An enhanced model parameter estimation by a slow-fast decomposition. . . (and AVERAGING)

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Programs and Algorithms of Numerical Mathematics,
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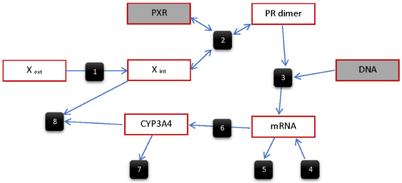
Back to PANM 19: XME Model & Slow-fast . . .

At least *three* time-scales of XME induction model:

1. *Drug (Rifampicin) transport* into blood and liver occurs in minutes: **'fast' time-scale** $T_0 = t$,
2. *CYP3A4 enzyme induction* is evolving in hours **'slow' time-scale** $T_1 = \epsilon_1 t$,
3. Drug degradation rate undergoes changes in days: **'even slower' time-scale** $T_2 = \epsilon_2 t$.



XME model according to Luke 2010 (and Jurjen Duintjer Tebbens 2019)

Outline

1. Introduction – Motivation
   - Slow-fast process #1 (a PK model)
2. Slow-fast ODEs & Methods: MMS – Averaging
   - Method of multiple scales (MMS)
   - Averaging & Theorem Krylov-Bogoliubov-Mitropolski
3. Case study (weakly damped pendulum)
   - Slow-fast process #2 (underdamped oscillations)
   - Numerical error analysis
   - Conclusion

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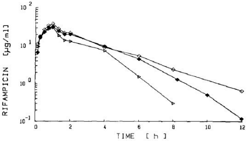

Fig. 2. Rifampicin serum concentration-time curves from patient 4 following intravenous administration of 600 mg rifampicin on day 1 (◇), day 8 (◆) and day 22 (▷)

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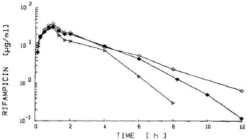

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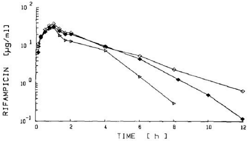

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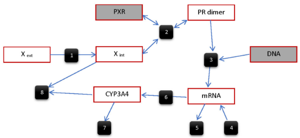
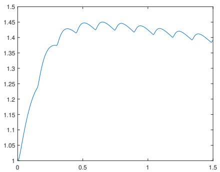
- **Method of averaging!** (Krylov-Bogoliubov-Mitropolski)

Slow-fast process #1 (a PK model):

Drug *rifampicin* metabolism and the PXR-mediated XME induction process





- Left: Graph representation of the network associated to a drug metabolism, there are 8 reactions, 5+1 state variables and ≈12 model parameters.
- Right: Numerical simulation of time series data of (CYP3A4)mRNA fold induction for periodic forcing (dial dosing of drug *rifampicin*).

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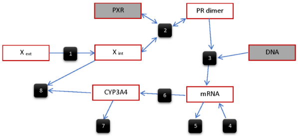

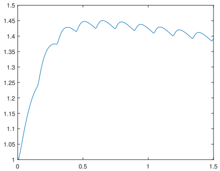

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J. D. Tebbens, C. Matonoha, A. Matthios, Š. Papáček: On parameter estimation in an *in vitro* compartmental model for drug-induced enzyme production in pharmacotherapy. Applications of Mathematics, 64 (2019), 253-277.

Method of multiple scales (MMS) for *slow-fast* ODEs

Two time-scales: **fast t and slow ϵt**

- General IVP (n-order ODE): Dynamics of state variables $y \in \mathbb{R}$ is:

$$\frac{\mathrm{d}^n\, y(t,\epsilon;p)}{\mathrm{d}t^n} = f\left(\frac{\mathrm{d}^{n-1}\, y(t,\epsilon;p)}{\mathrm{d}t^{n-1}}, \dots, y(t,\epsilon;p)\right), \tag{1}$$

with the corresponding initial conditions, $p \in \mathbb{R}^q$ and $\epsilon \ll 1$.

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- By the chain rule

$$\frac{\mathrm{d}\,(\bullet)}{\mathrm{d}t} = \frac{\partial(\bullet)}{\partial t} + \epsilon \frac{\partial(\bullet)}{\partial \tau}, \qquad (2)$$

  we can transform ODE (1) into a system of PDEs (each PDE corresponds to a power of ϵ).

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  we can transform ODE (1) into a system of PDEs (each PDE corresponds to a power of ϵ).
- Naïve implementation of MMS (disregarding *solvability conditions*) generates wrong results (secular terms), see Fig. 1 below.

Method of averaging (Theorem #1)

- Consider the IVP for a system of ODEs for $x(t) \in \mathbb{R}^n$

$$\dot{x} = \epsilon f(x,t), \quad x(0) = x_0. \tag{3}$$

- Here, $f : \mathbb{R}^n \times \mathbb{T} \to \mathbb{R}^n$ is a Lipschitz continuous function of $x(t) \in \mathbb{R}^n$ and a continuous function of $t \in \mathbb{T}$.
- For $R > 0$, let

$$B_R(x_0) = \{x(t) \in \mathbb{R}^n \,|\, |x - x_0| < R\}.$$

and

$$M = \sup_{x \in B_R(x_0),\, t \in \mathbb{T}} |f(x,t)|.$$

- Then there is a unique solution of the IVP,

$$x : (-T/\epsilon, T/\epsilon) \to B_R(x_0) \subset \mathbb{R}^n$$

that exists for $|t| < T/\epsilon$, where $T = \frac{R}{M}$.

