Some numerical issues in PBPK modelling for efficient pharmacotherapy

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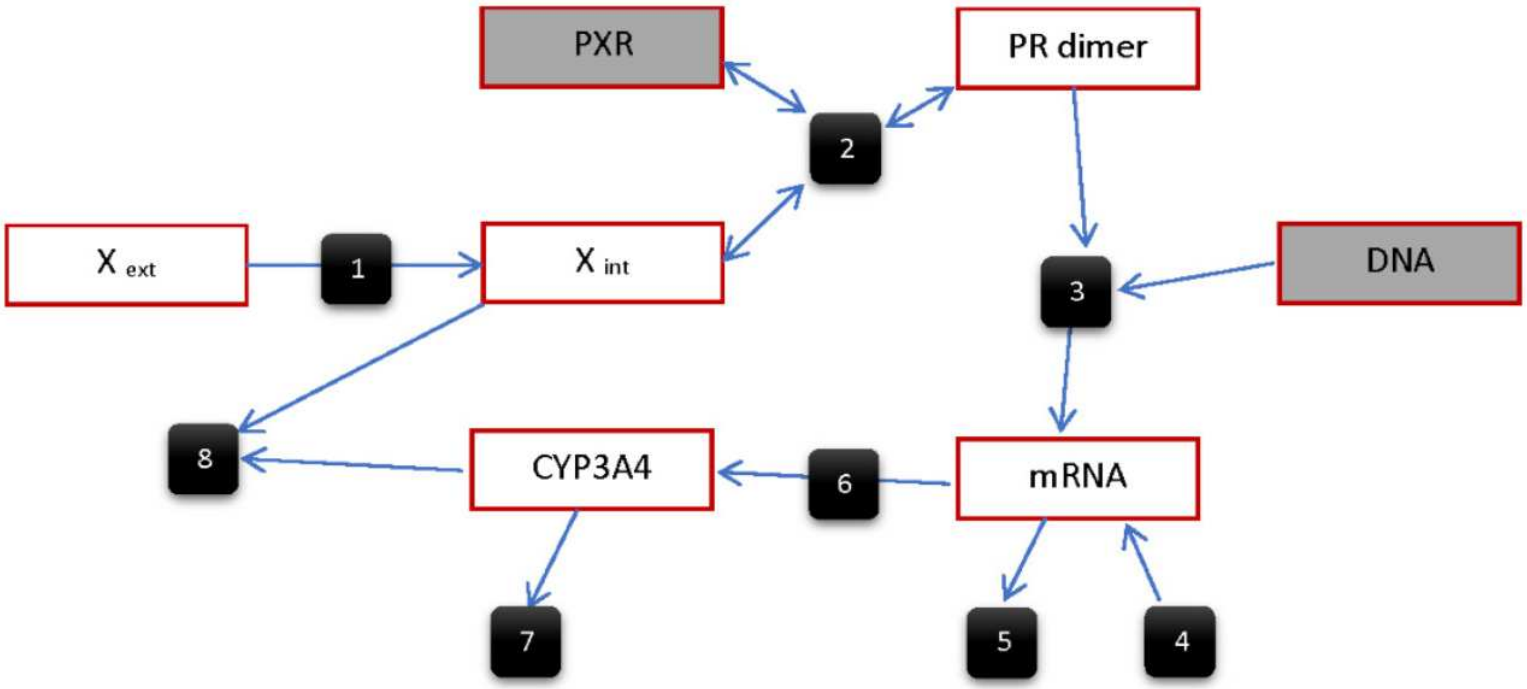
Jurjen

