 2: Time courses of the linearised model for three input periods.

The relation between input frequency and output amplitude can now be expressed in terms of a transfer function as:

$$G(s) = \boldsymbol{c}^T(s\boldsymbol{I} - \boldsymbol{A})^{-1}\boldsymbol{b} + d$$

wherein $\boldsymbol{s}$ is the Laplace variable. The transfer function can now be used to collect the responses of the linearised system to sinusoidal inputs over a wide range of frequencies with the help of a Bode plot . Its magnitude is defined as:

$$M(\omega) = \log_{10}|G(i\omega)|$$

and represents the logarithmic ratio of the output and the input amplitude.

For the given pool/precursor model the transfer function is:

$$G(s) = \frac{\alpha_1}{\alpha_2}\frac{\beta s}{s^2 + 2\gamma s + \gamma^2}$$

and with $\alpha_1 = \beta = \gamma = 1$ and $\alpha_2 = 0.25$ the Bode plot of the linearised pool/precursor model is displayed in Fig. 3.

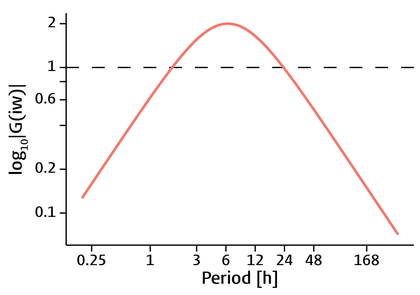

Figure 3: Bode plot

CONCLUSION

Frequency-domain response analysis ...

- ... is a fast pen and paper method to asses drug dosing regimen.
- ... is highly comparable with the computationally expensive nonlinear model simulations.
- ... identifies drug dosing periods for which plasma concentration amplitude is attenuated/amplified in the response.

... **allows for analytical drug dosing regimen optimisation.**

RESULTS

We applied FdRA to five distinct PD models [7] in up to four flavours (Fig. 4 left column). We observed that the pool/precursor model as well as the autoregulation model with negative feedback are the only ones to attenuate long period dosing regimen while all others amplify plasma concentration amplitudes. Short period dosing regimen are attenuated in all models. Next, we excited the nonlinear versions of the models with a one compartment IV bolus PK and performed computationally expensive FdRA for drugs of different half-lives. Surprisingly, this numerical FdRA resulted in similar Bode plot shapes (Fig. 4 right column) as compared to analytical FdRA. But, due to the linearisation in the analytical FdRA only the numerical FdRA can resolve all flavours of the models.

