Adding spatial resolution to a pharmacodynamic model for nuclear receptors behavior

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The traditional approach to compute the therapeutic effect of drugs is by usage of a **compartmental model**.

It divides the part of the body to be studied in **compartments** in which the concentrations of the involved substances (drugs, receptors, metabolizing enzymes) are assumed to be *homogeneously* distributed.

Examples of compartments include the blood circulatory system, intracellular and extracellular fluid, adipose tissue, organs, cells, but they can represent abstract units as well.

Compartmental models are particularly suited for drugs binding to membrane receptors and very popular in physiologically based pharmacokinetic (PBPK) models for clinical pharmacy.

But they are employed as well for the more complicated behavior of nuclear receptors:

A model for ligand-binding to the nuclear PXR receptor



Schematic representation of the modelled PXR-mediated processes. Numbered squares represent the following reactions: (1) the xenobiotic enters the cell; (2) PXR binds to the xenobiotic, leading to formation of PXR/RXR α heterodimer; (3) PXR/RXR α 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.



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).

A model for ligand-binding to the nuclear PXR receptor

This process is represented by the following equations:

$$\frac{d X_{\text{ext}}(t)}{dt} = d(t) - k_{imp} X_{\text{ext}}(t) + k_{exp} X_{\text{int}}(t)$$

$$\frac{d X_{\text{int}}(t)}{dt} = k_{imp} X_{\text{ext}}(t) - k_{exp} X_{\text{int}}(t) - k_{assoc} X_{\text{int}}(t) (s_{PXR} - PR(t))$$

$$-k_{met} CYP3A4(t)X_{\text{int}}(t) + k_{dis} PR(t)$$

$$\frac{d PR(t)}{dt} = k_{assoc} X_{\text{int}}(t) (s_{PXR} - PR(t)) - k_{dis} PR(t)$$

$$\frac{d mRNA(t)}{dt} = k_{mRNA} PR(t) - k_{mRNA,deg} mRNA(t) + p_{mRNA,back}$$

$$\frac{d CYP3A4(t)}{dt} = k_{cyp} mRNA(t) - k_{cyp,deg} CYP3A4(t)$$

with variables (substance concentrations)

X _{ext}	=	Xenobiotic concentration outside the cell
X _{int}	=	Xenobiotic concentration inside the cell
PR	=	PXR/RXR heterodimer concentration
mRNA	=	mRNA concentration
CYP3A4	=	CYP3A4 concentration

A model for ligand-binding to the nuclear PXR receptor

and where

d(t)	=	time-dependent	dosing	function
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- k_{imp} = first order import constant for the xenobiotic
- k_{exp} = first order export constant for the xenobiotic
- k_{assoc} = association rate constant for PXR/RXR heterodimer formation
- s_{PXR} = the total system PXR concentration (binded and free)
- *k_{met}* = second order metabolic constant
- k_{dis} = first order dissocation constant
- k_{mRNA} = first order transcription rate constant for mRNA
- $k_{mRNA,deg}$ = first order degradation coefficient for mRNA
- $p_{mRNA,back}$ = background production rate for mRNA
 - k_{CVP} = first order translation rate constant for CYP3A4
 - $k_{cyp,deg}$ = first order degradation coefficient for CYP3A4

Pharmacokinetic models

The systems of ODE's result from the assumed physical and chemical properties of the involved processes and are often **stiff**.

The compartmental modeling procedure has been used for decades. Dedicated PBPK software exists: CellDesigner, ADAPT, Simcyp, NONMEM.

PBPK models can be highly sophisticated multi-compartmental models for the action of several substances, including *feedback loops and drug-drug interaction*. Repeated dosing can be simulated as well by extension of the initial conditions.

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 part of the **model's 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** (see the next slide).

Curve fitting (mostly sum of squares minimization or maximum likelihood estimation) represents constrained optimization: the desired parameters are mostly positive and must lie in physically meaningful intervals. In fact, the parameter estimation problems may be ill-posed and **regularization** may be necessary. Sometimes a sensitivity analysis is performed.

