Sensitivity analysis of bacterial chemotaxis models

Judit Danis and Tamás Turányi
Institute of Chemistry, Eötvös University (ELTE),
Budapest, Hungary

Introduction

The increasing amount of accumulated knowledge in molecular and cell biology has led to a cooperation between life sciences, mathematics and computational sciences. This way scientific results of novel type can be achieved. Although the biological systems are not known in all details, numerical models exist that can predict some features of a biological system.

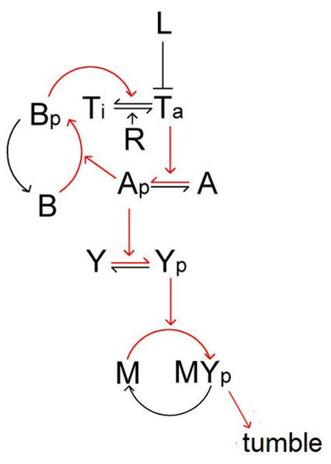
The signalling pathways of bacterial chemotaxis are relatively simple, but bear several important features of the signalling pathways of higher organisms. In this work, sensitivity analysis of the mathematical chemotaxis models of bacteria *Escherichia coli* and *Bacillus subtilis* were carried out and the most important parameters of the signal transduction cascades were determined. Global and local similarity of the sensitivity functions were found, which have important consequences on the identificability of biological models.

Bacterial chemotaxis

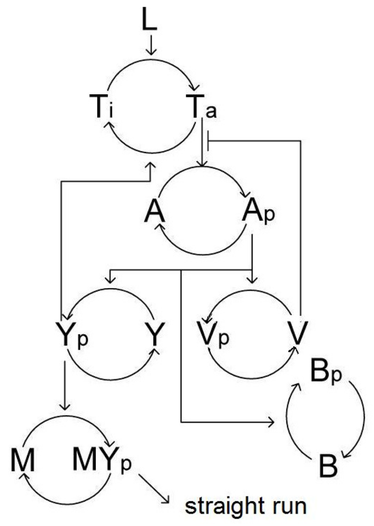
Chemotaxis is the process by which cells sense changes in their chemical environment and move to more favourable conditions [1]. By detecting the concentrations of attractants or repellents, bacteria move by changing the frequency of straight runs and reorientating tumbles. Flagellated bacteria like *Escherichia coli* or *Bacillus subtilis* detect the changes of the gradients of chemicals with specific receptors and move accordingly by changing the rotation of the flagella. The process is controlled by an intracellular signalling pathway between the receptor and the flagellar motor.
The genes involved in chemotaxis are homologous in the different bacteria species, but there are differences between the number of pathway components and the mechanism of the pathway.

Modelling bacterial chemotaxis

The detailed biochemical kinetics models of Rao *et al.* for the chemotaxis of *E. coli* and *B. subtilis* were reproduced from their article [2] and from the accompanied Matlab code. The model of *E. coli* is based on experimental data, while the model of *B. subtilis* is based on the *E. coli* model, modified on the basis of experimental observations and theoretical aspects. The mechanism of the chemotaxis is different in the two species.



Reaction network of the *E. coli* model

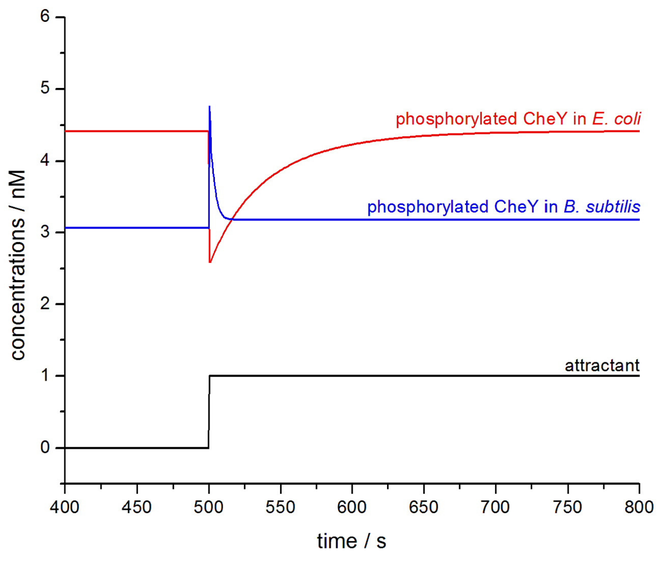


Reaction network of the *B. subtilis* model

Legends:

attractant	L
active and inactive receptors	T_a, T_i
proteins of the signalling cascade	A, B, R, Y, V
phosphorylated proteins	Ap, Bp, Yp, Vp
motor protein	M
motor protein - CheYp complex	MYp

Time course simulations



Software

The model was encoded in SBML [3] with the help of code COPASI [4-5]. COPASI was also used to calculate the concentration – time functions of the regulatory proteins at various conditions. The response of the models to the change of the attractant concentrations was tested using several different scenarios. The parameter scan function of COPASI was used to calculate the local sensitivity functions of the models.

Sensitivity analysis

A dynamical model can be described 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, $\mathbf{Y}$ is the n-vector of variables, $\mathbf{p}$ is the m-vector of parameters, $\mathbf{Y}_0$ is the vector of the initial values of the variables, and $\mathbf{f}$ 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:

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

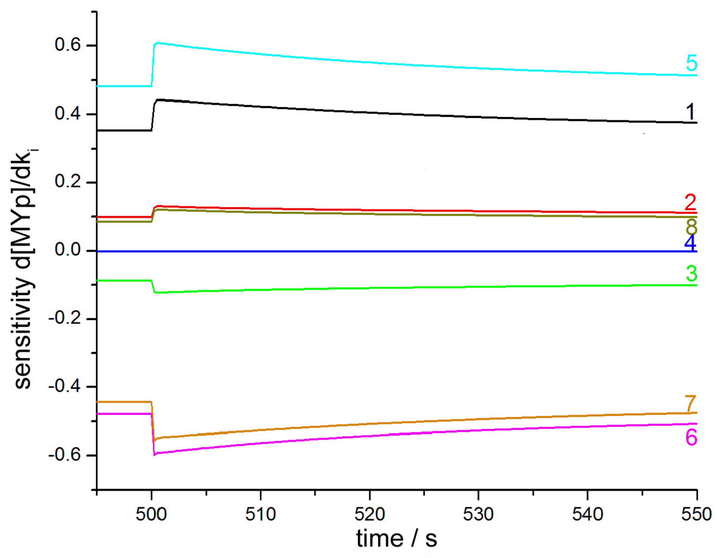
where $\mathbf{S}(t)=\{\partial Y_i/\partial p_k\}$ is the time dependent local sensitivity matrix, $\mathbf{J}$ is the Jacobian ($\mathbf{J}=\{\partial f_i/\partial Y_j\}$) and matrix $\mathbf{F}$ contains the derivatives of the right-hand-side of the ODE with respect to the parameters ($\mathbf{F}=\{\partial f_i/\partial p_k\}$). 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.

In the case of a general mathematical model, no relation is expected among the rows and/or the columns of the sensitivity matrix [6]. However, in several chemical kinetic systems special relations have been observed [7-8] between the sensitivity functions.
The **local similarity of the sensitivity functions** means that ratio s_{ik}/s_{jk} depends on time t and the model results Y_i and Y_j selected, but it is independent of the parameter p_k perturbed.
Global similarity of the sensitivity functions means that ratio s_{ik}/s_{im} is constant in time t (within an interval). A consequence of the global similarity of the sensitivity functions is that an infinite set of the parameters (defined by the ratios of the sensitivity functions) may result in identical model results, thus the model parameters cannot be identified [9].

