On some open questions in a pharmacodynamic model for nuclear receptors behavior

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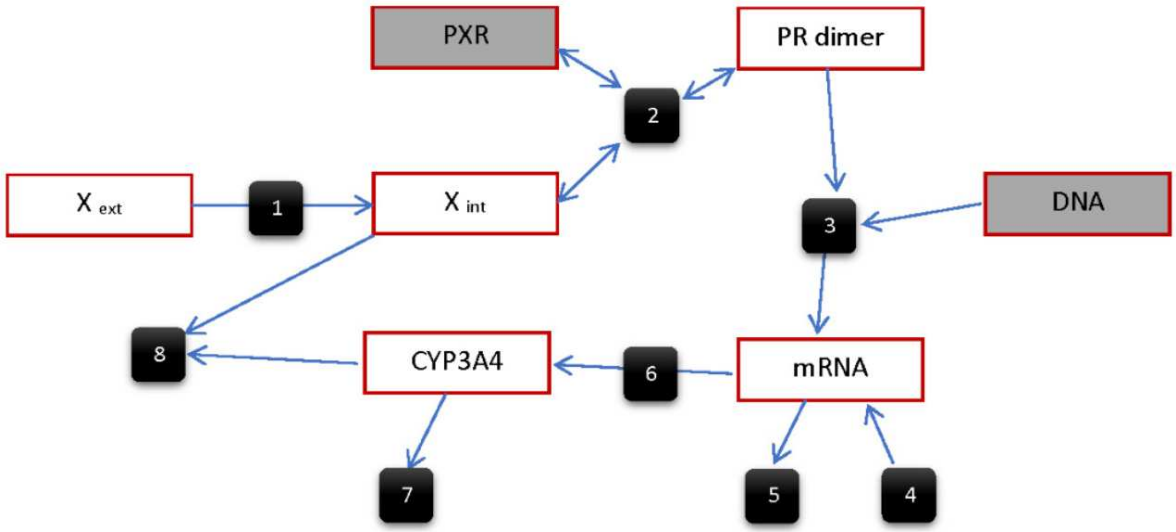
Pharmacokinetic model for the action of Rifampicin



Schematic representation of the modelled PXR-mediated processes, introduced by Luke (compartmental model). Numbered squares represent the following reactions: (1) the xenobiotic enters the cell; (2) PXR binds to the xenobiotic, leading to formation of PXR/RXRα heterodimer; (3) PXR/RXRα dimer binds to DNA, increasing transcription; (4) mRNA background production; (5) degradation of mRNA; (6) the translation of mRNA forms the protein; (7) degradation of the CYP3A4 protein; (8) the CYP3A4 protein metabolizes the xenobiotic.

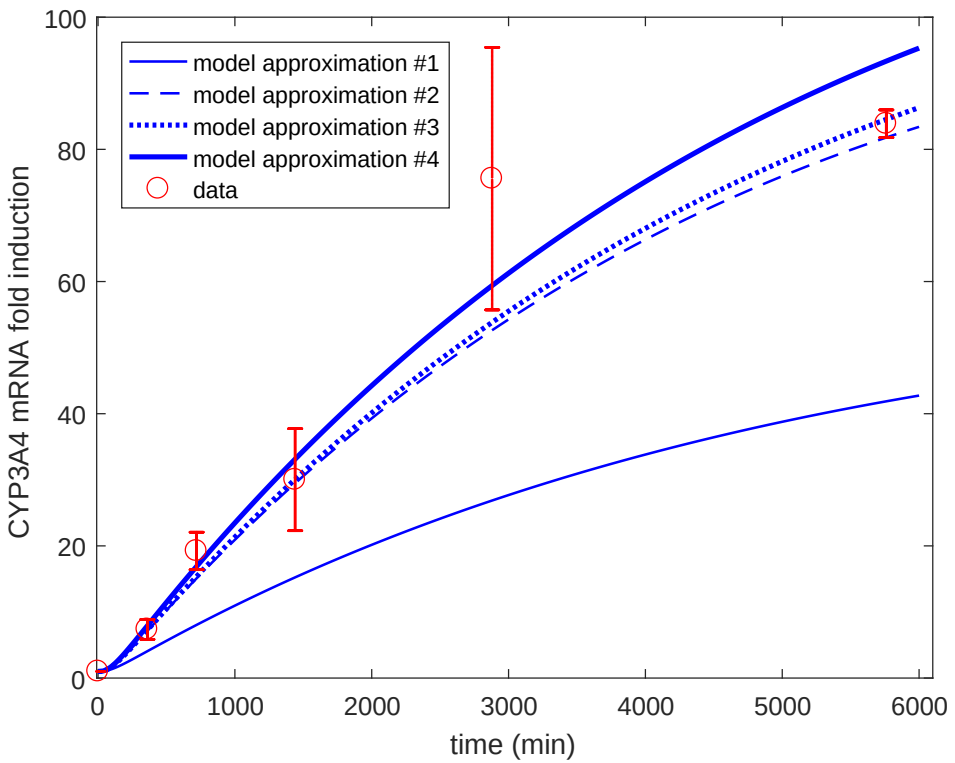
This process is represented by the system of nonlinear ODE of the form