A PBPK model for the action of Rifampicin

Curve fitting of the mRNA fold induction for various values of s_{PXR} and p_{mRNA,back}:



Notice the outlier at time t = 2880 caused by inappropriate physical circumstances that might be ignored.

Pharmacokinetic model for the action of Rifampicin

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The parameter estimation makes the computational costs significantly more expensive:

- The iterative optimization process requires *repeated* computation of the ODE model.
- Thus in fact a *sequence* of systems of ODE's needs to be solved.
- Efficient optimization procedures therefore have a large impact on total costs.

Modeling and parameter estimation are often alternated for iterative refinement.

Models can be very (experimental) data-driven. In addition to parameter fitting there is a tendency to perform *model fitting* as well, 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 (defining so-called *transit compartments*).

This is one motivation for including spatial resolution.

Further reasons to add spatial resolution to the models could be:

- 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 in those compartments, where physiological properties or observations suggest heterogenous distributions.

Mathematically this leads to a mixed system of PDEs coupled with ODEs.

For the above Rifampicin model, we may assume that the most interesting localized reactions take place in the cytoplasm and consider the following coupling:

A mixed PDE/ODE model



A mixed PDE/ODE model for the action of Rifampicin

$$\begin{split} v_{ext} \frac{d X_{ext}(t)}{dt} &= d(t) - \frac{k_{imp}}{\sigma_{ext}} X_{ext}(t) + \frac{k_{exp}}{\sigma_{ext}} \int_{\Gamma_{ext}} X_{int}(t, x) dS \\ \partial_t X_{int}(t, x) &= D_{int} \Delta X_{int}(t, x) - k_{assoc} X_{int}(t, x) PXR(t, x) \\ -k_{met} CYP3A4(t, x) X_{int}(t, x) + k_{dis} PR(t, x) \\ \partial_t PXR(t, x) &= D_{PXR} \Delta PXR(t, x) - k_{assoc} X_{int}(t, x) PXR(t, x) + k_{dis} PR(t, x) \\ \partial_t PR(t, x) &= D_{PR} \Delta PR(t, x) + k_{assoc} X_{int}(t, x) PXR(t, x) - k_{dis} PR(t, x) \\ \frac{d mRNA_{nuc}(t)}{dt} &= \frac{k_{mRNA,nuc}}{\sigma_{nuc}} \int_{\Gamma_{nuc}} PR(t, x) dS - k_{mRNA,deg} mRNA_{nuc}(t) \\ + p_{mRNA,back} + \frac{k_{nuc}}{\sigma_{nuc}} \left(\int_{\Gamma_{nuc}} mRNA_{cyt}(t, x) dS - mRNA_{nuc}(t) \right) \\ \partial_t mRNA_{cyt}(t, x) &= D_{CYP3A4} \Delta CYP3A4(t, x) + k_{cyp} mRNA_{cyt}(t, x) \\ -k_{cyp,deg} CYP3A4(t, x). \end{split}$$

with additional variables

PXR	=	Free (unbinded) PXR concentration
mRNA _{nuc}	=	mRNA concentration in the nucleus
mRNA _{cvt}	=	mRNA concentration in the cytoplasm

A mixed PDE/ODE model for the action of Rifampicin

and additonal parameters

v_{ext}	=	volume of exterior com	partment
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- σ_{ext} = surface of cell exposed to the exterior compartment
 - D_S = diffusion coefficient (or matrix) for substance S in the cytoplasm
- σ_{nuc} = surface of the nucleus
- $k_{mRNA,nuc}$ = first order transcription rate constant for mRNA in the nucleus
 - k_{nuc} = first order transport coefficient for mRNA from nucleus to cytoplasm