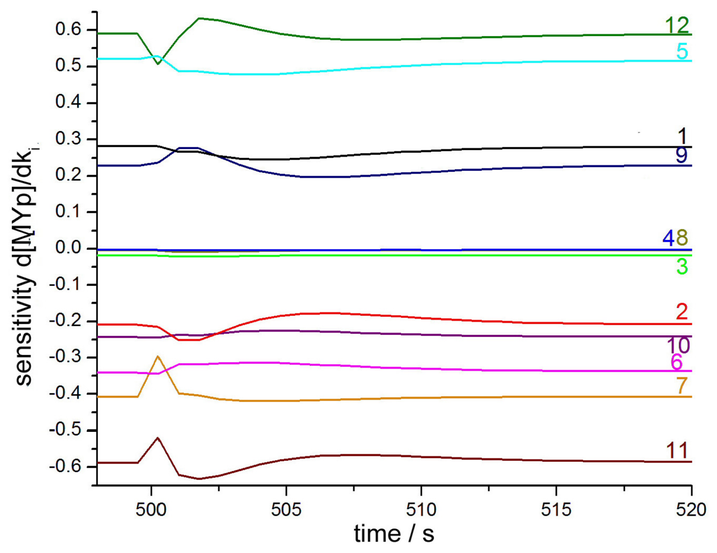
Sensitivity analysis of the models

Sensitivity–time functions were calculated at several conditions for both models. Most but not all of the sensitivity curves exhibited similarity. Global and local similarities of the sensitivity functions were found for several parameter groups and a part of the species.

Sensitivity - time curves of the *E. coli* model



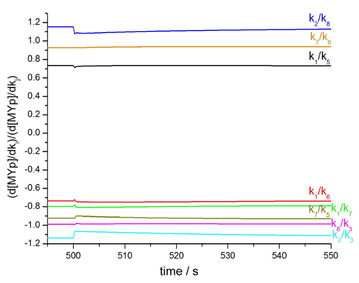
Sensitivity - time curves of the *B. subtilis* model



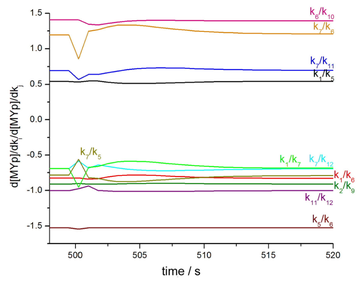
Identification of global similarity is demonstrated on the example of the motor protein - CheYp complex (MYp). This complex causes the *E. coli* cells to tumble and the *B. subtilis* cells to run. The groups of the globally similar parameters are different in the two models.

Identification of global sensitivity

in the *E. coli* model



in the *B. subtilis* model



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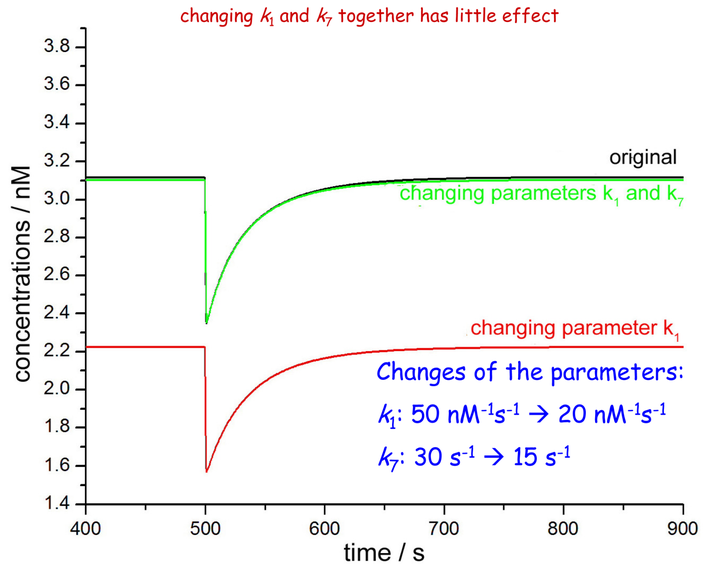
Compensation of the effect of parameter changes

Global similarity of the sensitivity functions indicate that changing one parameter in the corresponding parameter group can be compensated by changing another parameter of the same group.

The example below investigates the change of the concentration-time function of motor protein - phosphorylated CheY complex, which controls the response of the cell, due to parameter changes.

