Monte-Carlo Simulation of Metabolic Fluxes: Implications for Making Informative Experimental Measurements and Evaluating Systemic Impact of Enzymopathies

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Abstract

Genome-scale models provide a concise representation of available data about a biological process and can provide predictions of cellular behaviors which are difficult to observe. Constraint-based modeling is an approach that constrains cellular behavior through the imposition of physico-chemical laws, resulting in a solution space in which a cell's behavior must lie. Uniform random sampling of this constrained solution space allows for the unbiased appraisal of the implications of the imposed physico-chemical constraints upon the reconstructed metabolic network. The in silico sampling procedure was applied to the steady state flux space of the human red blood cell metabolic network under simulated physiologic conditions yielded the following key results: 1) probability distributions for all metabolic fluxes were computed for all fluxes and showed a wide variety of shapes that could not have been inferred without computation; 2) correlation coefficients were calculated between all fluxes, determining the level of independence between any two fluxes, and identifying highly correlated reaction sets; and 3) the system-wide effects of the change in one (or a few) variables (i.e. a simulated enzymopathy or setting a flux range based on measurements of physiological considerations) were computed, showing that not only do the ranges allowed to various fluxes change, but also their probability distributions and the correlations between metabolic fluxes. Taken together, this in silico sampling procedure provides a maturing of the constraint-based approach to modeling by allowing for the unbiased and detailed assessment of the impact of the applied constraints on the reconstructed network.

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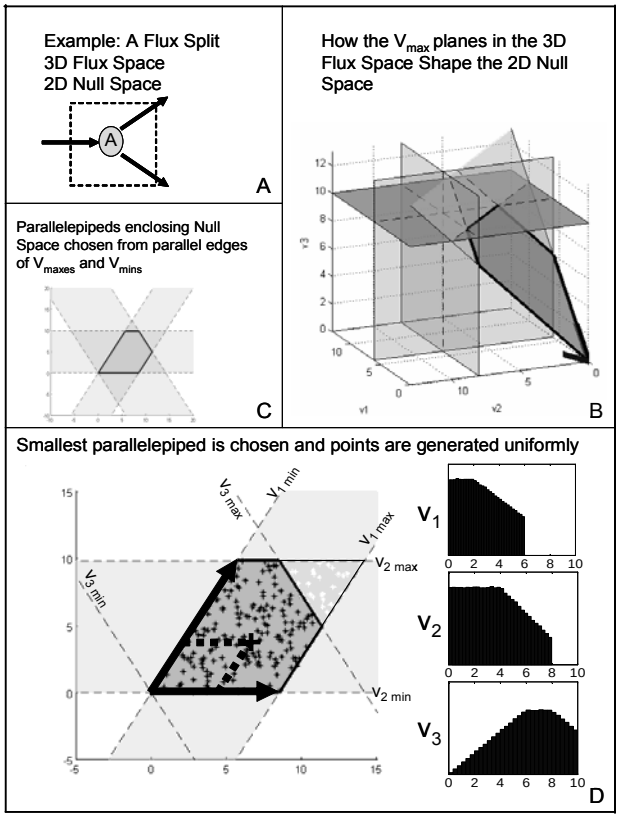

Figure 1. Algorithm for boxing in solution space with parallelepiped and generating uniform random samples. A simple flux split was used as an example to demonstrate how the *in silico* sampling procure works (A). The two dimensional null space is constrained by the Vmax planes corresponding to the three reactions in the network (B). Once the null space is capped off by the reaction Vmax values, combinations choosing two of the three sets of parallel constraints leads to forming three potential parallelepipeds (C). The smallest of these parallelepipeds is chosen and uniform random points within the parallelepiped are generated (D) based on uniform weightings on the basis vectors defining the parallelepiped (shown as black arrows). Points within the solution space are kept and those that fall out of the solution space are discarded. The fraction of the points generated inside the parallelepiped that fall within the solution space is called the "hit fraction." The hit fraction multiplied by the volume of the parallelepiped yields the volume of the solution space.

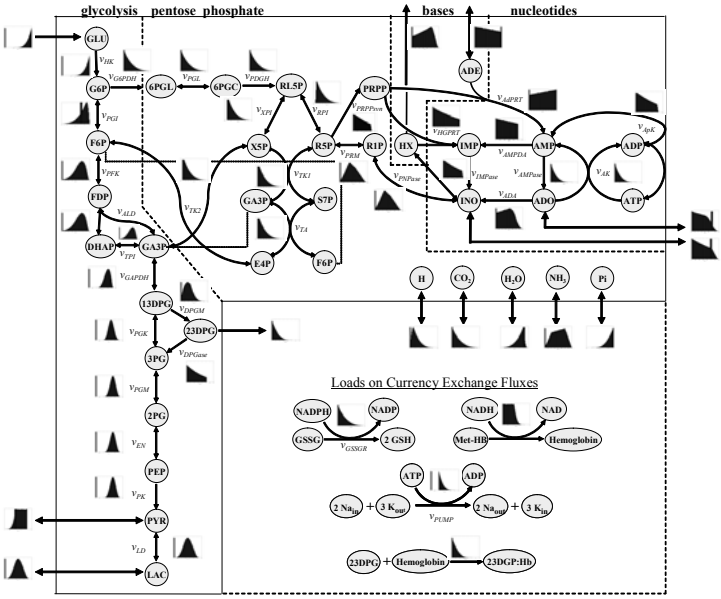

Figure 2: Probability flux distributions for human red blood cell.

The red blood cell model with maximum flux constraints was sampled using the *in silico* algorithm. The histograms next to each reaction represents the number of solutions satisfying the constraint conditions at each flux value. This gives information about the solution space's sensitivity to each constraint.