The boundary conditions for the cytoplasm are, with the boundary of the cytoplasm consisting of the exterior boundary Γ_{ext} and the boundary with the nucleus Γ_{nuc} :

$$\begin{array}{rcl} D_{int} \partial_n X_{int}(t,x) &=& 0 & \text{on } \Gamma_{nuc} \\ \upsilon_{ext} D_{int} \partial_n X_{int}(t,x) &=& \frac{k_{imp}}{\sigma_{ext}} X_{ext}(t) - \frac{k_{exp}}{\sigma_{ext}} X_{int}(t,x) & \text{on } \Gamma_{ext} \\ D_{PXR} \partial_n PXR(t,x) &=& 0 & \text{on } \Gamma_{nuc} \cup \Gamma_{ext} \\ D_{PR} \partial_n PR(t,x) &=& 0 & \text{on } \Gamma_{nuc} \cup \Gamma_{ext} \\ D_{mRNA} \partial_n mRNA_{cyt}(t,x) &=& 0 & \text{on } \Gamma_{ext} \\ D_{mRNA} \partial_n mRNA_{cyt}(t,x) &=& -\frac{k_{nuc}}{\sigma_{nuc}} \left(mRNA_{cyt}(t,x) - mRNA_{nuc}(t) \right) & \text{on } \Gamma_{nuc} \\ D_{CYP3A4} \partial_n CYP3A4(t,x) &=& 0 & \text{on } \Gamma_{nuc} \cup \Gamma_{ext} \end{array}$$

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A first simple mixed PDE/ODE model

A first, very simple attempt towards computation of the previous model is to consider only three substances:

- u₁ the ligand outside the cell
- u₂ the ligand binded to the receptor in the cytoplasm
- u_3 the mRNA in the nucleus (here simply activated without transport)

$$\begin{array}{rcl} u_1' & = & d(t) - k_1 u_1 - \frac{s_{12}}{v_1} k_{12} \left(u_1 - \frac{1}{R} u_2 \right) \\ u_2' & = & -k_2 u_2 + \frac{s_{12}}{v_2} k_{12} \left(u_1 - \frac{1}{R} u_2 \right) \\ u_3' & = & p_3 - k_3 u_3 + p_{23} u_2 \end{array}$$

To add spatial resolution, replace $u_2(t)$ by $\tilde{u}_2(t, x)$, $x \in \Omega$:

$$u'_{1} = d(t) - k_{1}u_{1} - \frac{s_{12}}{v_{1}}\tilde{k}_{12}\left(u_{1} - \frac{1}{R}\int_{\Gamma_{ext}}\tilde{u}_{2} \,\mathrm{dS}\right)$$

$$\frac{\partial}{\partial t}\tilde{u}_{2} - D\Delta\tilde{u}_{2} = -k_{2}\tilde{u}_{2} \quad \text{for all } x \in \Omega$$

$$-D\nabla\tilde{u}_{2} \cdot \mathbf{n} = -\tilde{k}_{12}\left(u_{1} - \frac{1}{R}\tilde{u}_{2}\right) \quad \text{for } x \in \Gamma_{ext}, \quad \text{zero otherwise}$$

$$u'_{3} = p_{3} - k_{3}u_{3} + p_{23}\int_{\Gamma_{ext}}\tilde{u}_{2} \,\mathrm{dS}$$

 $\Gamma_{ext},\,\Gamma_{nuc}\subset\partial\Omega$ represent the interfaces with the other two compartments.

A first simple mixed PDE/ODE model

We assume that Ω is a 1D domain, $\Omega = [0, 1]$ and let R = 1. In this case

$$\oint_{\Gamma_{ext}} \tilde{u}_2 \, \mathrm{d}S = \tilde{u}_2(t,0), \quad \oint_{\Gamma_{nuc}} \tilde{u}_2 \, \mathrm{d}S = \tilde{u}_2(t,1), \quad \text{and} \quad \Delta \tilde{u}_2 = \frac{\partial^2}{\partial x^2} \tilde{u}_2.$$

