Introduction to Metabolic Modelling

Delhi Workshop 1; Structural Modelling of Metabolism; Day 1

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Preamble

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Designer Babies

"Within a decade or two, it may be possible to screen kids almost before conception for an enormous range of attributes, such as how tall they're likely to be, what body type they will have, their hair and eye color, what sorts of illnesses they will be naturally resistant to, and even, conceivably, their IQ and personality type." Michael D. Lemonick, Time Magazine 11 Jan 1999.

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Virtual Biochemistry

virtual liver network

A major national initiative funded by the German Federal Ministry for Education and Research

Virtual Liver Network

The Virtual Liver will be a dynamic model that represents, rather than fully replicates, human liver physiology morphology and function, integrating quantitive data from all levels of organisation.

SiC!: The Silicon Cells

A silicon cell is a precise replica of (part of) a living cell. It is based on experimentally determined rate laws and parameter values, i.e. only on data, not on fitted values or assumptions. It merely calculates the system biology implications of the molecular properties that are already known. Silicon cell is not a package of software for simulations. The international silicon cell program thereby differs (i cell biology that can be us models for the purpose o down-loading to one's ow (http://www.genomatica.c calculates kinetics, rather

Feature Article

The Virtual Human: Towards a Global Systems Biology of Multiscale, Distributed Biochemical Network Models

Douglas B. Kell

School of Chemistry and The Manchester Centre for Integrative Systems Biology, The Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester, UK

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Simulated Life

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Why Model Metabolism?

It came first!

- Metabolism is essential: it is a fundamental process of all living organisms, encompassing all the chemical conversions that convert nutrients into new cellular materials and provide energy for other processes such as movement.

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- We understand how the genes encode metabolism. But how do we exploit that understanding to predict metabolic responses?
- One application area: metabolic engineering.
- Another: design of effective drug therapies.
- Other cell processes should yield to a similar approach: signal transduction; cell cycle; apoptosis.

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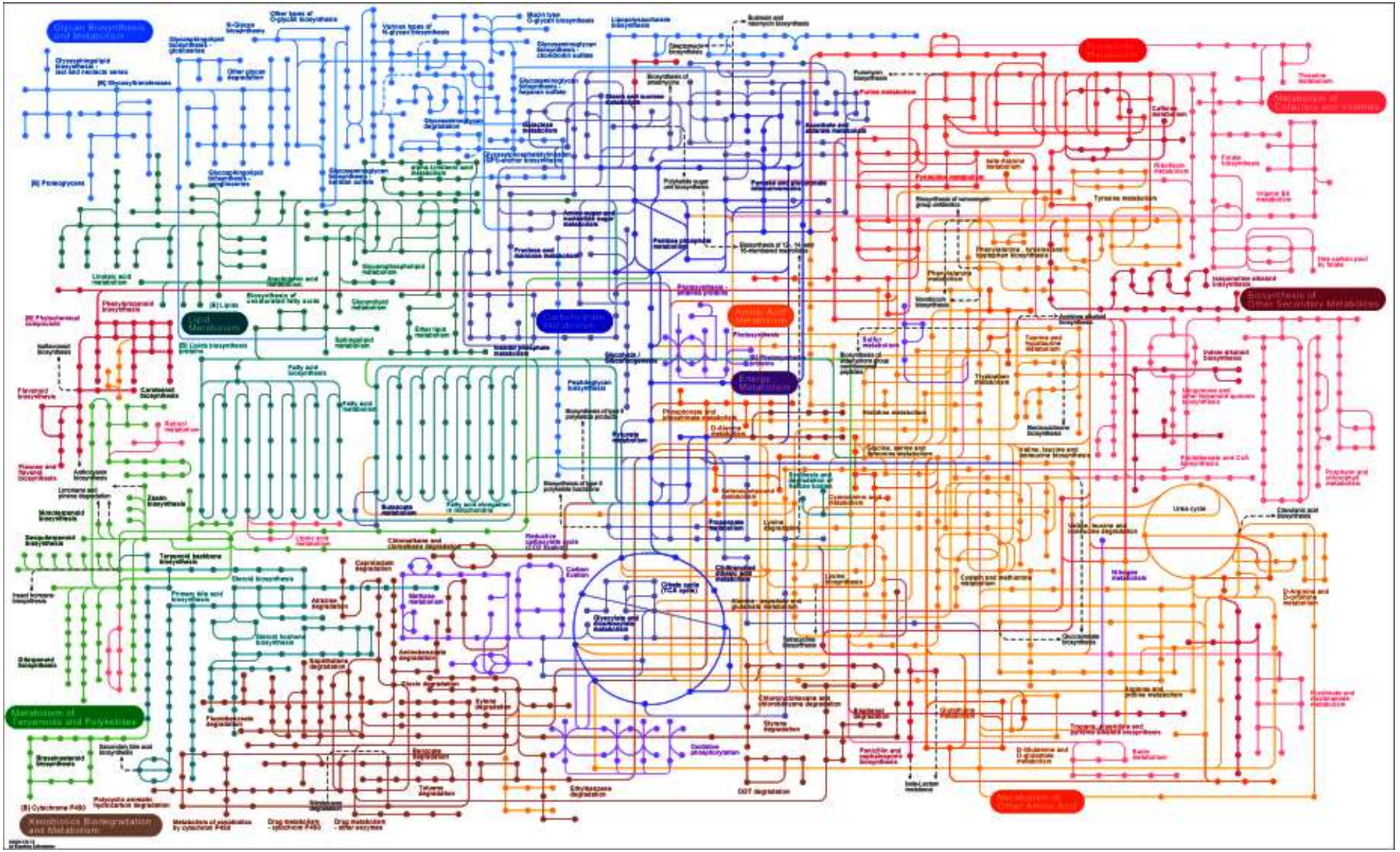
The Metabolic Network