$$x'(t) = Ax(t) + b(x(t)), \quad t \in [0, T], \quad x(0) = x_0 \tag{1}$$

Parameter estimation

Many pharmacologic phenomena can be modelled as long as we know the correct equations for the underlying processes and the correct values of the involved parameters. Typically, only a part of the model parameters is known from literature or obtainable from direct experimental measuring. **Parameter estimation** is an integral part of the modeling process itself. It is done through collecting of in vitro or in vivo data from donors and subsequent curve fitting. It makes the computational costs significantly more expensive.

Curve fitting of the mRNA fold induction for various values of unknown estimated parameter:



Spatial resolution

Important reasons and motivations to include **spatial resolution**:

- There is a tendency to perform model fitting when the underlying biophysical processes are not understood or too complicated. For example, delay of substance transport is sometimes modeled, without knowledge of its biophysical cause or its location, through artificially increasing the number of compartments.
- In some clinical applications spatial information is indispensable, for instance when the drug is efficient only if it reaches very precise organ locations (e.g. the retina for eye diseases).
- Because elevated drug concentrations are often toxic, it is crucial to monitor not only the average drug level all over a compartment, but to detect possible localized maxima as well. Similarly, approaching the so-called no-observed-adverse-effect levels should be detectable locally, inside compartments.
- In other applications, spatial resolution may not seem necessary at first sight, but might reveal unexpected explanations for observed pharmacological phenomena.

While substances can often be assumed to be homogenously distributed, it would be beneficial to provide spatial resolution only in those compartments, where physiological properties or observations suggest heterogenous distributions. Mathematically this leads to a **mixed system of PDEs coupled with ODEs**.

Slow-fast phenomena

Some reactions can be classified as fast, some are in between, and some are slow. The existence of **slow-fast phenomena** in the network represents difficulties for numerical simulation of all species in the network but opportunities to reduce the system order applying the delayed quasi steady-state approximation (D-QSSA) method introduced by Vejchodský et al. We apply it to a simplified model of a chemical reaction network with mass conservation property and encompassing mass transport (by a diffusion process) between an outer and inner compartment containing enzymatic reactions leading to the Michaelis-Menten kinetics (Briggs and Haldane).

Let $x(t) = (x_F^T(t), x_S^T(t))$ be the partitioning of $x(t)$ and let system (1) be rewritten as

$$x_F'(t) = f(x_S(t)) - g(t)x_F(t), \quad x_S'(t) = h(x_F(t), x_S(t)). \tag{2}$$

The QSSA of $x_F(t)$ and the reduced ODE system for $x_S(t)$ are defined as

$$x_F^{qss}(t) = \frac{f(x_S(t))}{g(t)}, \quad x_S'(t) = h(x_F^{qss}(t), x_S(t)). \tag{3}$$

The D-QSSA of $x_F(t)$ and the reduced ODE system for $x_S(t)$ are defined as

$$x_F^{dqss}(t) = \frac{f(x_S(t-\tau(t)))}{g(t-\tau(t))}, \quad x_S'(t) = h(x_F^{dqss}(t), x_S(t)). \tag{4}$$

Constant delay

The value $\tau(t) = 1/g(t)$ is called a **delay**. However, it generally depends on other (slow) system components, which causes some numerical issues when solving delayed differential equations by a computer algebra system. Thus, the natural question is to consider a constant delay τ, e.g. by solving the minimization problem

$$\tau^* = \arg\min_{\tau} \|\bar{x}(t) - x^{dqss}(t)\|^2 \quad \text{s.t.} \quad 0 < \underline{\tau} \leq \tau \leq \overline{\tau} < T, \tag{5}$$

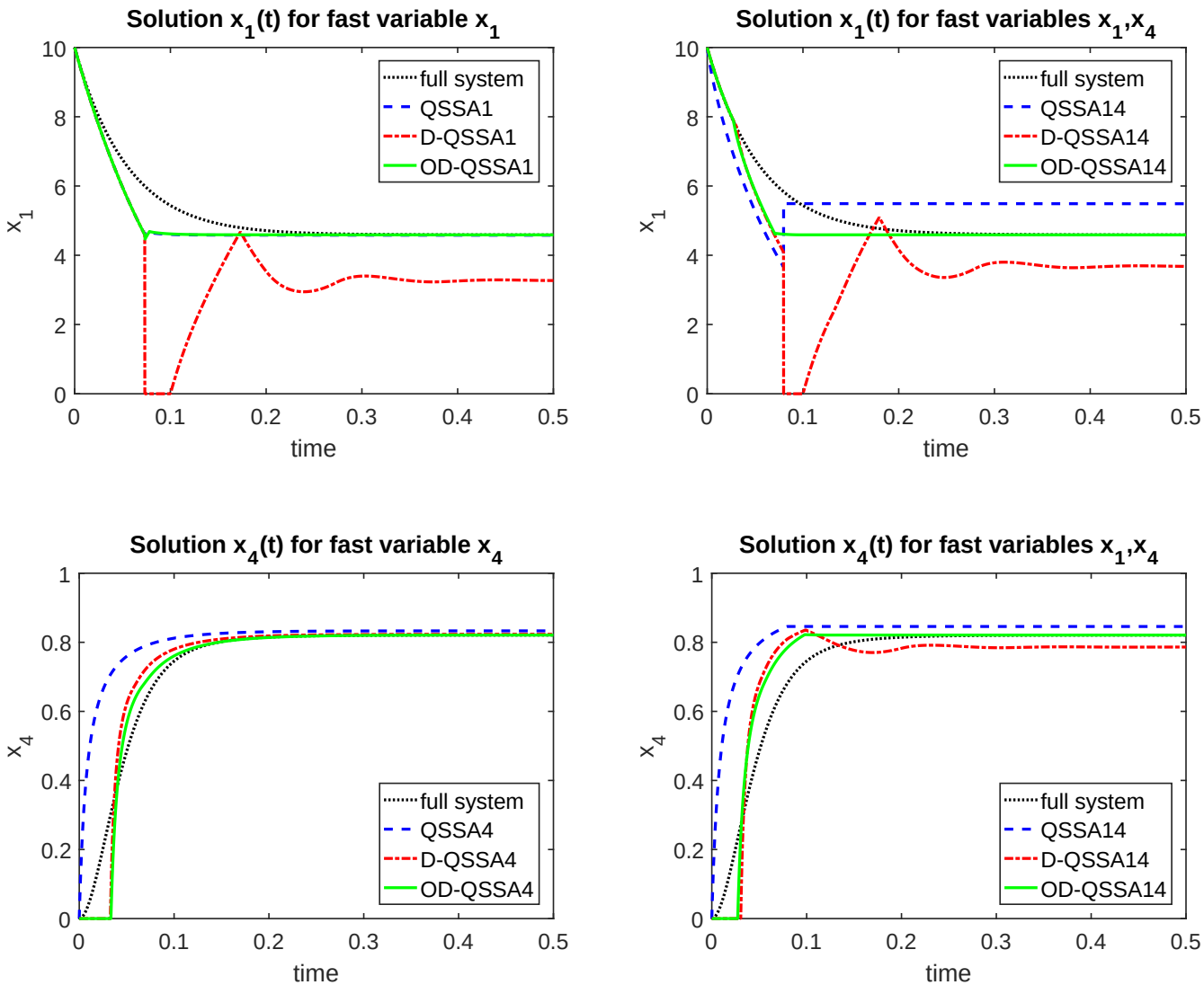
where $\bar{x}(t)$ is a solution to original system (2) or experimental data, etc.

The assumptions for D-QSSA are not too restrictive and D-QSSA is applicable to most chemical systems based on the law of mass action. While the standard QSSA ignores the time needed by fast variables to reach their steady states, the advantage of D-QSSA is the possibility of a time delay introduction improving the approximation accuracy.

Finding optimal delay(s) is not computationally expensive as the optimization problem is small-scale; on the other hand, in order to compute an optimal delay, we need an approximate solution or at least some measured data.

The question is about optimal delay(s) τ for the same fast variable(s) but for various time intervals. For $t \in [0, 0.5]$ we see only a fast dynamics but the system has also a small dynamics which is different and will be seen for larger times, e.g. for $t \in [0, 100]$.

Numerical results



Solutions x_1, x_4 using four different strategies: full system (2), QSSA approach, D-QSSA approach with $\tau(t) = 1/g(t)$, and D-QSSA approach with optimal constant delay τ.

References

- Luke N.S., DeVito M.J., Shah I., El-Masri H.A.:
  Development of a quantitative model of pregnane X receptor (PXR) mediated xenobiotic metabolizing enzyme induction.
  Bulletin of mathematical biology, vol. 72(7), p. 1799–1819 (2010).
- Vejchodský T., Erban R., Maini P.K.:
  Reduction of chemical systems by delayed quasi-steady state assumptions.
  arXiv (2014), p. 1–26, arXiv:1406.4424.
- Briggs G.E., Haldane J.B.:
  A note on the kinetics of enzyme action.
  Biochem J. 19, p. 338–339 (1925).
- Duintjer Tebbens J., Matonoha C., Matthios A., Papáček Š.:
  On Parameter Estimation in an In Vitro Compartmental Model for Drug-induced Enzyme Production in Pharmacotherapy.
  Applications of Mathematics, vol. 64(2), p. 253—277 (2019).