From in vitro to in vivo model

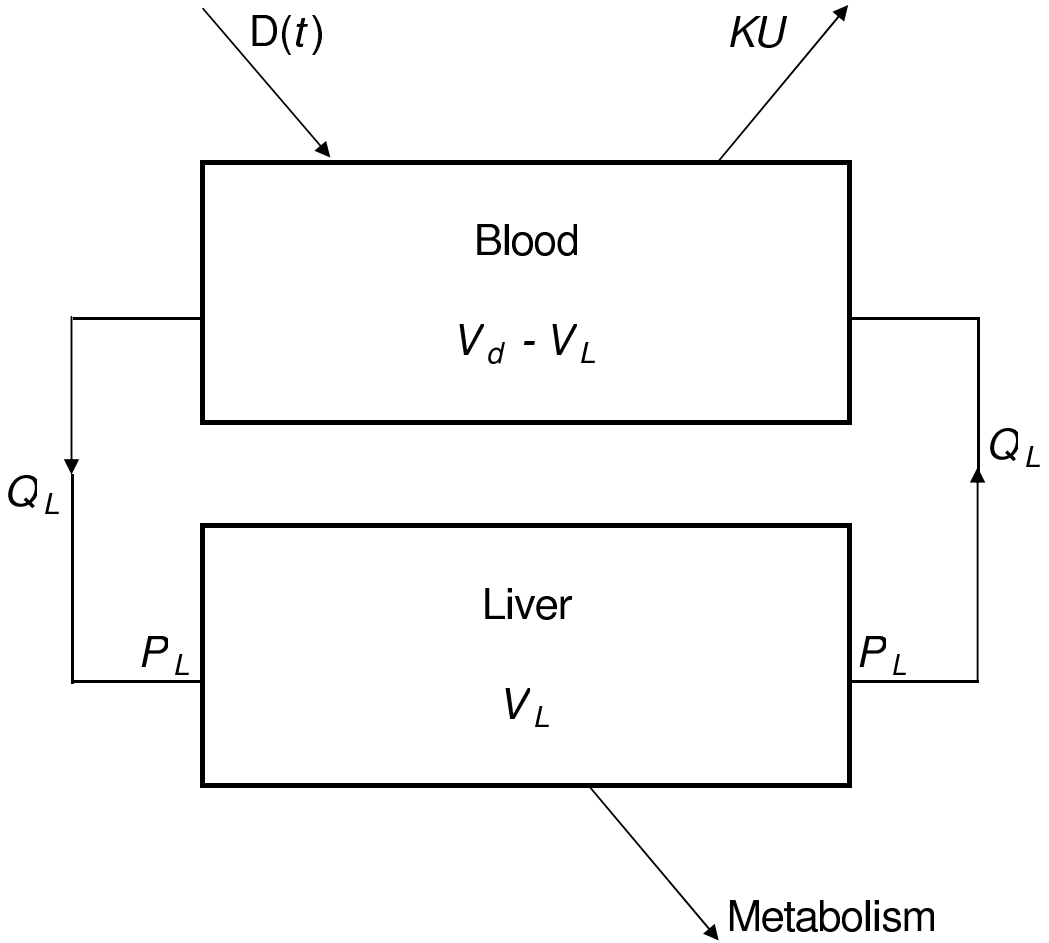
A physiologically based pharmacokinetic (PBPK) model for the action of rifampicin:



$$X_{ext}(t) \to X_B(t), \quad X_{int}(t) \to X_L(t)$$

From in vitro to in vivo model

Schematic of the two compartment pharmacokinetic model used to determine distribution of rifampicin in vivo:



In vivo model

$$\frac{d\mathrm{X_B}(t)}{dt} = \frac{\mathrm{D}(t) + Q_L \cdot \frac{\mathrm{X_L}(t)}{P_L} - Q_L \cdot \mathrm{X_B}(t) - KU \cdot \mathrm{X_B}(t)}{V_d - V_L}$$

$$\frac{d\mathrm{X_L}(t)}{dt} = \frac{Q_L}{V_L} \cdot \left(\mathrm{X_B}(t) - \frac{\mathrm{X_L}(t)}{P_L}\right) - k_{assoc} \cdot \mathrm{X_L}(t) \cdot (PXR_{tot} - \mathrm{PR}(t))$$
$$- k_{met} \cdot \mathrm{CYP3A4}(t) \cdot \mathrm{X_L}(t) + k_{dis} \cdot \mathrm{PR}(t)$$

$$\frac{d\mathrm{PR}(t)}{dt} = k_{assoc} \cdot \mathrm{X_L}(t) \cdot (PXR_{tot} - \mathrm{PR}(t)) - k_{dis} \cdot \mathrm{PR}(t)$$

$$\frac{d\mathrm{mRNA}(t)}{dt} = k_3 \cdot \mathrm{PR}(t) - mRNAdeg \cdot \mathrm{mRNA}(t) + mRNAbck$$

$$\frac{d\mathrm{CYP3A4}(t)}{dt} = k_4 \cdot \mathrm{mRNA}(t) - cypdeg \cdot \mathrm{CYP3A4}(t)$$

In vivo model

Functions dependent on time t [min]:

- $X_B(t)$ [μM] – concentration of rifampicin in the blood
- $X_L(t)$ [μM] – concentration of rifampicin in the liver
- $PR(t)$ [μM] – concentration of PXR-RXR heterodimer
- $mRNA(t)$ [μM] – rate of mRNA production;

  fold induction $mRNA_{fold}(t) = mRNA(t)/mRNA(0)$
- $CYP3A4(t)$ [μM] – change in CYP3A4 protein levels;

  fold induction $CYP3A4_{fold}(t) = CYP3A4(t)/CYP3A4(0)$
- $D(t)$ [mg/min] – function describing intravenous rifampicin dosing

In vivo model

Known parameters obtained from literature:

- $Q_L = 1.3$ [L/min] – blood flow rate
- $V_L = 1.815$ [L] – volume of the liver
- $V_d = 15.7$ [L] – overall volume of distribution
- $K_d = 8.36$ [μM] – binding affinity constant
- $k_3 = 39.3$ [min^{-1}] – transcription rate constant
- $k_4 = 2.5$ [min^{-1}] – translation rate constant
- $mRNAdeg = 0.04$ [min^{-1}] – degradation coefficient for mRNA
- $cypdeg = 2.7 \cdot 10^{-4}$ [min^{-1}] – CYP3A4 degradation rate parameter
- $k_{assoc} = \frac{k_{dis}}{K_d}$ [$(\mu\text{M min})^{-1}$] – association rate constant for the formation of the PXR-RXR heterodimer

In vivo model

Unknown parameters to be optimized:

- PXR_{tot} [μM] – total concentration of PXR in the system
- k_{dis} [min^{-1}] – first order dissociation constant
- $mRNAbck$ [μM/min] – background mRNA production rate
- k_{met} [$(\mu\text{M min})^{-1}$] – second order metabolic constant
- KU [L/min] – urinary excretion rate
- P_L [unitless] – liver/blood partition coefficient

In vivo model

Initial conditions:

- $\mathrm{D}(t)$ – a dose of 600 mg of rifampicin administered intravenously over 60 minutes, repeatedly every day: $\mathrm{D}(t) = D_t$ for $t \in [0, 60] \cup [1440, 1500] \cup \ldots$ and $\mathrm{D}(t) = 0$ otherwise, where $D_t = 10$
- $\mathrm{X_B}(0) = D_t$ – initial concentration of rifampicin in the blood is equal to the dose of rifampicin being administered
- $\mathrm{X_L}(0) = 0$ – concentration within the liver has an initial value of zero
- $\mathrm{PR}(0) = 0$ – there is no concentration of PXR-RXR heterodimer initially
- $\mathrm{mRNA}(0) = mRNA_{ss} = \frac{mRNAbck}{mRNAdeg}$ – initial value is assumed to be the steady state value
- $\mathrm{CYP3A4}(0) = CYP3A4_{ss} = \frac{k_4}{cypdeg} \cdot mRNA_{ss}$ – initial value is assumed to be the steady state value

Parameter estimation

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

$$J(q_*) = \min_q J(q), \quad \text{where} \quad J(q) = \sum_{i=1}^{N} (f(t_i, q) - R_i)^2$$

and

- q_* is the optimal parameter set that minimizes the ordinary least squares (OLS) cost function J
- R represents the rifampicin levels in blood (values $X_B(t)$) presented in Loos, see the next slide
- $f(t_i, q)$ is the time course model result (solution of ODEs)
- N is a number of observations

Experimental data for $X_B(t)$

Time values of rifampicin concentration in blood ($X_B(t)$), repeated dosing 600 mg during 60 minutes every day

Time	0	20	40	60	80	100
day 1	10.0	26.1	33.7	38.3	27.8	23.0
day 8	8.80	23.7	27.8	33.7	23.7	20.2
day 22	6.81	19.6	24.5	30.0	19.6	14.7

Time	120	240	360	480	600	720
day 1	21.5	10.7	5.62	2.45	*	0.64
day 8	19.6	9.38	4.35	1.38	0.45	0.12
day 22	13.8	7.26	1.67	0.32	*	*

$*$ indicates missing data

Loos U., Musch E., Jensen J.C., Mikus G., Schwabe H.K., Eichelbaum M.
Pharmacokinetics of oral and intravenous rifampicin during chronic administration.
Klin. Wochenschr. **63** (1985), 1205–1211.

Software

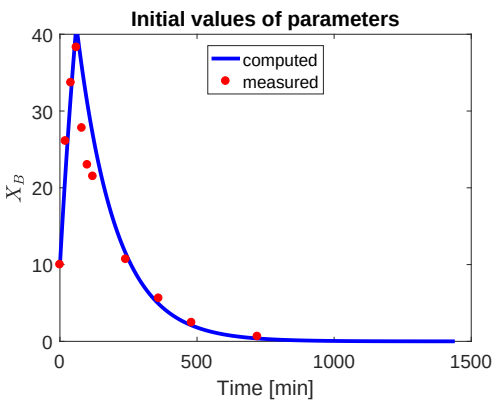
Computation of the ordinary least squares cost function J for optimal parameters: two-level problem:

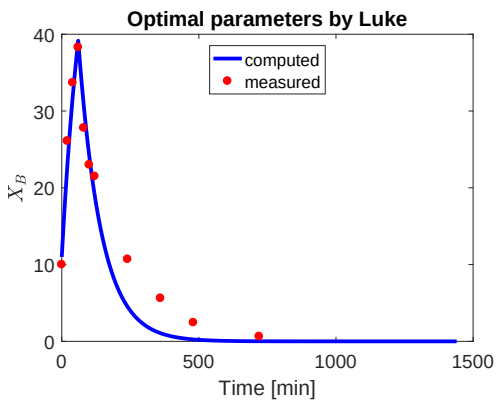
- outer problem – minimization of J subject to q
  software used: UFO (Ladislav Lukšan et al.)
  http://www.cs.cas.cz/luksan/ufo.html
  method used: line-search variable metric method for direction determination
- inner problem – solution of a system of ODEs ($f(t_i, q)$)
  software used: ODEPACK (Alan Hindmarsh)
  https://people.sc.fsu.edu/~jburkardt/f77_src/odepack/odepack.html
  method used: method based on backward differentiation formulas (stiff), chord iteration with a user-supplied full Jacobian

