Integration of sensitivity and bifurcation analysis to detect critical processes in cell signalling pathways

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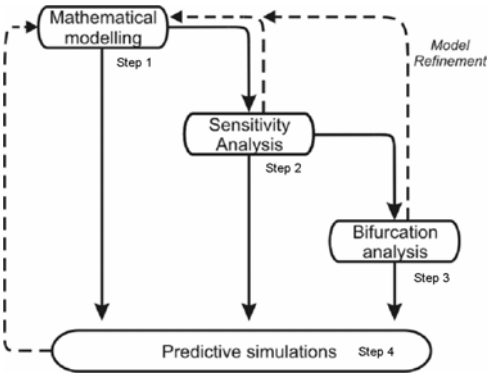
Scheme of our Methodology



1. Mathematical modelling:

Set up the mathematical model using ordinary differential equations.

2. Sensitivity analysis:

Rank model parameters according to their sensitivity indices.

3. Qualitative bifurcation analysis:

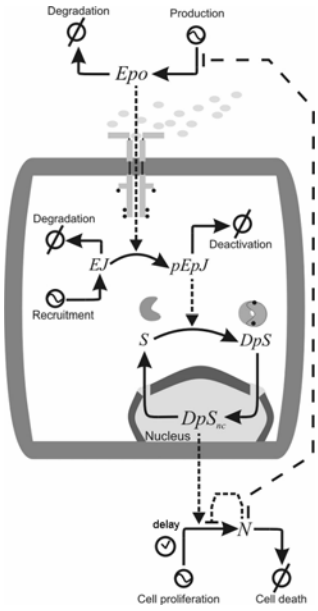
Determine the bifurcation points and stability Regions by using qualitative bifurcation analysis.

4. Predictive simulations:

Simulation of critical dynamic properties when we change the values of selected model parameters.

Case Study

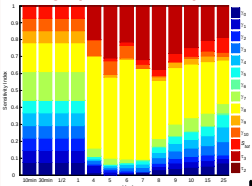
1.Mathematical Model



Mathematical model composed of JAK2-STAT5 signalling pathway and proliferation model of red blood cells. For details of the model see [1].

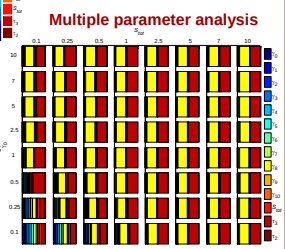
3. Sensitivity Analysis

Single parameter analysis



Single parameter analysis: Sensitivity index values when a critical parameter (τ_3) is modified, keeping others unchanged.

Multiple parameter analysis



Multiple parameter analysis: Sensitivity index values when two critical parameters are modified, keeping others unchanged.

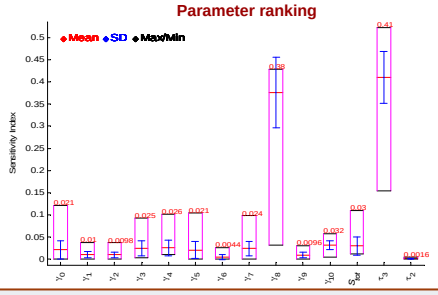
γ	Rate constant
τ	Time delay
S_{tot}	Total amount of STAT5

Parameter Table

After the above analysis, we get the following critical parameter ranking list:

$$SARK = \{\tau_3, \gamma_8, \gamma_{10}, S_{tot}, \gamma_3, \gamma_4, \gamma_7, \gamma_5, \gamma_0\}$$

Parameter ranking



3. Qualitative Bifurcation Analysis

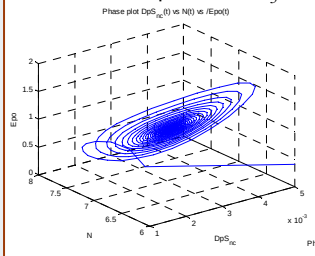
Based on the biological information we have another parameter ranking list:

$$BFRK = \{\gamma_0, \gamma_2, S_{tot}, \gamma_6, \tau_3, \gamma_{10}, \gamma_8\}$$

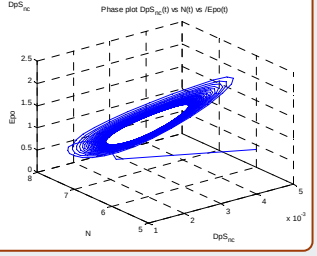
The intersection of the two sets are:

$$SARK \cap BFRK = \{\gamma_0, S_{tot}, \tau_3, \gamma_{10}, \gamma_8\}$$

Then we use bifurcation analysis to investigate the modulation of parameter τ_3.



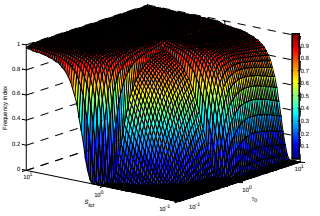
No optimized simulation results: the model displays an aperiodic oscillation and gradually reaches the steady state.



Optimized simulation results: the model displays a periodic oscillation, where *N* oscillates between 6.2 and 7.2; *Epo* oscillates between 0.8 and 1.6; DpS_{nc} oscillates between 0.0035 and 0.0015.

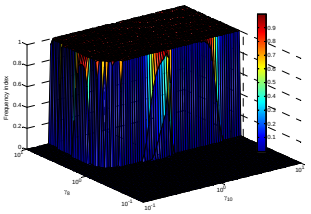
4. Predictive Simulations

In this part we investigate how the dynamic property of the model changes when the values of pairs of critical parameters (γ_0-S_{tot} and γ_8-γ_{10}) are modified in an interval of biologically relevant values.



Frequency index plot of the parameter γ_0 and S_{tot}

Frequency index plot of the parameter γ_8 and γ_{10}



From the above two figures, we get three conclusions of the dynamic property of the model changes with the modified critical parameter values as follows:

1. Blue area (Frequency index less than 0.1): the oscillation of the model weakens very fast to the steady state.

2. Red area (Frequency index greater than 0.9): the model can display the stable periodic oscillation.

3. Transition area (Frequency index between 0.1 and 0.9): the model displays aperiodic oscillation, which weakens much slower than the red area, the smaller the value of frequency index is, faster the oscillation weakens.

Summary

We developed a methodology, combining sensitivity and bifurcation analysis.

We performed systematic simulations changing the value of critical parameters, observing their influence on the dynamics.

The method succeeded in detecting critical processes in sub-cellular dynamics.

The whole procedure validates the feasibility of our methodology. The next step is to develop a software package for general use.

References

[1] J. Vera et al. (2008): A systems biology approach to analyse amplification in the JAK2-STAT5 signalling pathway. *BMC Systems Biology*, 2:38.

[2] S. Nikolov. (2008): Stability and bifurcation behavior of genetic regulatory systems with two delays. *Comptes rendus de l'Academie bulgare des Sciences*, 61(5), 585-594.

[3] H. Schmidt et al. (2006): Systems Biology Toolbox for MATLAB: A computational platform for research in Systems Biology, *Bioinformatics*, 22(4), 514-515.

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