

Investigating cellular regulation with PySCeS/Kraken

Brett G. Olivier*, Johann M. Rohwer, Jan-Hendrik S. Hofmeyr

Triple-J Group for Molecular Cell Physiology, Department of Biochemistry
University of Stellenbosch, Stellenbosch, South Africa

*E-mail: bgoli@sun.ac.za

Introduction

Rate characteristics are an important tool in investigating and understanding the regulation of cellular systems [1]. However, they can be computationally expensive to generate when high resolution, multi-dimensional results are required. In this contribution we introduce PySCeS/Kraken which has been developed to solve this problem.

In Fig. 1 we define a model biosynthetic pathway and investigate the effect of changing the binding affinity of Enzyme 1 for its immediate product A. S and P are boundary species and the system's flux rate characteristic is generated by varying P over its equilibrium range (in this case $K_{eq1} \times K_{eq2} \times K_{eq3} = 4 \times 10^4$) and plotting the steady-state flux. It has been observed



Figure 1: *A linear three enzyme pathway subject to end product inhibition.* Enzyme 1 is modelled using a cooperative allosterically inhibited reversible Hill equation, while Enzymes 2 and 3 are typical reversible Michaelis-Menten reactions.

that by increasing the binding strength of R1 for its immediate product A produces multiple steady-state solutions which leads to hysteresis in the flux characteristics. To visualise this behaviour we need to generate a two parameter rate characteristic, varying both P and $A_{0.5}$, whilst calculating both the system's flux and stability. In practice, this means using continuation algorithms to calculate both stable and unstable steady-state solutions and evaluating the maximum eigenvalue as a measure of system stability. However using our current modelling software, PySCeS (<http://pysces.sf.net>) [2], it soon became apparent that generating high resolution rate characteristics was not practical due to, amongst other problems, excessively long computational times and hardware memory limitations.

Distributed processing with PySCeS/Kraken

Our solution was to develop the Kraken grid framework which allows certain PySCeS functions (e.g. parameter scanning) to be split into separate tasks and executed in parallel using a cluster of networked machines. It has been implemented in Python and consists of high level controllers which control a set of worker nodes that, in turn, interact with PySCeS.

Controllers can be constructed using a toolkit of threaded network components that allows for both sequential and parallel jobs to be executed on the worker nodes. A controller

typically consists of the following modules: a *model server* that provides model descriptions, a *task sequencer* that splits an analysis into multiple jobs, a *job controller* that instructs nodes to get a model description, initialise it and perform the analysis, and a *data assembler* that retrieves stored data from the worker nodes and prepares it for post processing.

Worker nodes accept commands using a simple (extendible) control language, run the required analysis and store the results until requested by the controller.

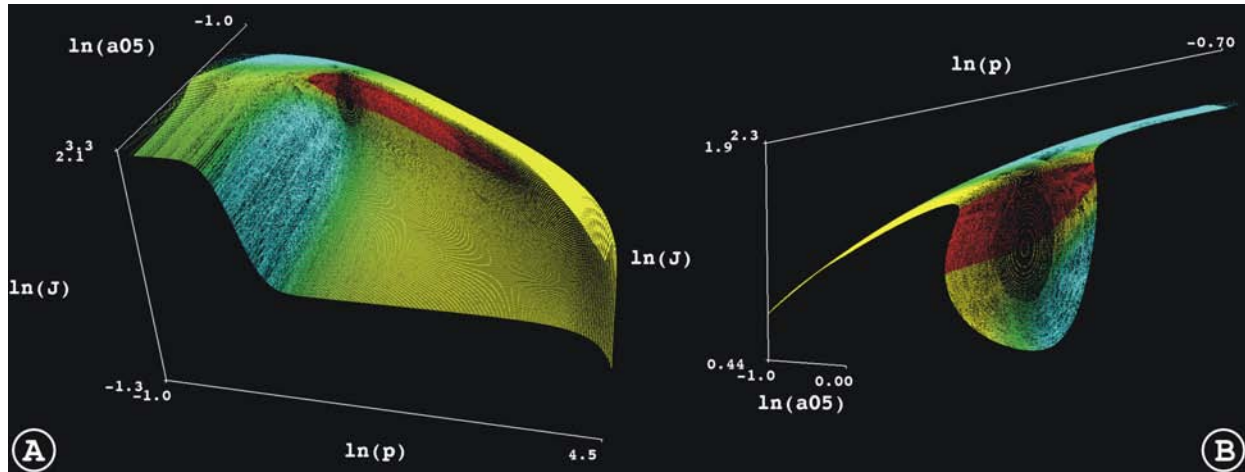


Figure 2: *Three dimensional rate characteristics generated with PySCeS/Kraken. A shows the overall effect of increasing the binding of Enzyme 1 to A when investigating the flux response of the system to a change in P. The colours reflect the systems stability where red indicates an unstable state while all other colours are stable. B is a magnified view of the hysteresis and isola regions.*

In Fig. 2 we show an example of the high resolution rate characteristics generated by Kraken (images produced using MayaVi (<http://mayavi.sf.net>) which clearly show the hysteretic regions and the overall changes in system stability. This combination of biological theory with software development will allow us to more deeply explore complex regulatory behaviour in a variety of cellular systems.

References

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