The first simple mixed PDE/ODE model then has the form

$$\begin{aligned} u_1'(t) &= d(t) - k_1 u_1(t) - \frac{s_{12}}{v_1} \tilde{k}_{12} \left(u_1(t) - \tilde{u}_2(t, 0) \right) \\ \frac{\partial}{\partial t} \tilde{u}_2(t, x) - D \frac{\partial^2}{\partial x^2} \tilde{u}_2(t, x) &= -k_2 \tilde{u}_2(t, x) \quad \text{for all } x \in (0, 1) \\ D \frac{\partial}{\partial x} \tilde{u}_2(t, 0) &= -\tilde{k}_{12} \left(u_1(t) - \tilde{u}_2(t, x) \right) \quad \text{for } x = 0 \\ D \frac{\partial}{\partial x} \tilde{u}_2(t, 1) &= 0 \quad \text{for } x = 1 \\ u_3'(t) &= p_3 - k_3 u_3(t) + p_{23} \tilde{u}_2(t, 1) \end{aligned}$$

Initial conditions are set to be

$$u_1(0) = u_1^{init}, \quad \tilde{u}_2(0, x) = 0 \quad \forall x \in [0, 1], \quad u_3(0) = p_3/k_3.$$

The following graphs give consecutively the solutions u_1 , \tilde{u}_2 and u_3 obtained from 1D discretization ($\Omega = [0, 1]$) and using equidistant mesh with N = 100 spatial points. The diffusion *D* is chosen as the scalar D = 0.01, other parameters are taken from the (sometimes fitted) values in the original model.



Simplest PDE/ODE model



There is a clear delay due to the diffusion in the cytoplasm.

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Slightly extended PDE/ODE model

To come closer to the desired model, we can add a fourth substance u_4 representing the mRNA-induced metabolizing enzyme in the cytoplasm. Be aware of the feedback loop - the enzyme metabolizes not only disease-causing substances, but the ligand as well:

$$\begin{array}{rcl} u_1' &=& \frac{d(t)}{v_1} - k_1 u_1 - \frac{s_{12}}{v_1} k_{12} \left(u_1 - \frac{1}{R_{12}} u_2 \right) \\ u_2' &=& -k_2 u_2 - k_{met} u_2 u_4 + \frac{s_{12}}{v_1} k_{12} \left(u_1 - \frac{1}{R_{12}} u_2 \right) \\ u_3' &=& p_3 - k_3 u_3 + \frac{s_{23}}{v_3} p_{23} u_2 - \frac{s_{23}}{v_3} k_{23} \left(u_3 - \frac{1}{R_{34}} u_4 \right) \\ u_4' &=& -k_4 u_4 + k_{34} \left(u_3 - \frac{1}{R_{34}} u_4 \right) \end{array}$$

Replacing $u_2(t)$ by $\tilde{u}_2(t, x)$ and $u_4(t)$ by $\tilde{u}_4(t, x)$, $x \in \Omega$, we obtain

$$\begin{split} u_{1}' &= \frac{d(t)}{v_{1}} - k_{1}u_{1} - \frac{s_{12}}{v_{1}}\tilde{k}_{12}\left(u_{1} - \frac{1}{R_{12}}\int_{\Gamma_{ext}}\tilde{u}_{2}\,\mathrm{d}S\right) \\ \frac{\partial}{\partial t}\tilde{u}_{2} - D_{2}\Delta\tilde{u}_{2} &= -k_{2}\tilde{u}_{2} - k_{met}\tilde{u}_{2}\tilde{u}_{4} \quad \text{for all } x \in \Omega \\ -D_{2}\nabla\tilde{u}_{2}\cdot\mathbf{n} &= -\tilde{k}_{12}\left(u_{1} - \frac{1}{R_{12}}\tilde{u}_{2}\right) \quad \text{for } x \in \Gamma_{ext}, \quad \text{zero for } x \in \Gamma_{nuc} \\ u_{3}' &= p_{3} - k_{3}u_{3} + \frac{s_{23}}{v_{3}}p_{23}\int_{\Gamma_{nuc}}\tilde{u}_{2}\,\mathrm{d}S - \frac{s_{23}}{v_{3}}\tilde{k}_{23}\left(u_{3} - \frac{1}{R_{34}}\int_{\Gamma_{nuc}}\tilde{u}_{4}\,\mathrm{d}S\right) \\ \frac{\partial}{\partial t}\tilde{u}_{4} - D_{4}\Delta\tilde{u}_{4} &= -k_{4}\tilde{u}_{4} \quad \text{for all } x \in \Omega \\ -D_{4}\nabla\tilde{u}_{4}\cdot\mathbf{n} &= -\tilde{k}_{23}\left(u_{3} - \frac{1}{R_{34}}\tilde{u}_{4}\right) \quad \text{for } x \in \Gamma_{nuc}, \quad \text{zero for } x \in \Gamma_{ext} \end{split}$$