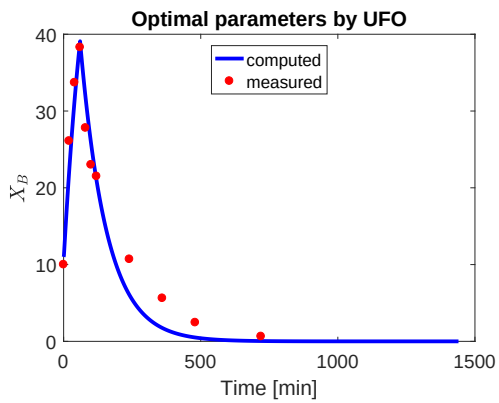
Optimal parameters for 1 day

The ordinary least squares cost function J for optimal parameters computed by Luke and UFO using the data for 1 day only.

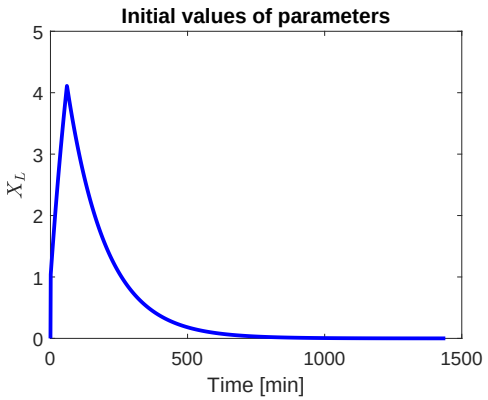
parameter	initial value	optimal value by Luke	optimal value by UFO
PXR_{tot}	9.47D–7	1.35D–1	3.43D–5
k_{dis}	1.03D–4	1.03D–4	1.08D–3
$mRNAbck$	2.83D–7	4.23D–7	1.00D–8
k_{met}	2.47D–5	2.47D–5	1.00D–8
KU	1.00D–1	1.67D–1	1.52D–1
P_L	1.00D–1	1.11D–2	4.31D–1
J	185.2735	97.3111	87.0709

