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Dynamic simulation of the human red blood cell metabolic network

Neema Jamshidi[1], Jeremy S. Edwards[2,3], Tom Fahland[1], George M. Church[2] and Bernhard O. Palsson[1]

[1]Department of Bioengineering, University of California—San Diego, La Jolla, CA 92093, USA, [2]Department of Genetics, Harvard Medical School, Boston, MA 02115, USA and [3]Department of Chemical Engineering, University of Delaware, Newark, DE 19711, USA

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ABSTRACT

Summary: We have developed a Mathematica® application package to perform dynamic simulations of the red blood cell (RBC) metabolic network. The package relies on, and integrates, many years of mathematical modeling and biochemical work on red blood cell metabolism. The extensive data regarding the red blood cell metabolic network and the previous kinetic analysis of all the individual components makes the human RBC an ideal 'model' system for mathematical metabolic models. The Mathematica package can be used to understand the dynamics and regulatory characteristics of the red blood cell.

Availability: The Mathematica package and an example file can be downloaded from http://gcrg.ucsd.edu

INTRODUCTION

Our current understanding of many biological processes can be largely credited to the study of model experimental systems, such as *Drosophila*, *E.coli*, and *S.cerevisiae*, and in the post-genome era, the study of integrated cellular functions will involve computational analysis. It is likely that the study of complex integrated cellular processes will follow the tradition in biological research and also begin with, and proceed through, the study of 'model systems'.

In particular, the human red blood cell metabolic network has played a special role in the development of mathematical models of metabolism given its simplicity, accessibility, and detailed knowledge of its molecular components (Worthington and Rosemeyer, 1976; Otto *et al.*, 1977; Morelli *et al.*, 1978). Mathematical models of red cell metabolism have been studied since the early 1970s (Ataullakhanov *et al.*, 1981; Holzhutter *et al.*, 1985). Since then, they have steadily grown in scope leading to comprehensive red cell metabolic models in the late 1980s and 1990s (Joshi and Palsson, 1989; Mulquiney and Kuchel, 1999).

We have developed a red blood cell dynamic modeling package within Mathematica. The purpose of this software package is to provide a comprehensive model of the red cell metabolism to the scientific community that is broadly accessible and operates on most standard computational platforms.

OVERVIEW OF THE MODEL

The RBC metabolic model consists of kinetic expressions for 35 enzymes, six transport channels, sodium and potassium leak fluxes, and the Na^+–K^+ ATPase pump. The kinetic expressions used in the model were based on many years of research by many investigators (e.g. Roigas *et al.*, 1965; Worthington and Rosemeyer, 1976; Otto *et al.*, 1977; Morelli *et al.*, 1978; Vandenberg *et al.*, 1986). The model includes only the kinetics of the metabolic network, does not include osmotic pressure, electroneutrality constraints (Werner and Heinrich, 1985) and hemoglobin binding (Yoshida and Dembo, 1990).

Functions have been written to interface the RBC kinetic model to the Mathematica software package. The basic operation of the package is to integrate the mass balance equations and simulate the changes that occur in the metabolite concentrations and enzyme fluxes over time. Other capabilities include: (1) graphical depiction of the metabolic network with steady state fluxes and pool sizes; (2) finding the steady state of the system; (3) temporal decomposition of the metabolic network; (4) generation of phase planes; and (5) the simulation of enzymopathies.

IMPLEMENTATION

An example Mathematica notebook is available online to provide a comprehensive demonstration of the capabilities of the red blood cell package. The basic functions of the package are to: (1) identify the steady state solution; (2) integrate the differential equations; and (3) output the solutions for data interpretation.

The RBC package can be used to identify steady state solutions of the metabolic network. A steady state is found using the 'findroots' RBC package function. The

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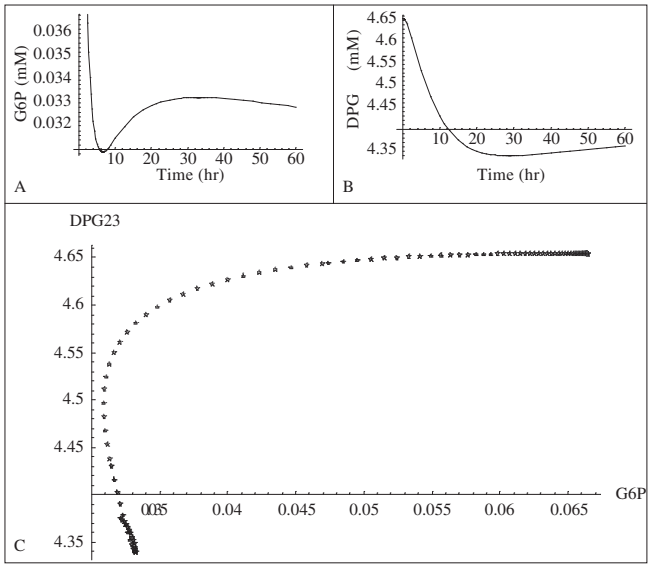

Fig. 1. Simulation of the RBC metabolic network to an applied ATP load. (A) The time varying concentration of G6P. (B) The time varying concentration of 2,3-DPG. (C) The phase plane of G6P vs 2,3-DPG.

RBC package function 'findroots', calls the built-in Mathematica function 'FindRoot'. The 'findroots' function is central to many other RBC package functions, for example, the 'map' function calls 'findroots' and draws the metabolic map and 'decomp' decomposes the system into dynamical independent variables around the root.

The system of mass balance of equations can also be integrated by the RBC package by several different functions (i.e. diffeq, fluxdiffeq, phaseplane, poolplot, energycharge). The difference in the functions is primarily in the output that is returned to the user. The same internal function is called in the implementation of each of the above functions. The RBC simulator function calls the Mathematica function 'NDSolve' to numerically solve the coupled nonlinear ordinary differential equations. Mathematica has the numerical capabilities to solve the system of equations that defines the dynamic metabolic function of the RBC and it implements the Gear methodology based on the LSODE package (Wolfram, 1991).

An example output from the system is shown in Figure 1. The simple example illustrates the rapid motion of the G6P concentration and the very slow motion of the 23DPG concentration.

CONCLUSION

Although simple compared to other cells, the RBC metabolic network offers insights into the general principles of cellular metabolism that can subsequently be applied to more complex metabolic networks. Since the dynamics of even simple metabolic networks are very difficult to conceptualize as a whole, simulations will be increasingly important for the analysis of complex biological systems. The RBC simulation package described herein can be used as the computational 'model system' for the study of integrated cellular processes. This package allows one to develop a more general understanding and appreciation of the principles governing the behavior of metabolic networks.

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