Slightly extended PDE/ODE model

Assuming again that $\Omega = [0, 1]$ and letting $R_{12} = R_{34} = 1$, we obtain

$$\begin{aligned} u_1'(t) &= \frac{d(t)}{v_1} - k_1 u_1 - \frac{s_{12}}{v_1} \tilde{K}_{12}(u_1(t) - \tilde{u}_2(t, 0)) \\ \frac{\partial}{\partial t} \tilde{u}_2(t, x) - D_2 \frac{\partial^2}{\partial x^2} \tilde{u}_2(t, x) &= -k_2 \tilde{u}_2(t, x) - k_{met} \tilde{u}_2(t, x) \tilde{u}_4(t, x) \quad \text{for all } x \in (0, 1) \\ D_2 \frac{\partial}{\partial x} \tilde{u}_2(t, 0) &= -\tilde{K}_{12} (u_1(t) - \tilde{u}_2(t, 0)) \quad \text{for } x = 0 \\ \frac{\partial}{\partial x} \tilde{u}_2(t, 1) &= 0 \quad \text{for } x = 1 \\ u_3'(t) &= p_3 - k_3 u_3(t) + \frac{s_{23}}{v_3} p_{23} \tilde{u}_2(t, 1) - \frac{s_{23}}{v_3} \tilde{k}_{23}(u_3(t) - \tilde{u}_4(t, 1)) \\ \frac{\partial}{\partial t} \tilde{u}_4(t, x) - D_4 \frac{\partial^2}{\partial x^2} \tilde{u}_4(t, x) &= -k_4 \tilde{u}_4(t, x) \quad \text{for all } x \in (0, 1) \\ \frac{\partial}{\partial x} \tilde{u}_4(t, 0) &= 0 \quad \text{for } x = 0 \\ -D_4 \frac{\partial}{\partial x} \tilde{u}_4(t, 1) &= -\tilde{k}_{23} (u_3(t) - \tilde{u}_4(t, 1)) \quad \text{for } x = 1 \end{aligned}$$

Initial conditions are set to be

$$u_1(0) = u_1^{init}, \quad \tilde{u}_2(0, x) = 0 \quad \forall x \in [0, 1], \quad u_3(0) = p_3/k_3, \quad \tilde{u}_4(0, x) = 0 \quad \forall x \in [0, 1]$$

Notice the nonlinear term $\tilde{u}_2 \tilde{u}_4$.

Slightly extended PDE/ODE model



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A 1D mixed PDE/ODE model for the action of Rifampicin



A 1D mixed PDE/ODE model for the action of Rifampicin

Now consider a 1D mixed PDE/ODE model for the action of Rifampicin. Again, we have

$$\int_{\Gamma_{ext}} W(t,x) dS = W(t,0), \quad \int_{\Gamma_{nuc}} W(t,x) dS = W(t,1)$$

and thus the system of mixed PDE/ODE equations has the form

$$\begin{split} v_{ext} \frac{d X_{ext}(t)}{dt} &= d(t) - \frac{k_{imp}}{\sigma_{ext}} X_{ext}(t) + \frac{k_{exp}}{\sigma_{ext}} X_{int}(t,0) \\ \partial_t X_{int}(t,x) &= D_{int} \Delta X_{int}(t,x) - k_{assoc} X_{int}(t,x) PXR(t,x) \\ -k_{met} CYP3A4(t,x)X_{int}(t,x) + k_{dis}PR(t,x) \\ \partial_t PXR(t,x) &= D_{PXR} \Delta PXR(t,x) - k_{assoc} X_{int}(t,x) PXR(t,x) + k_{dis}PR(t,x) \\ \partial_t PR(t,x) &= D_{PR} \Delta PR(t,x) + k_{assoc} X_{int}(t,x) PXR(t,x) - k_{dis}PR(t,x) \\ \frac{d mRNA_{nuc}(t)}{dt} &= \frac{k_{mRNA,nuc}}{\sigma_{nuc}} PR(t,1) - k_{mRNA,deg} mRNA_{nuc}(t) \\ + p_{mRNA,back} + \frac{k_{nuc}}{\sigma_{nuc}} (mRNA_{cyt}(t,1) - mRNA_{nuc}(t)) \\ \partial_t mRNA_{cyt}(t,x) &= D_{CYP3A4} \Delta CYP3A4(t,x) + k_{cyp} mRNA_{cyt}(t,x) \\ - k_{cyp,deg} CYP3A4(t,x) \end{split}$$

