Introduction
Analysis of biological oscillators as well as other biological systems is often based on the establishment of quantitative dynamical models, which however require accurate kinetic data. Since these data are often missing, hard or even impossible to obtain, computer simulations are used in a combination with different optimisation procedures to tune the dynamical response of the model with experimental observations. We describe a computational framework for efficient analysis of biological oscillators. We demonstrate the framework on a computational model of p53-Mdm2 feedback loop oscillator.

Establishment of computational model(s)

Theory
Computational models are established on the basis of the literature and experimental data, and on the basis of expert knowledge.

Application
We apply the framework on a deterministic model of cellular p53 regulation derived from (Leenders and Tuszynski, 2013).

\[
\frac{dp53}{dt} = k_0 - k_1[p53][Mdm2_{nuclear}] - d_{p53}p53,
\]

\[
\frac{d[RNA\text{\_nuclear}]}{dt} = k_m + k_2 \frac{[p53]^3}{k_3^3 + [p53]^3} - k_0[RNA\text{\_nuclear}],
\]

\[
\frac{d[RNA\text{\_cytoplasmic}]}{dt} = k_0[RNA\text{\_nuclear}] - d_{tc}[RNA\text{\_cytoplasmic}],
\]

\[
\frac{d[Mdm2\text{\_cytoplasmic}]}{dt} = k_7[RNA\text{\_cytoplasmic}] - k_1[Mdm2\text{\_cytoplasmic}],
\]

\[
\frac{d[Mdm2\text{\_nuclear}]}{dt} = k_1[Mdm2\text{\_cytoplasmic}] - d_{mn}[Mdm2\text{\_cytoplasmic}]^2 - k_3[Mdm2\text{\_nuclear}][ARF],
\]

\[
\frac{d[ARF]}{dt} = k_s - d_{ARF} - k_4[Mdm2\text{\_nuclear}][ARF].
\]

Definition of observed characteristics

Theory
Characteristics define an appropriate dynamical response of the model. Some examples of such characteristics for oscillatory systems are (1) the behaviour oscillatory or not, (2) period of oscillations, (3) amplitude of oscillations and (4) oscillation spikiness. Desired behaviour can be tuned on the basis of selected characteristics.

Application
We observe the oscillation periods, which should equal approximately 5 hours (Geva-Zatorsky et al., 2010). We measure the oscillation periods on the timecourse of p53 protein concentrations obtained with the simulations performed on a deterministic model of cellular p53 regulation.

Model analysis

Theory
The dynamical response of the model is analysed in dependence on unknown parameter values. When the dimensionality of unknown parameters is small, relatively simple methods, such as parameter sweeping analysis can be used. However, when we are dealing with a larger number of unknown parameters, which is usually the case in real scenarios, more advanced methods, such as sensitivity analysis should be used.

Application

We assess the sensitivity of the oscillation periods in dependence on the values of unknown parameters, which are in our case p53 production (k), ARF production (k), basal MDM2 mRNA production (k), p53 induced MDM2 mRNA production (k), MDM2 nuclear import (k) and MDM2 autoubiquitination (d).

References: