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Computational framework for the analysis of biological oscillators and its application to p53-Mdm2 interaction

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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).

$$\frac{d[p53]}{dt} = k_p - k_1[p53][MDM2_{nuclear}] - d_p[p53],$$

$$\frac{d[RNA_{nuclear}]}{dt} = k_m + k_2 \frac{[p53]^{1.8}}{k_D{}^{1.8}+[p53]^{1.8}} - k_0[RNA_{nuclear}],$$

$$\frac{d[RNA_{cytoplasmic}]}{dt} = k_0[RNA_{nuclear}] - d_{rc}[RNA_{cytoplasmic}],$$

$$\frac{d[MDM2_{cytoplasmic}]}{dt} = k_T[RNA_{cytoplasmic}] - k_i[MDM2_{cytoplasmic}],$$

$$\frac{d[MDM2_{nuclear}]}{dt} = k_i[MDM2_{cytoplasmic}] - d_{mn}[MDM2_{cytoplasmic}]^2$$
$$-k_3[MDM2_{nuclear}][ARF],$$

$$\frac{d[ARF]}{dt} = k_a - d_a[ARF] - k_3[MDM2_{nuclear}][ARF].$$

Definition of observed characteristics

Theory

Characteristics define an appropriate dynamical response of the model. Some examples of such characteristics for oscillatory systems are (1) is 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.

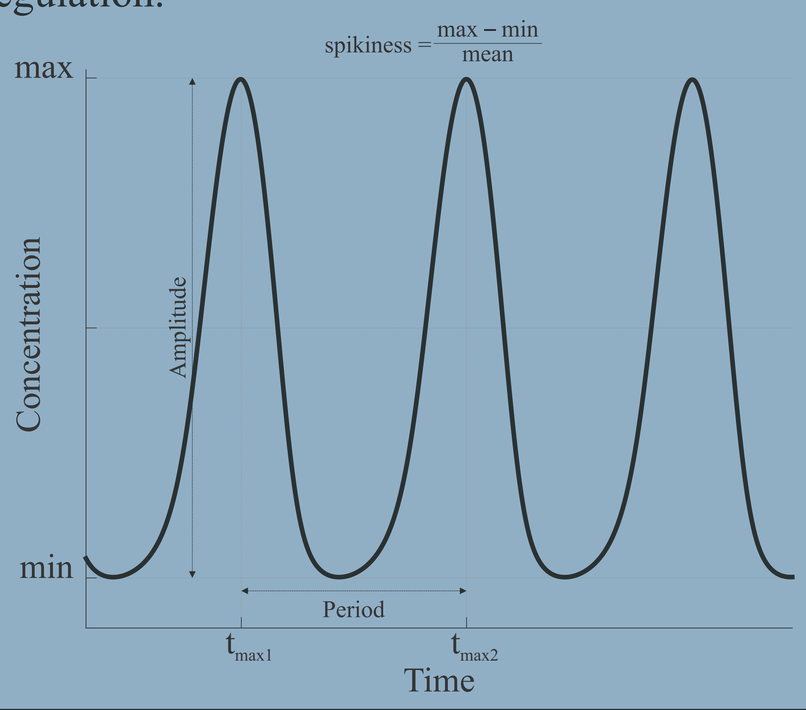

Figure 1: Characterisation of oscillatory dynamics.

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_p), ARF production (k_a), basal MDM2 mRNA production (k_m), p53 induced MDM2 mRNA production (k_2), MDM2 nuclear import (k_i) and MDM2 autoubiquitination (d_{mn}).