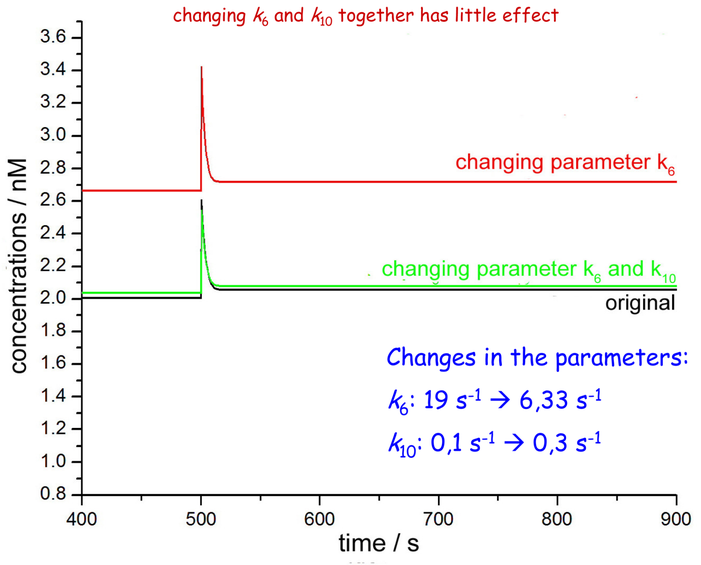
Concentration of MYp in *E. coli*

changing k_1 and k_7 together has little effect



Concentration of MYp in *B. subtilis*

changing k_6 and k_{10} together has little effect



The concentration-time curves of all other species moved back to the original position after the change of both parameters.

Take-home messages

- **Sensitivity analysis of systems biology models** is a powerful tool for the identification of the important parameters and pathways.
- **Global similarity of the sensitivity functions** means that parameters belonging to globally similar sensitivity functions can compensate each other. Consequently, the corresponding models cannot be identified.
- Global similarity of the sensitivity functions is **especially interesting for biological models**, because it may refer to a potential failure correcting system [9].
- The intracellular signalling pathways of bacterial chemotaxis are simpler versions of human signalling pathways, important in **several diseases** including **cancer**.
- The failure correcting system identified by the global similarity can be used for the **design of new medical drugs**.
- ***A new approach to treating diseases***: changing a globally similar rate parameter by changing the concentration of the related enzyme instead of fixing the demaged pathway. This approach may open up new possibilities.

References

[1] S. L. Porter, G. H.Wadhams, J.P. Armitage: Signal processing in complex chemotaxis pathways *Nat. Rev. Microbiol.* **9**, 153-165 (2011)
[2] C. V. Rao, J. R. Kirby, A.P. Arkin: Design and diversity in bacterial chemotaxis: a comparative study in *Escherichia coli* and *Bacillus subtilis*. *PloS Biol.*, **2**, 239-252 (2004)
[3] SBML: The Systems Biology Markup Language, http://sbml.org
[4] S. Hoops, S. Sahle, R. Gauges, C. Lee, J. Pahle, N. Simus, M. Singhal, L. Xu,, P. Mendes, U. Kummer: COPASI--a COmplex PAthway SImulator. *Bioinformatics*, **22**, 3067-3074 (2006)
[5] Copasi: Complex Pathway Simulator Version 4.6 (Build 32) released May 21, 2010 http://www.copasi.org
[6] T. Turányi: Sensitivity analysis of complex kinetic systems: Tools and applications, *J. Math. Chem.*, **5**, 203-248 (1990)
[7] H. Rabitz: Systems analysis at the molecular scale *Science*, **246**, 221-226 (1989)
[8] I. Gy. Zsély, J. Zádor, T. Turányi: Similarity of sensitivity functions of reaction kinetic models *J. Phys. Chem. A*, **107**, 2216-2238 (2003)
[9] A. Lovrics, I. Gy. Zsély, A. Csikász-Nagy, J. Zádor, T. Turányi, B. Novák Analysis of a budding yeast cell cycle model using the shapes of local sensitivity functions *Int. J. Chem. Kinetics*, **40**, 710-720 (2008)