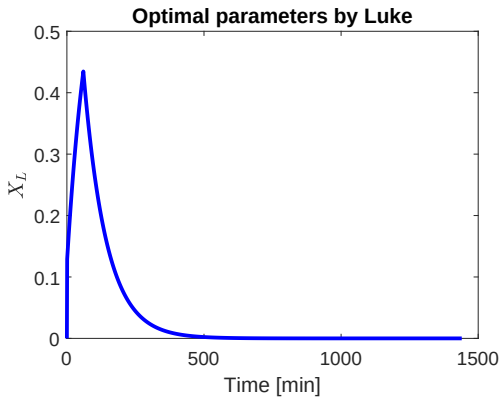


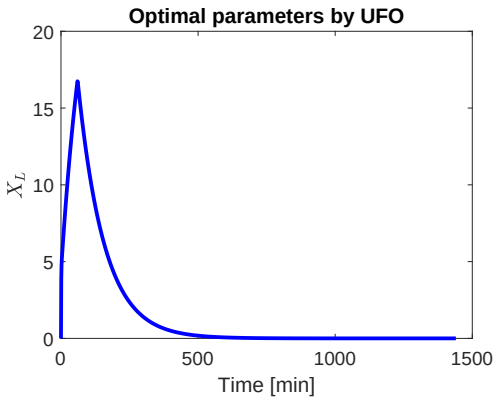


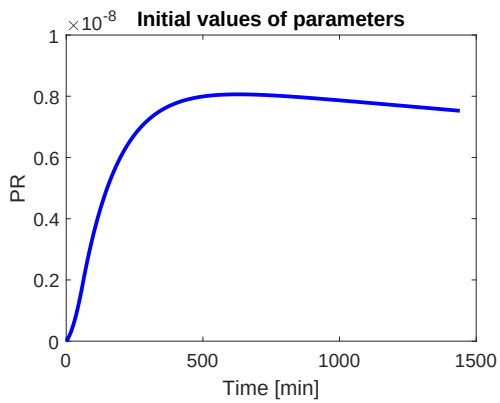


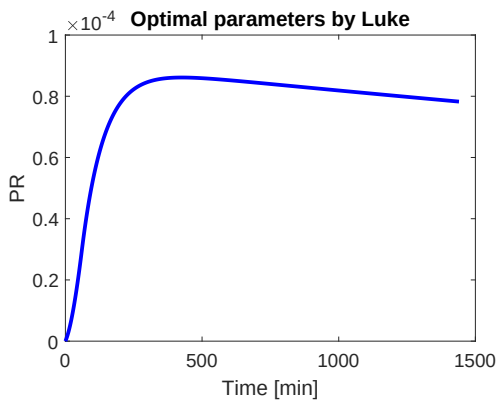
Functions $X_L(t)$, $PR(t)$ – 1 day

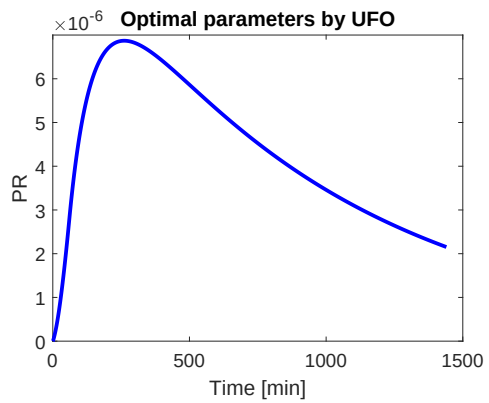




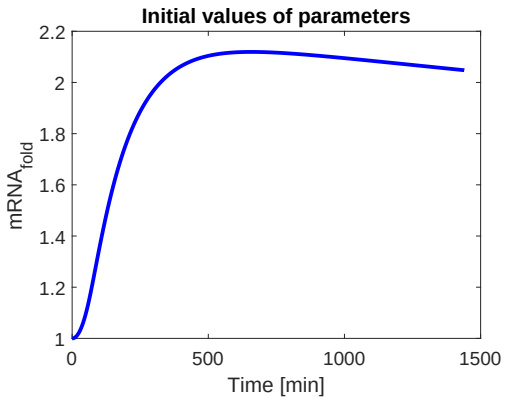


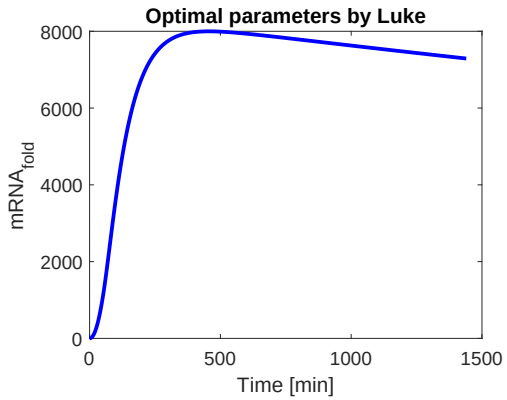


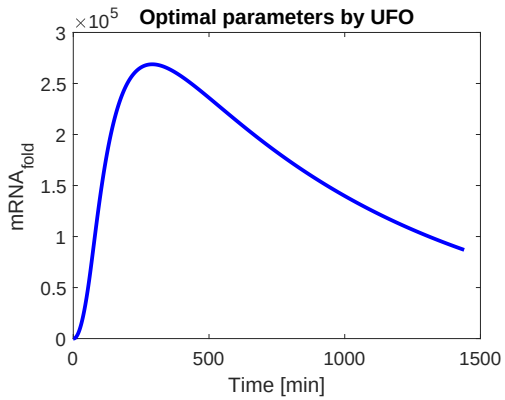


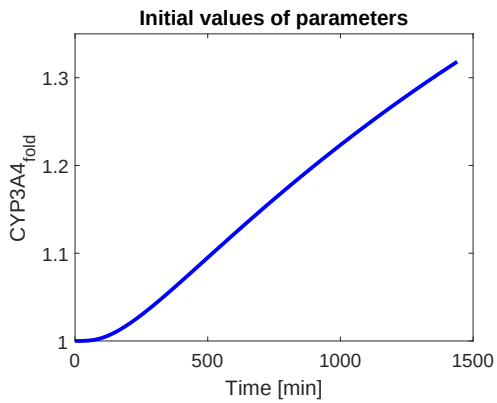