Boundary conditions are:

$$\begin{aligned} -\upsilon_{ext} D_{int} \frac{\partial}{\partial x} X_{int}(t, x)|_{x=0} &= \frac{k_{imp}}{\sigma_{ext}} X_{ext}(t) - \frac{k_{exp}}{\sigma_{ext}} X_{int}(t, 0) \\ D_{int} \frac{\partial}{\partial x} X_{int}(t, x)|_{x=1} &= 0 \\ D_{PXR} \frac{\partial}{\partial x} PXR(t, x)|_{x=0} &= D_{PXR} \frac{\partial}{\partial x} PXR(t, x)|_{x=1} = 0 \\ D_{PR} \frac{\partial}{\partial x} PR(t, x)|_{x=0} &= D_{PR} \frac{\partial}{\partial x} PR(t, x)|_{x=1} = 0 \\ D_{mRNA} \frac{\partial}{\partial x} mRNA_{cyt}(t, x)|_{x=0} &= 0 \\ D_{mRNA} \frac{\partial}{\partial x} mRNA_{cyt}(t, x)|_{x=1} &= -\frac{k_{nuc}}{\sigma_{nuc}} \left(mRNA_{cyt}(t, 1) - mRNA_{nuc}(t) \right) \\ D_{CYP3A4} \frac{\partial}{\partial x} CYP3A4(t, x)|_{x=0} &= D_{CYP3A4} \frac{\partial}{\partial x} CYP3A4(t, x)|_{x=1} = 0 \end{aligned}$$

Initial conditions are:

for all $x \in [0, 1]$.

A 1D mixed PDE/ODE model for the action of Rifampicin

The parameters are taken from the literature and have the values:

$$\begin{aligned} k_{imp} &= k_{exp} = 6.55 \cdot 10^{-3}, & k_{met} = 2.47 \cdot 10^{-5}, & k_{mRNA,deg} = 4 \cdot 10^{-2} \\ k_{dis} &= 1.03 \cdot 10^{-4}, & k_{assoc} = k_{dis}/5.6, & p_{mRNA,back} = 2.83 \cdot 10^{-7} \\ k_{cyp} &= 2.5, & k_{cyp,deg} = 2.7 \cdot 10^{-4}, & k_{mRNA,nuc} = 39.3, & k_{nuc} = 306 \\ \upsilon_{ext} &= 1.0, & \sigma_{ext} = 1.1 \cdot 10^{-5}, & \sigma_{nuc} = 2.36 \cdot 10^{-6} \end{aligned}$$

These values are usually used in the model above for computational purposes but it is not sure that they are correct for this model. So, it may be better to use fitted values of some parameters (e.g. $p_{mRNA,back}$).

The values of diffusion coefficients

$$D_{int}$$
, D_{PXR} , D_{PR} , D_{mRNA} , D_{CYP3A4}

are unknown.

Initial conditions are:

$$X_{ext}^{init} = 10$$
, $mRNA_{nuc}^{init} = 2 \cdot 10^{-5}$, $d(t) = 0$,

i.e., no dosing added into the system but with initial nonzero xenobiotic concentration outside the cell.

