Abstract

Extreme pathways are a mathematically defined set of generating vectors that describe the conical steady state solution space for flux distributions through metabolic networks. The extreme pathways of the well-characterized human red blood cell metabolic network were calculated and interpreted in a biochemical and physiological context. The 39 Type I and II extreme pathways were divided into groups based on such criteria as their cofactor and by-product production, and carbon inputs including those that: 1) convert glucose to pyruvate, 2) interchange pyruvate and lactate, 3) produce 2,3-diphosphoglycerate that binds to hemoglobin, 4) convert inosine to pyruvate, 5) induce a change in the total adenine pool, and 6) dissipate ATP. Results from a full kinetic model of red cell metabolism written in Mathematica® were anticipated based solely on an interpretation of the extreme pathway structure.

Extreme Pathway Analysis of Red Cell Metabolism

1) Construct S matrix of 39 metabolites, 32 internal reactions, 12 primary and 7 currency exchange fluxes
2) Apply algorithm [1] to determine conically independent set of extreme pathway vectors using fundamental steady state mass balance: 

\[ \mathbf{S} \mathbf{v} = \mathbf{0} \]

3) Extreme pathways define conical solution space in which all steady state solutions (corresponding to a cell’s phenotype) must lie
4) Cone is “capped off” based on the maximum flux capacity of each pathway

Extreme pathway generating vectors (white arrows) define the steady state flux cone (green). A steady state flux vector (blue) must lie inside cone.

V_{max} Limited Pathways

Changes in V_{max} produce changes in the solution space and hence the cell’s metabolic capabilities.

A) Indicates the full capabilities of the system where the cone is capped off at the minimum V_{max} for each pathway.

B) Simulates an enzymopathy in which the maximum flux capacity of V_i is greatly reduced. This reduction in the maximum capacity results in a shift down the p_i axis thus significantly shrinking the size and volume of the steady state solution cone and hence the metabolic capabilities of the system.

Summary

The extreme pathways for the red blood cell can give a concise representation of red cell metabolism as well as a way to interpret its metabolic physiology. For more information see gcrg.ucsd.edu

References


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