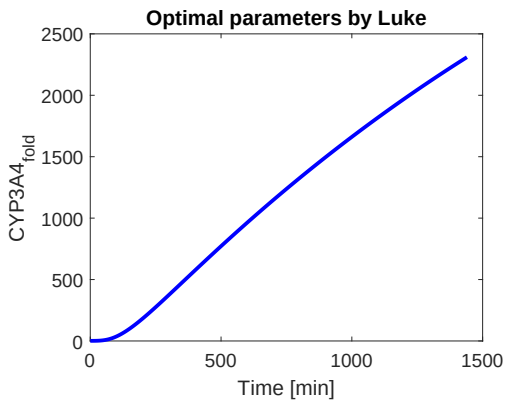
Functions mRNA(t), CYP3A4(t) – 1 day

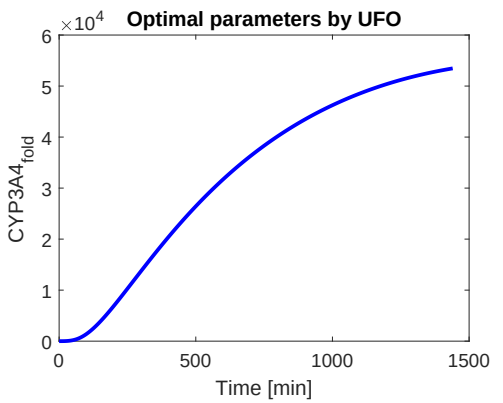








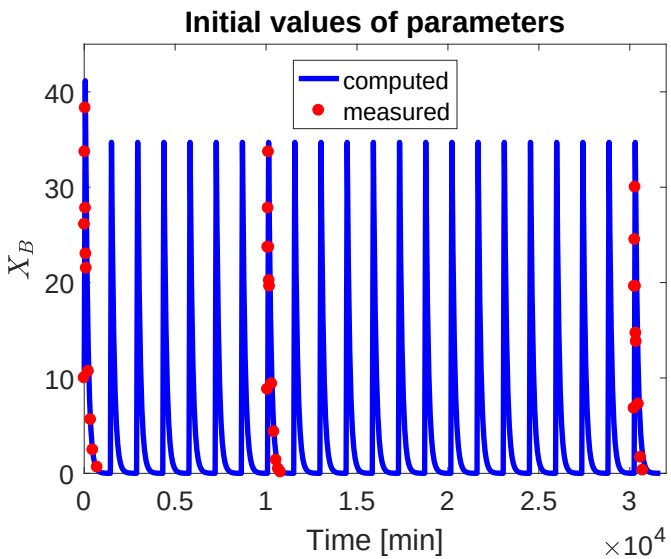


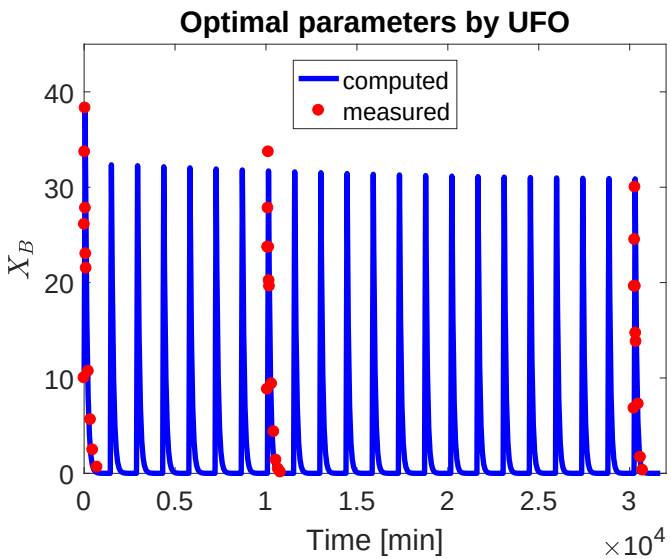


Optimal parameters for 22 days

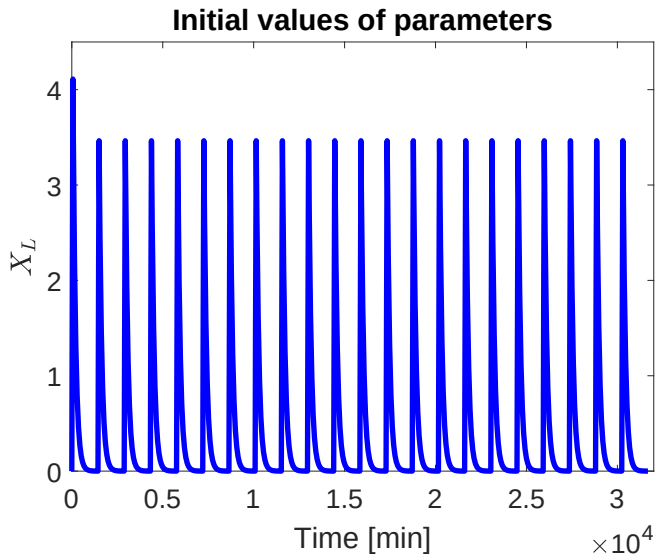
The ordinary least squares cost function J for optimal parameters computed by UFO using the data for 22 days.