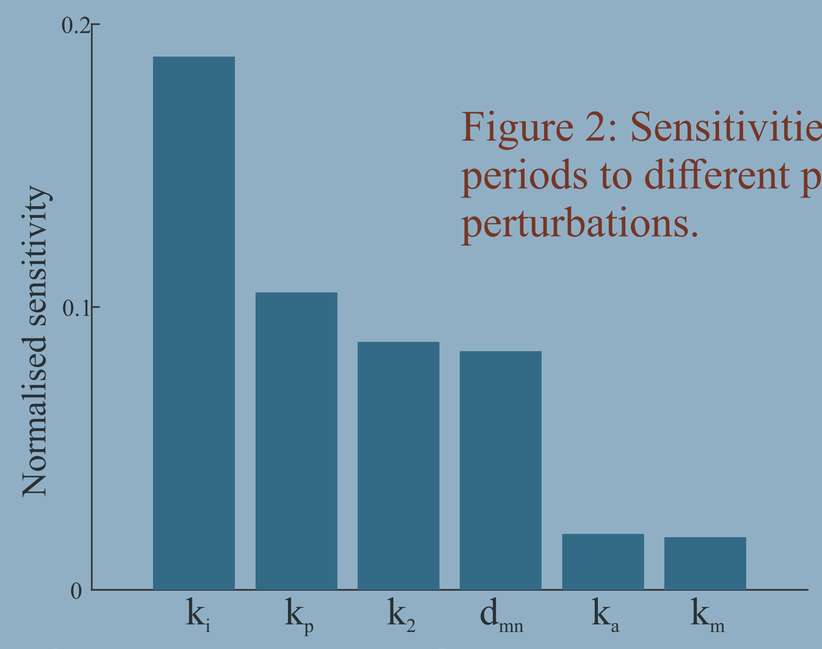

Figure 2: Sensitivities of oscillation periods to different parameter perturbations.

Tuning the response of the model

Theory

Tuning the unknown parameter values is performed in accordance with the specified dynamical response of the model. Here, different optimisation techniques can be applied. When the parameters are roughly known, we can apply local methods with fast convergence, such as Nelder-Mead method, which do not guarantee the discovery of the globally best solution. These can be identified with global methods, such as genetic algorithms, which exhibit large computational complexity.

Application

We apply the process of tuning the oscillation periods to the toy model of cellular p53 regulation, in which a larger emphasis is given on the unknown parameters, which were shown to significantly affect the oscillation periods (we identified the parameter k_i as the most influential, and k_p, k_2 and d_{mn} as having a moderate influence). The tuning is performed using a combination of genetic algorithms (global optimisation) and Nelder-Mead method (local optimisation).

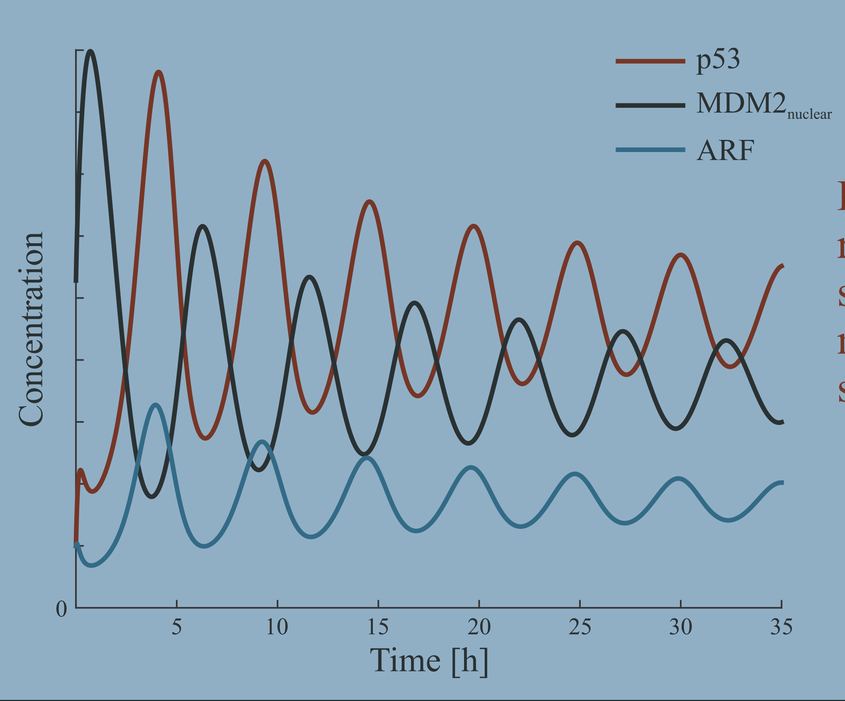

Figure 3: Simulation results obtained on a single amongst many viable solutions.

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Geva-Zatorsky, N., Dekel, E., Batchelor, E., Lahav, G., and Alon, U. (2010). Fourier analysis and systems identification of the p53 feedback loop. Proc. Natl. Acad. Sci. U.S.A. 107, 13550–13555, doi: 10.1073/pnas.1001107107.

Leenders, G. B., and Tuszynski, J. A. (2013). Stochastic and deterministic models of cellular p53 regulation. Frontiers. Oncol. 3, doi: 10.3389/fonc.2013.00064.