Sensitivity analysis of a generic cell-cycle model

Eszter Sipos-Szabó, János Tóth
Budapest University of Technology and Economics (BUTE), Hungary

Ildikó Pál, István Gy. Zsély, Tamás Turányi
Institute of Chemistry, Eötvös University (ELTE), Budapest, Hungary

Attila Csikász-Nagy
Centre for Computational and Systems Biology, Trento, Italy

Introduction

The cell cycle control is based on the role of Cdk (Cyclin dependent protein kinase) molecules in coordinating the events of DNA synthesis, spindle formation, nuclear division, and cell separation. After the cell division, for a long period only the cell size increases (phase G1), followed by the DNA synthesis (phase S/G2). Finally, two identical nuclei and then two daughter cells are formed (mitotic phase M of the cell cycle). A series of mathematical models, using sets of differential and algebraic equations, have been created to describe the change of enzyme concentrations during a cell cycle in wild-type cells and in various mutants.

The cell cycle model investigated here was created by Csikász-Nagy et al. in 2006 [1]. This generic cell cycle model is able to simulate several types of living cells in such a way that for each cell type the differential-algebraic system of equations are identical, but the values of the parameters are different. This common system of differential-algebraic equations contains 14 variables and 86 parameters. In our studies, parameter sets related to budding yeast, fission yeast and mammal cells were investigated.

Sensitivity analysis

A dynamical model can be characterized by the following initial value problem

$$\mathrm{d}\mathbf{Y}/\mathrm{d}t = \mathbf{f}(\mathbf{Y},\mathbf{p}) \qquad \mathbf{Y}(0) = \mathbf{Y}^0$$

where *t* is time, **Y** is the *n*-vector of variables, **p** is the *m*-vector of parameters, $\mathbf{Y}_0$ is the vector of the initial values of the variables, and **f** is the right-hand-side of the differential equations.
The local sensitivity function $s_{ik}(t)$ can be calculated by solving the following initial value problem:

$$\dot{\mathbf{S}} = \mathbf{J}\mathbf{S} + \mathbf{F} \qquad \mathbf{S}(0) = \mathbf{0}$$

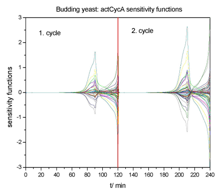
where $\mathbf{S}(t)==\{\partial Y_i/\partial p_k\}$ is the time dependent local sensitivity matrix, **J** is the Jacobian ($\mathbf{J}=\{\partial f_i/\partial Y_j\}$) and matrix **F** contains the derivatives of the right-hand-side of the ODE with respect to the parameters ($\mathbf{F}=\{\partial f_i/\partial p_k\}$). The $s_{ik}(t)$ local sensitivity functions show the effect of a small perturbation of parameter *k* on the change of variable *i* at time *t*.

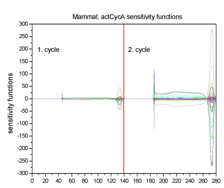
Calculation of sensitivity functions

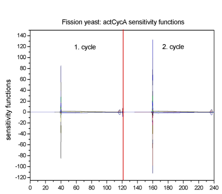
Local sensitivity functions of the generic cell cycle model were calculated for all variables and all parameters for each of the three cell types. Integration of the differential equations and calculation of sensitivities were carried out by subroutine DASAC that had been distributed with the SENKIN code [2].

Non-periodic sensitivity functions

Period time is a function of the values of kinetic parameters, therefore the peaks of the sensitivity functions were continously increasing:







Making the sensitivity functions periodic

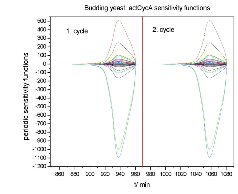
One characteristic feature of the sensitivity functions of periodic models is that their amplitude is a linearly increasing function of time, if the period time of the model depends on the parameter value. The following relation exists between the "raw" (increasing) sensitivities and the "cleaned" (periodic) sensitivities:

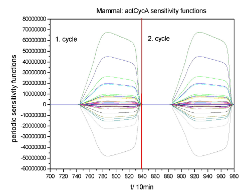
$$\partial C_i(t)/\partial\alpha_j = -t/\tau\,(\partial\tau/\partial\alpha_j)\,\partial C_i(t)/\partial t + (\partial C_i(t)/\partial\alpha_j)_\tau$$

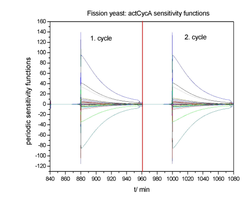
To eliminate the dominating first term, we can take into account that the second term is periodic, and for large *t* the first term is dominating. However, the first term can be approximated using singular value decomposition. Having deduced this first term from the sensitivity functions, the cleaned sensitivity functions are obtained which are periodic in the case of an oscillatory reaction. This method was elaborated by Zak et al. [4] who developed further the earlier method of Larter [5].

Using *Mathematica*, all raw (non-periodic) sensitivity functions were converted to periodic sensitivity functions.

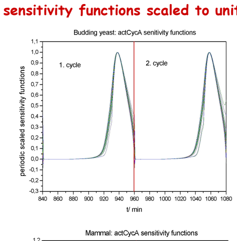
Periodic sensitivity functions

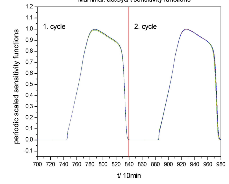


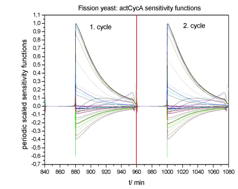




Periodic sensitivity functions scaled to unit peak value

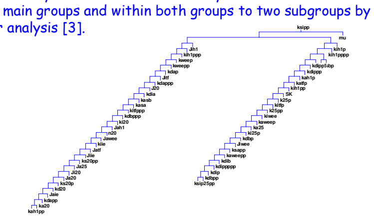






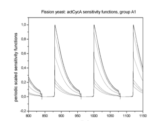
Clustering the shapes of sensitivity functions

Figures of the scaled, periodic sensitivity functions show, that the sensitivity functions of budding yeast and mammalian cells are globally similar. Global similarity of the sensitivity functions of another cell cycle model have been investigated [6]. The shapes of the sensitivity functions of the fission yeast cells could be sorted to two main groups and within both groups to two subgroups by cluster analysis [3].



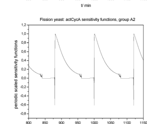
Sensitivity function groups of the fission yeast cells

Group A1:
parameters
2, 3, 6, 7, 8, 9, 10, 15, 28, 29, 37, 48, 56, 67, 70, 72, 73, 85.



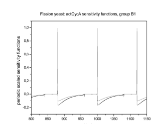
Group A2:

parameters
21, 26, 27, 39

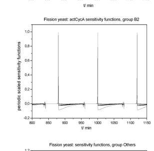


Group B1:

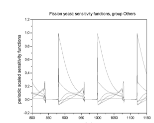
parameters
36, 42, 49, 51, 55, 58, 75, 80



Group B2:
parameters
11, 14, 17, 19, 20, 22, 25, 31, 35, 41, 52, 53, 57, 62, 63, 64, 66, 68, 71, 76, 82, 84, 86



Group X:
not similar parameters
1, 16, 38, 40



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