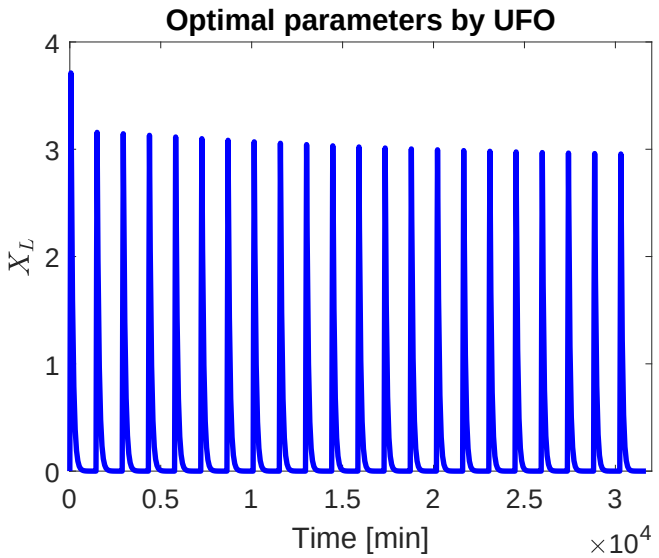
parameter	initial value	optimal value by UFO
PXR_{tot}	9.47D–7	6.7385D–3
k_{dis}	1.03D–4	4.7560D–5
$mRNAbck$	2.83D–7	6.4921D–3
k_{met}	2.47D–5	1.0790D–4
KU	1.00D–1	1.0639D–1
P_L	1.00D–1	1.0006D–1
J	911.3656	510.3724