Theorem #2 (Krylov-Bogoliubov-Mitropolski)

Approximation error estimation

With the same notation as the previous theorem:

- There exists a unique solution

  $$\bar{x} : (-T/\epsilon, T/\epsilon) \to B_R(x_0) \subset \mathbb{R}^n$$

  of the averaged equation

  $$\dot{\bar{x}} = \epsilon \bar{f}(\bar{x}), \quad \bar{x}(0) = x_0, \tag{4}$$

  where $\bar{f}(x) = \frac{1}{2\pi} \int_T f(x,t)\mathrm{d}t$.

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- Assume ...
  Then there exist constants $\epsilon_0 > 0$ and $C > 0$ such that for all $0 \leq \epsilon \leq \epsilon_0$

$$|x(t) - \bar{x}(t)| \leq C\,\epsilon \quad \text{for} \quad |t| \leq T/\epsilon. \tag{5}$$

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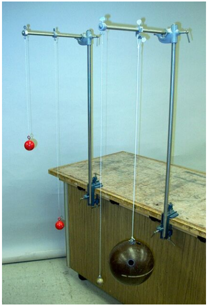
J.A. Sanders, F. Verhulst and J. Murdock, Averaging Methods in Nonlinear Dynamical Systems, Springer, 2007.

(simpler) Two time-scale process #2:

Initial value problem of a weakly damped pendulum (with small oscillations)

ODE for position (angle) $y \in \mathbb{R}$:

$$\frac{\mathrm{d}^2 y}{\mathrm{d}t^2} + \omega_0^2\, y = -2\delta\, \frac{\mathrm{d}\, y}{\mathrm{d}t},$$



with I.C. : $y(0) = 1$, $\dot{y}(0) = 0$,

where $\omega_0^2 = \frac{g}{l}$, and $\boxed{\epsilon \equiv \frac{\delta}{\omega_0} \ll 1.}$

By rescaling the time $t_{scaled} \equiv t\omega$

$$\boxed{\ddot{y} + y = -2\epsilon\, \dot{y},} \qquad (6)$$

where $\dot{y} = \frac{\mathrm{d}\, y}{\mathrm{d}t_{scaled}}$.

Using (2) & perturbartion series for y, e.g. $\boxed{y \simeq y^{(0)} + \epsilon\, y^{(1)}}$, the governing ODE (6) is transformed → PDEs.

Naive implementation of MMS

(disregarding solvability conditions)

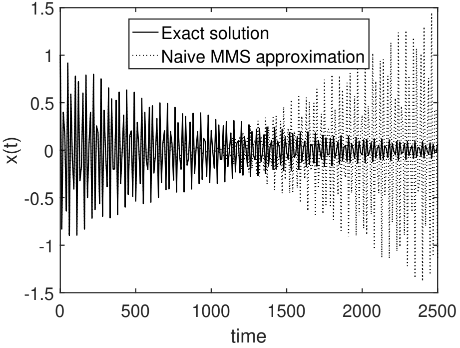


Figure 1: Comparison of the exact solution (6) (solid black curve) with the naive MMS approximation (dotted curve).

Case study - analytical solution

For computational experiments we will take equation (6)

$$\boxed{\ddot{y} + y = -2\epsilon\,\dot{y}, \quad y(0) = 1,\ \dot{y}(0) = 0}$$

Analytical solution is known:

$$y_{\text{exact}}(t) = \exp(-\epsilon t)\left(\cos(\omega t) + \frac{\epsilon}{\omega}\sin(\omega t)\right),$$

where $\omega = \sqrt{1-\epsilon^2}$.

Case study - method of averaging #1

$$\boxed{\ddot{y} + y = -2\epsilon\,\dot{y}, \quad y(0) = 1,\ \dot{y}(0) = 0}$$

- Transformation $y = r\sin(t-\phi),\ \dot{y} = r\cos(t-\phi)$
- (r,ϕ) satisfies the system

$$\dot{r} = \epsilon\cos(t-\phi)(-2r\cos(t-\phi)) \equiv \epsilon f_r(t)$$

$$\dot{\phi} = \epsilon\frac{1}{r}\sin(t-\phi)(-2r\cos(t-\phi)) \equiv \epsilon f_\phi(t)$$

- Applying averaging principle we obtain approximate solution of the system

$$\boxed{\dot{\bar{r}} = \epsilon\bar{f}_r, \quad \dot{\bar{\phi}} = \epsilon\bar{f}_\phi}$$

$$\bar{f}_r = \frac{1}{2\pi}\int_0^{2\pi} f_r(t)\,\mathrm{d}t, \quad \bar{f}_\phi = \frac{1}{2\pi}\int_0^{2\pi} f_\phi(t)\,\mathrm{d}t.$$

