Systems biology analysis of a drug metabolism (with slow-fast. . .)

Štěpán Papáček, Volodymyr Lynnyk and Branislav Rehák
Institute of Information Theory and Automation of the CAS, Prague, CZ
papacek@utia.cas.cz

Problem motivation ✠ Assumptions ✠ IVP/BVP Formulation ✠ Data ✠ Numerical issues ✠ Conclusion

IN the systems biology literature, complex systems of biochemical reactions (in form of ODEs) have become increasingly common. This *issue of complexity* is often making the modelled processes (e.g. drug metabolism, XME induction, DDI) difficult to intuit or to be computationally tractable, discouraging their practical use. As follows, we present a method of model reduction based on *slow-fast decomposition*, which can be employed to alleviate this issue [1-4]. We seek to provide a brief and consistent case study of a timescale exploitation method and its application in the context of one special biochemical reaction network model (drug rifampicin metabolism associated with the PXR-mediated XME induction process [5-6]), see Fig. 1.

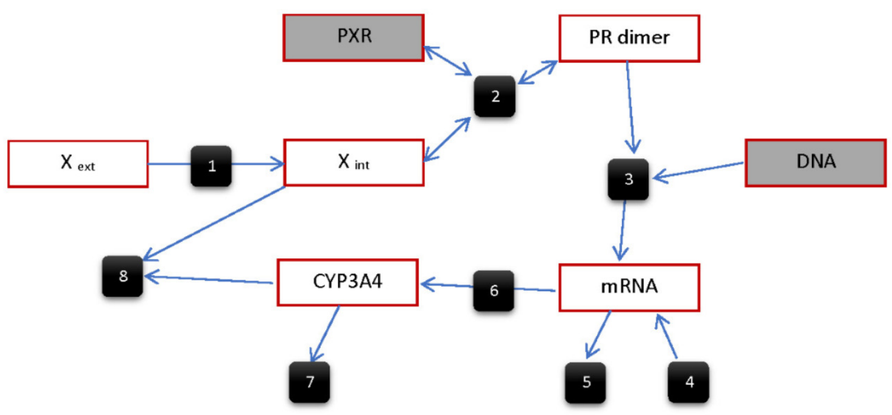

Figure 1: *Graph representation of the network associated to a drug metabolism and the PXR-mediated XME induction process. Reaction nodes identified by numbers represent reactions between species nodes (identified by letters).*

Number	Description of transport-reaction processes within the network
1	Xenobiotic (e.g. drug rifampicin) enters the cell either by diffusion (*in vitro*) or by intravenous/oral application (*in vivo*)
2	PXR binds to drug, formation of PR dimer (this reaction is reversible)
3	PR dimer binds to DNA (increasing transcription)
4	mRNA background production
5	mRNA degradation
6	translation of mRNA (CYP3A4 production)
7	degradation of CYP3A4 protein
8	drug degradation (metabolizing by CYP3A4)

LEt suppose: (i) the total amount of PXR is constant, (ii) the cell spatial resolution can be neglected (everything happens in one compartment), (iii) no delay due to the transport/translation of DNA/mRNA is considered, (iv) drug dosing has the immediate effect, i.e. $X_{int}(t_0) = X_0$ (where X_0 is the total amount of dose). The above assumptions result in reduction of state space dimension. Furthermore, both state variables and time are scaled to non-dimensional form using a diagonal matrix Θ composed from characteristic concentrations and a characteristic rate constant, e.g. $k_{dis}\ [s^{-1}]$, see [6] for the parameters notation. Thus, the dimensionless (slow) time is $\tau = k_{dis}t$, and

$$\Theta = diag(k_{sv}, PR_{qss}, mRNA_{ss}, CYP_{ss}), \qquad \mathrm{PR}_{qss} = \frac{u_1^0}{u_1^0+1}k_{SP}, \quad u_1^0 = \frac{X_0}{k_{sv}}.$$

ODE system can be written as

$$\frac{\partial x(\tau)}{\partial \tau} = Ax(\tau) + B(x(\tau)), \tag{1}$$

with the constant matrix (the linear part of the system)

$$A = \begin{pmatrix} -K_S & K_S & 0 & 0 \\ \frac{1}{K_M} & -1 & 0 & 0 \\ 0 & \frac{K_6 K_S K_M}{K_R} & -K_6 & 0 \\ 0 & 0 & K_9 & -K_9 \end{pmatrix} \tag{2}$$

and the vector representing nonlinear (quadratic) and constant (zero order) parts

$$B(x(\tau)) = \begin{pmatrix} K_S K_M \cdot x_1 \cdot x_2 - K_C \cdot x_1 \cdot x_4 + d_{ose}(\tau) \\ -x_1 \cdot x_2 \\ K_6 \\ 0 \end{pmatrix}, \tag{3}$$

where the dimensionless dosing function is $d_{ose}(\tau)$. The problem can be either formulated as IVP, with initial conditions $x(0) = \left(x_1^0, 0, 1, 1\right)^T$, or (for a periodic dosing) as BVP - assuming the periodicity of the solution: $x(\tau + T) = x(\tau)$.

QSSA - the quasi-steady state assumption is often used for model reduction. Here, if the PR complex (rescaled variable x_2) reaches 'quasi-equilibrium' (in fact $x_2'(t) = 0$ is defining the so-called slow manifold), the dimensionless model can be further simplified:

$$\begin{aligned} x_1'(t) &= -K_C \cdot x_1 x_4, \\ x_3'(t) &= K_6 \left(\tfrac{K_S}{K_R} \tfrac{x_1}{x_1+1} - x_3 + 1 \right), \\ x_4'(t) &= K_9 \left(x_3 - x_4 \right). \end{aligned} \tag{4}$$

The numerical issues (an appropriate error estimation) related to the comparison of just introduced models (1-4) are being studied.

Data Needed for further model identification (both w.r.t. model parameters & structure) are available either in form of time series of the xenobiotic (drug) concentration (for the *in vivo* model) or as the CYP3A4 fold induction (for the *in vitro* model). CYP3A4 mRNA induction (by rifampicin) was measured by J. Duintjer Tebbens *et al.* [6]: Hepatocytes (from 3 different cultures from 3 different liver donors) were cultured for 48 hours in the absence or presence of increasing concentrations of rifampicin, from 1 to 20 μM. The model ability to cope with nonlinear (Michaelis-Menten like) dose dependent behavior is crucial for the following model incorporation within a more complex system (e.g. virtual liver).

REsuming, on the paradigmatic example of rifampicin metabolism and the PXR-mediated Xenobiotic Metabolizing Enzyme (XME) induction process, we exposed an appealing tool of systems biology, i.e. model reduction based on slow-fast decomposition (QSSA). The adequacy of such approach rely on....

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