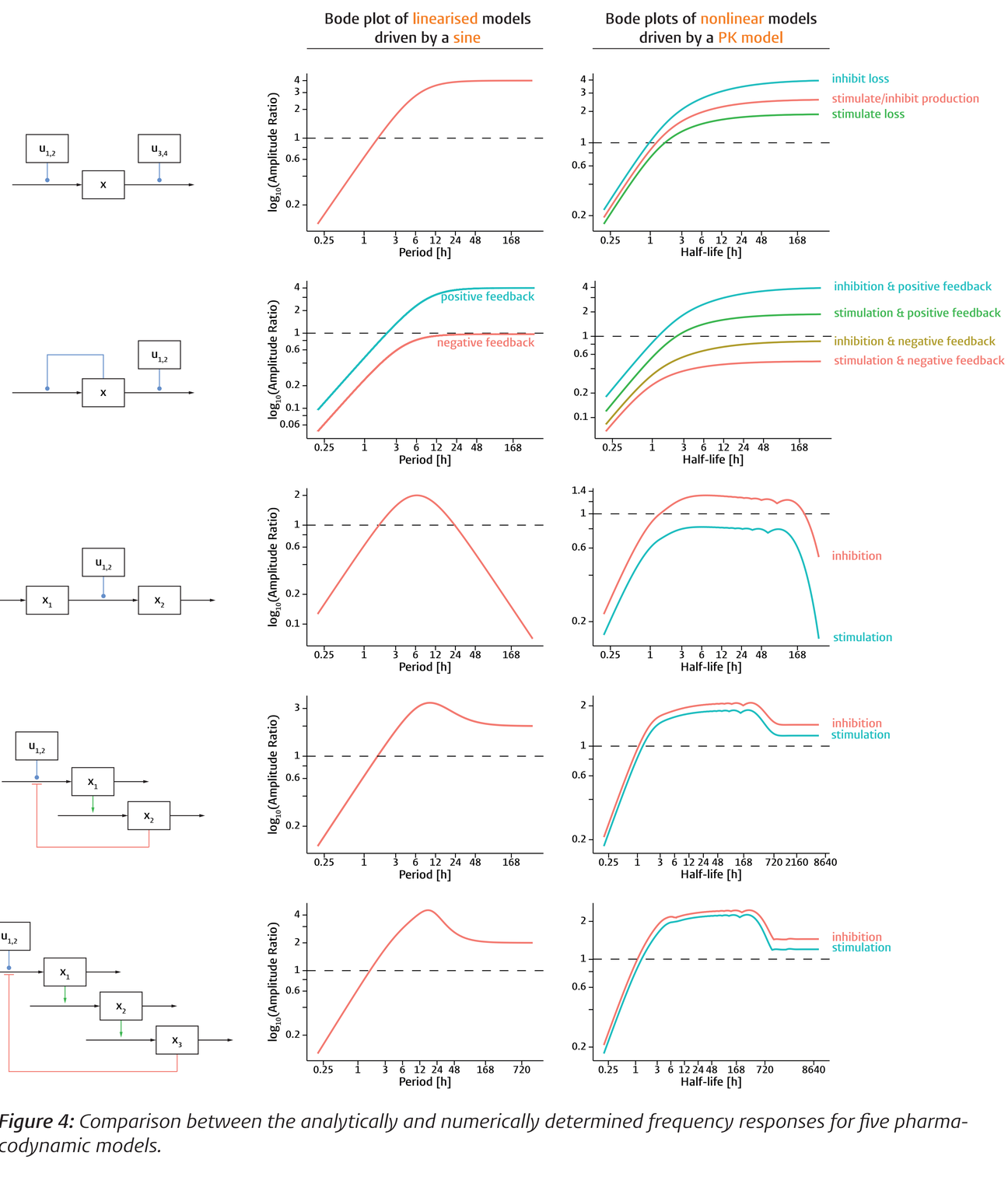

Figure 4: Comparison between the analytically and numerically determined frequency responses for five pharmacodynamic models.

AFFILIATIONS & FUNDING

1. Division of Pharmacology, Cluster Systems Pharmacology, LACDR, Leiden University, Leiden, The Netherlands
2. Leiden Experts on Advanced Pharmacokinetics and Pharmacodynamics (LAP&P) Leiden, The Netherlands
3. AstraZeneca, IMED Oncology DMPK, Hodgkin Building, Chesterford Research Park, United Kingdom
4. Certara QSP, Canterbury Innovation House, Canterbury, United Kingdom

REFERENCES

[1] Mitchell, A., Wei, P. & Lim, W. A. Science 350, 1379–1383 (2015).
[2] Åström, K. J. & Murray, R. M. (Princeton : Princeton University Press, 2008).
[3] Skogestad, S. & Postlethwaite, I. (Wiley, 2005).
[4] Mettetal, J. T., Muzzey, D., Gómez-Uribe, C. & van Oudenaarden, A. Science 319, 482–484 (2008).
[5] Muzzey, D., Gómez-Uribe, C. A., Mettetal, J. T. & van Oudenaarden, A. Cell 138, 160–171 (2009).
[6] Khalil, H. K. (Upper Saddle River, N.J. : Prentice Hall, 2002).
[7] Gabrielsson, J. & Hjorth, S. AAPS J 18, 64–91 (2016).