Case study - method of averaging #2

It holds

$$\bar{f}_r = \frac{1}{2\pi}\int_0^{2\pi} \cos(t-\phi)(-2r\cos(t-\phi)) = -r$$

$$\bar{f}_\phi = \frac{1}{2\pi}\int_0^{2\pi} \tfrac{1}{r}\sin(t-\phi)(-2r\cos(t-\phi)) = 0$$

and thus the system of equations is

$$\dot{\bar{r}} = -\epsilon\bar{r}, \quad \dot{\bar{\phi}} = 0$$

whose solution is

$$\boxed{\bar{r} = C_r\exp(-\epsilon t), \quad \bar{\phi} = C_\phi}$$

Case study - method of averaging #3

The averaging solution is then

$$y(t) = \bar{r}\sin(t-\bar{\phi}) = C_r \exp(-\epsilon t)\sin(t - C_\phi)$$

$$\dot{y}(t) = \bar{r}\cos(t-\bar{\phi}) = C_r \exp(-\epsilon t)\cos(t - C_\phi)$$

Initial conditions:

$$y(0) = C_r \sin(-C_\phi) = 1, \quad \dot{y}(0) = C_r \cos(-C_\phi) = 0,$$

which implies

$$\cos(-C_\phi) = 0 \quad \Rightarrow \quad C_\phi = \tfrac{3}{2}\pi$$

and

$$C_r = 1.$$

Finally,

$$y_{\text{aver}}(t) = \exp(-\epsilon t)\sin(t - \tfrac{3}{2}\pi) = \exp(-\epsilon t)\cos(t)$$

Case study - numerical approach (backward Euler)

$$\ddot{y} + y = -2\epsilon\,\dot{y}, \quad y(0) = 1,\ \dot{y}(0) = 0$$

- Transformation

$$x_1 = y, \quad x_2 = \dot{y}$$

leads to a system

$$\dot{x} + Ax = 0,$$

$$x = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, \quad A = \begin{pmatrix} 0 & -1 \\ 1 & 2\epsilon \end{pmatrix}$$

- Backward Euler method:

$$(I + \Delta t A)x(t + \Delta t) = x(t)$$

- Solutions:

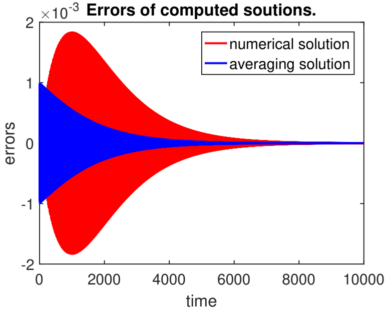
$$y_{\text{numer}}(t_j) = x_1(t_j), \quad j = 0, \ldots, m, \quad t_j = j\,\Delta t, \quad t_m = T$$

Case study - computational experiment #1

Comparison of errors:

$$y_{\text{exact}}(t_j) - y_{\text{numer}}(t_j), \quad y_{\text{exact}}(t_j) - y_{\text{aver}}(t_j)$$

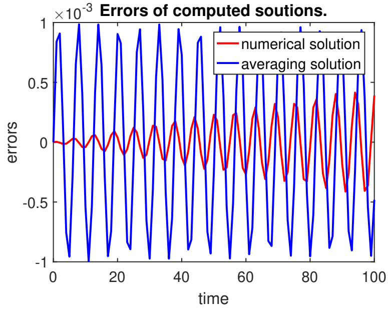
for ϵ =1.0E-3, Δt =1.0E-5, $T = 10000$.

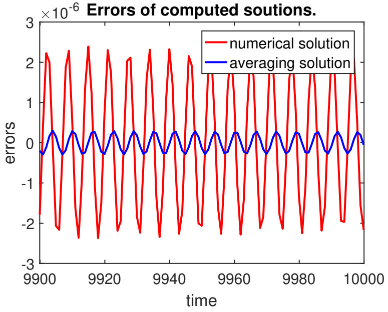


Case study - computational experiment #2

Initial and final time spans

Left: errors for initial time interval $t \in [0, 100]$,
Right: errors for final time interval $t \in [9900, 10000]$.





Conclusion – Future prospects

- The solution of slow-fast ODE, $x(t, \epsilon)$, is to be expected as a perturbation-series ($\tau = \epsilon\, t$):
  $x(t, \tau) = x^{(0)}(t, \tau) + \epsilon x^{(1)}(t, \tau) + \epsilon^2 x^{(2)}(t, \tau) + \dots$
- The suitability of the **Method of Multiple (time)Scales** (MMS) and mainly the **Averaging method** to approximate the solutions of perturbation problems.
- Naïve implementation of MMS generates wrong results (secular terms).
- Averaging method gives satisfactory results, the error is of order $C\, \epsilon$ (as predicted by the KBM theorem)
- Future: application of averaging method to our PK model

Thank you for your attention!