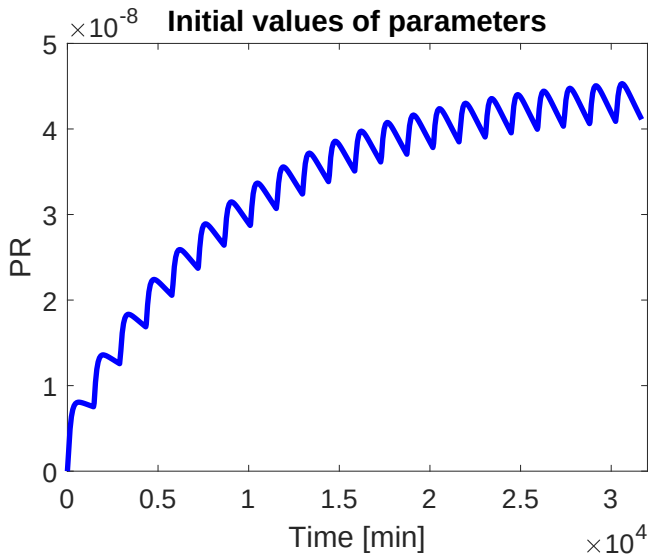


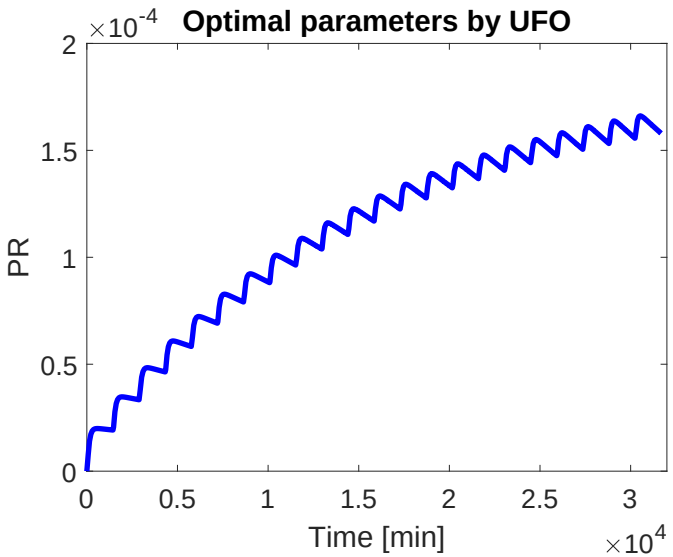


Functions $X_L(t)$, $PR(t)$ – 22 days

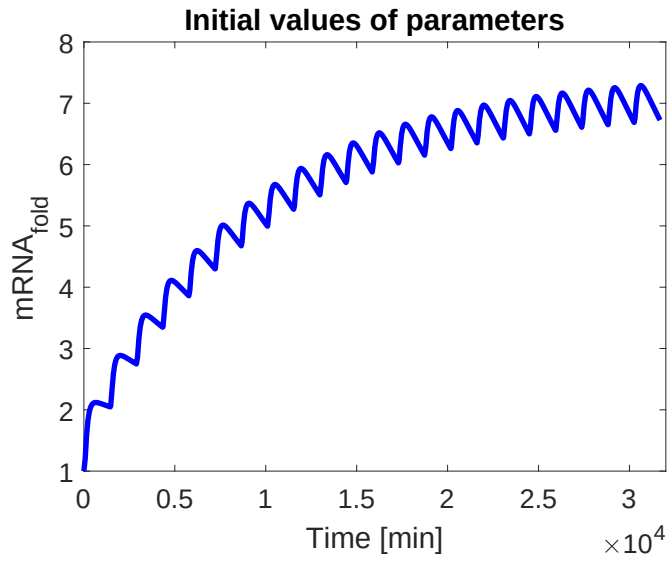


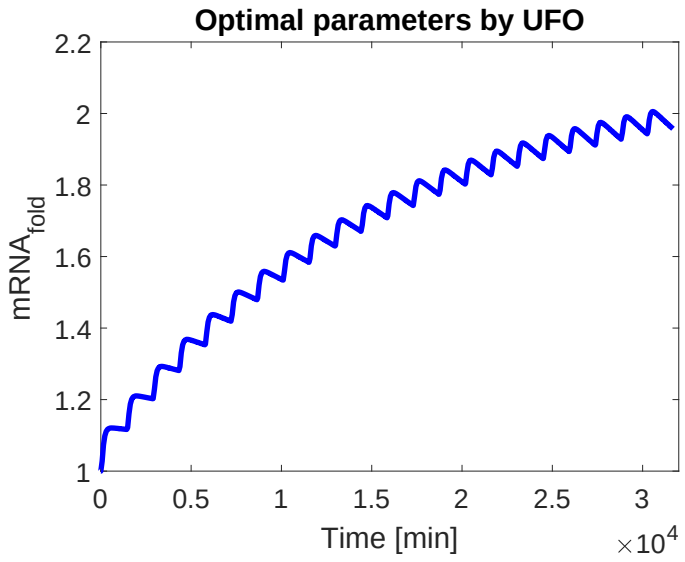


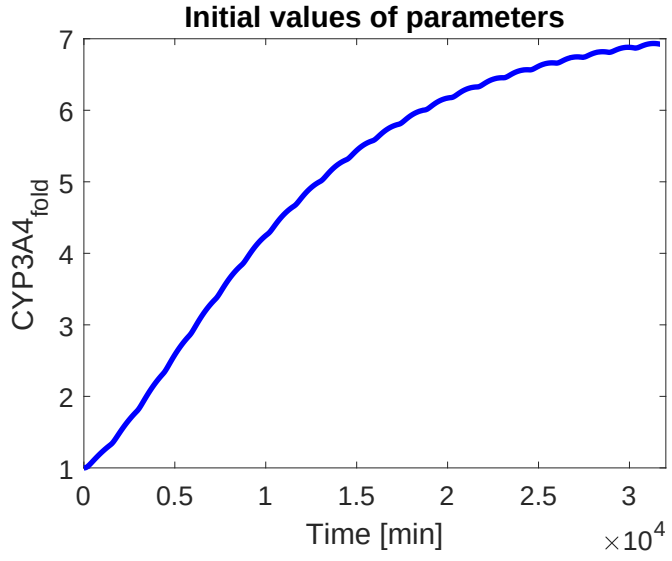


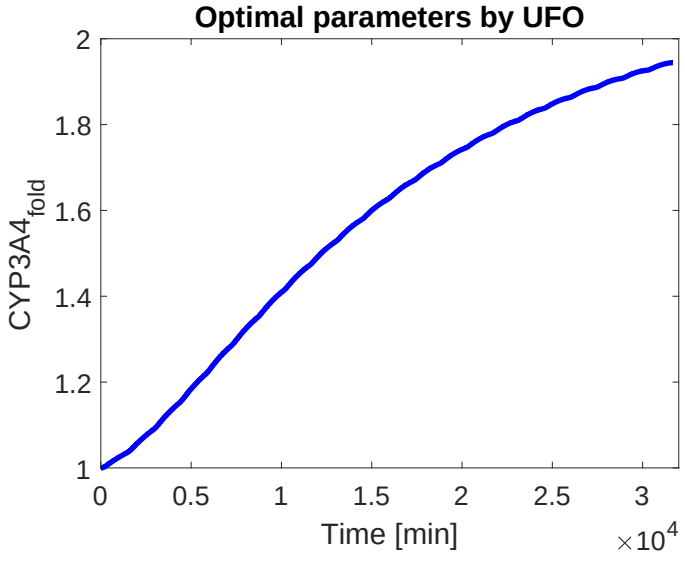


Functions mRNA(t), CYP3A4(t) – 22 days









Discussion

Discussion:

- Important: Need more experimental data! (There exist a lot of different local minima.)
- What parameters most influence the results? (The question of sensitivity analysis – preliminary done by Luke.)
- The obtained optimal parameters and corresponding functions must be physically correct – adding constraints or bounds to the optimization problem.
- How to choose local parameters in UFO and ODEPACK (method, initial approximation, time step in solving ODEs, step-length for direction determination,...)? They influence the solution obtained...
- Better software for solving stiff ODEs?
- Robust optimization method (quasi-Newton, Gauss-Newton)?
- ...

Štěpán