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6 The method for solving mixed PDE/ODE system

The method - two approaches

The main idea in solving the above PDE/ODE system is to replace the second derivative in the space variable by finite differences. We create an equidistant mesh $x_0, x_1, \ldots, x_{N-1}, x_N$ of N + 1 nodes, where $x_0 = 0$ and $x_N = 1$, and obtain a system of 5N + 7 ODEs. Notation:

$$u_1(t) \equiv X_{\text{ext}}(t), \quad u_2(t, \mathbf{x}) = X_{\text{int}}(t, x), \quad \dots, \quad u_7(t, \mathbf{x}) = \text{CYP3A4}(t, x),$$

where $\mathbf{x} = (x_0, \dots, x_N)^T \in \mathcal{R}^{N+1}$. We arrive to solving the ODE of the form

v'(t) = Av(t) + b(t)

where

$$v(t) = [u_1(t), u_2(t, \mathbf{x}), u_3(t, \mathbf{x}), u_4(t, \mathbf{x}), u_5(t), u_6(t, \mathbf{x}), u_7(t, \mathbf{x})]^T \in \mathcal{R}^{5N+7},$$

 $b(t) = [d(t)/v_{ext}, -k_{assoc}\mathbf{u}_{2}\mathbf{u}_{3} - k_{met}\mathbf{u}_{2}\mathbf{u}_{7}, -k_{assoc}\mathbf{u}_{2}\mathbf{u}_{3}, k_{assoc}\mathbf{u}_{2}\mathbf{u}_{3}, p_{mRNA, back}, \mathbf{o}, \mathbf{o}]^{T} \in \mathcal{R}^{5N+7}$

and A is a sparse constant matrix with model parameters (18N + 15 nonzero elements). We used two approaches:

- The software ODEPACK developed by Alan Hindmarsh
- The Crank-Nicolson or the backward Euler scheme. The time derivatives are replaced by finite differences with a time step Δt. This leads to solving a linear system of equations. From the values v(t) we obtain new values v(t + Δt).

In both cases, we obtained practically the same results.

The method - backward Euler Newton method

The time derivatives are replaced by finite differences with a time step Δt :

$$\mathbf{v}'(t) = A\mathbf{v}(t) + b(t) \quad \Rightarrow \quad \frac{\mathbf{v}(t^{j+1}) - \mathbf{v}(t^{j})}{\Delta t} = A\mathbf{v}(t^{j+1}) + b(t^{j+1})$$

$$[I - \Delta t A] v(t^{j+1}) - \Delta t b(t^{j+1}) = v(t^j)$$

In fact, the term $b(t^{j+1}) \equiv b(v(t^{j+1}))$ is nonlinear, so we use the Newton method. Denote

$$x \equiv v(t^{j+1}), \quad p(x) = [I - \Delta t A] x - \Delta t b(x), \quad q = v(t^j).$$

Then we seek x such that

$$F(x)\equiv p(x)-q=0.$$

The Newton method starts with $x^{(0)}$ and produces iterations $x^{(1)}, x^{(2)}, \dots, x^{(K)}$ such that

$$x^{(k+1)} = x^{(k)} + d^{(k)}$$
, where $J(x^{(k)})d^{(k)} = -F(x^{(k)})$,

where J(x) is a sparse Jacobi matrix of F(x) (23N + 20 nonzero elements). We take $x^{(0)} = v(t^{j})$ and $v(t^{j+1}) = x^{(K)}$. It holds

$$\begin{aligned} -F(x^{(0)}) &= & \Delta t \left[Av(t^{j}) + b(t^{j}) \right], \\ -F(x^{(k)}) &= & q - x^{(k)} + \Delta t \left[Ax^{(k)} + b(x^{(k)}) \right]. \end{aligned}$$

The algorithm for creating time evolutions $v(t^0), v(t^1), \ldots, v(t^m)$:

Determine model parameters matrix A, set $\overline{A} = \Delta t A$ and j = 0.

2 Determine vector
$$b(t^j)$$
 and set $\bar{b}(t^j) = \Delta t \, b(t^j)$.

3 Set
$$x^{(0)} = v(t^j)$$
 and $-F(x^{(0)}) = \bar{A}x^{(0)} + \bar{b}(x^{(0)})$.

3 Set
$$\tilde{A} = I - \bar{A}$$
 and $\tilde{b}(t^j) = -\bar{b}(t^j)$.

Set k = 0 and determine a Jacobi matrix $J(x^{(k)}) = F'(x^{(k)})$.

(b) Compute $d^{(k)}$ as a solution of a system $J(x^{(k)})d^{(k)} = -F(x^{(k)})$.

3 Set
$$x^{(k+1)} = x^{(k)} + d^{(k)}$$
 and $-F(x^{(k+1)}) = v(t^j) - \left[\tilde{A}x^{(k+1)} + \tilde{b}(x^{(k+1)})\right]$.

If $||d^k|| \le \varepsilon_d$ or $||F(x^{(k+1)})|| \le \varepsilon_F$ or k+1 = K then set $v(t^{j+1}) = x^{(k+1)}$ and GOTO step 10.

Update
$$J(x^{(k+1)})$$
, set $k := k + 1$ and GOTO step 6.

If
$$j + 1 < m$$
, set $j := j + 1$ and GOTO step 2.

Parameter estimation

Collecting of experimental data from donors and subsequent estimation of missing parameters (diffusion coefficients and others): the estimates are obtained through curve fitting, i.e. minimization of a sum of squares based on comparing observed and computed concentrations:

$$Z(q_*) = \min_q Z(q), \quad ext{where} \quad Z(q) = \sum_{j=1}^p (ar{u}(t_j,q) - R_j)^2$$

where

- q_{*} is the optimal parameter set that minimizes the ordinary least squares (OLS) cost function Z
- R represents the set of observed concentrations in times t_j, in this case the mRNA fold induction
- $\bar{u}(t_j, q)$ is the time course model result (solution of ODEs) in times t_j , in this case the average value of the mRNA fold induction over space variables, i.e.

$$\bar{u}(t_j, q) = \frac{1}{N+1} \sum_{i=0}^{N} u_6(t_j, x_i)$$

p is a number of observations

Software used: The UFO system (Ladislav Lukšan et al.)

http://www.cs.cas.cz/luksan/ufo.html

Methods used:

- Variable metric method (VM) it uses approximations of the Hessian matrix or its inverse
- Heuristic method (HM) it does not require continuity of the objective function

Note that the objective function is not smooth as it is a solution of a system of ODEs.

The results for the action of Rifampicin

The results for CYP3A4 mRNA fold induction when N = 2 and N = 10 follow. When minimizing function *Z*, the outlier at time t = 2880 is omitted from the set of observations.



The main mathematical and numerical challenges with a mixed PDE/ODE model are:

- Correct PDE-formulation of the processes, existence, uniqueness, stability of the (periodic) solution
- Computational costs become an important issue. We need efficient numerical methods for:
- Time- and space-discretization (finite elements mesh generation)
- The solution of the discretized nonlinear coupled PDE/ODE model (a (quasi-)Newton type method)
- The solution of linear systems (Krylov subspace methods, preconditioning, sequences of linear systems)
- The sum of squares minimization when estimating the parameters (curve fitting)

Recall that during parameter estimation, the model must be run repeatedly! It is a two-level problem:

- outer problem minimization of Z subject to q
- inner problem solution of a system of ODEs for $\bar{u}(t_j, q)$

References

One of very few attempts is this direction:



Claus J., Friedmann E., Klingmüller U., Rannacher R., Szekeres T.: Spatial aspects in the SMAD signaling pathway. Journal of mathematical biology, vol. 67(5), p. 1171-1197 (2013).

For issues related to coupled PDE/ODE's in this context see also:



Carraro T., Friedmann E., Gerecht D.: Coupling vs decoupling approaches for PDE/ODE systems modeling intercellular sianalina. Journal of computational physics, vol. 314, p. 522-537 (2016).

Related publications:



Duintjer Tebbens J., Azar M., Friedmann E., Lanzendörfer M., Pávek P.: Mathematical Models in the Description of Pregnane X Receptor (PXR)-Regulated Cvtochrome P450 Enzyme Induction International Journal of Molecular Sciences, vol. 19, p. 1785 (2018).



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).

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