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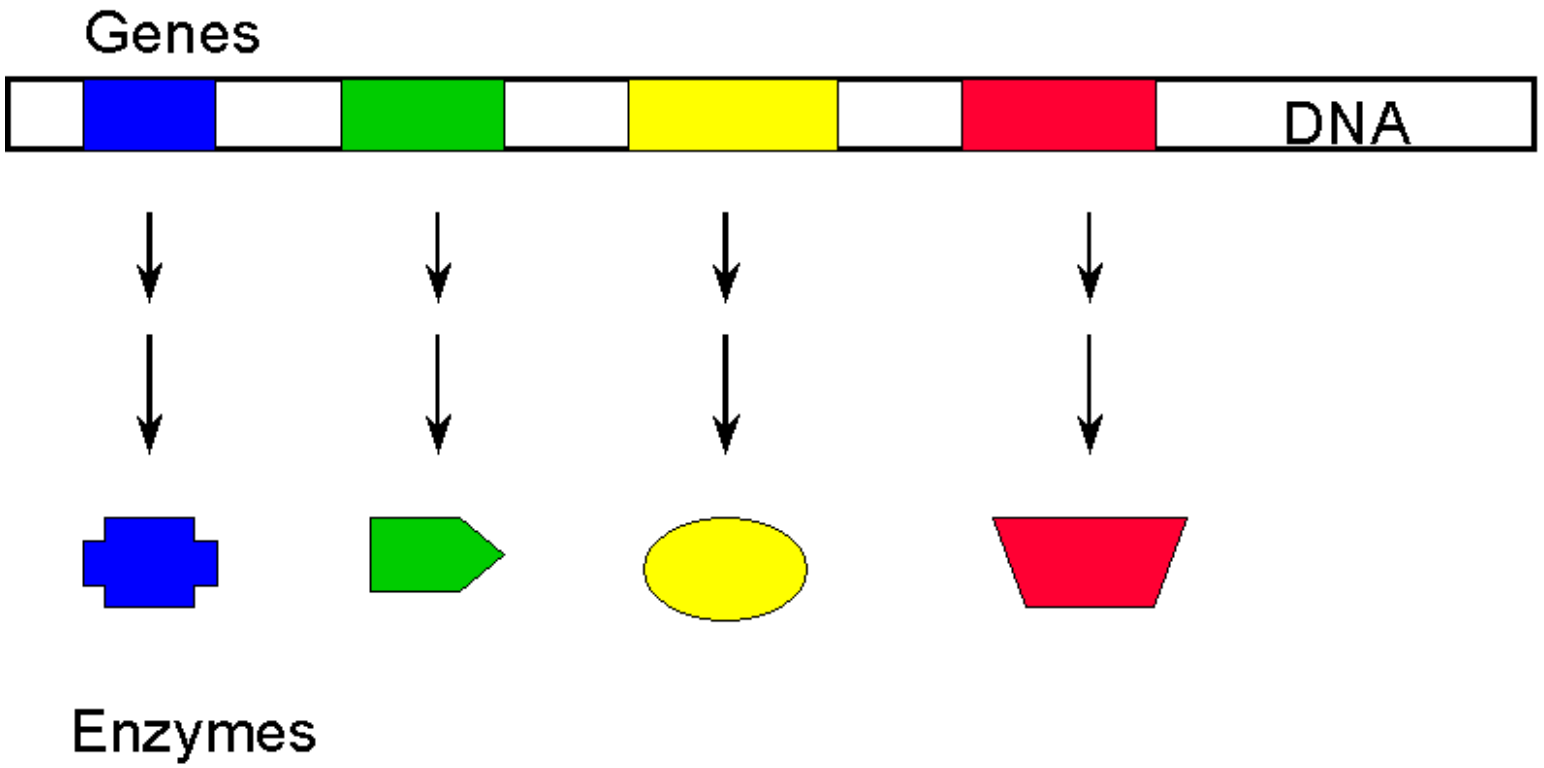
Genes and Metabolism



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Outline

- Types of models
- Theory of metabolic modelling

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Summary of Types of Metabolic Model

- Structural — needs reaction list; gives existence and number of routes; optimal stoichiometries; network flux values.

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- Stochastic — a type of kinetic model where numbers of molecules are counted rather than concentrations, and individual reaction events are simulated.
- Sensitivity analysis / Control analysis / S–systems — needs effective kinetics near steady–state; predicts control distribution, response of steady state to perturbations.

From Biochemistry to Model

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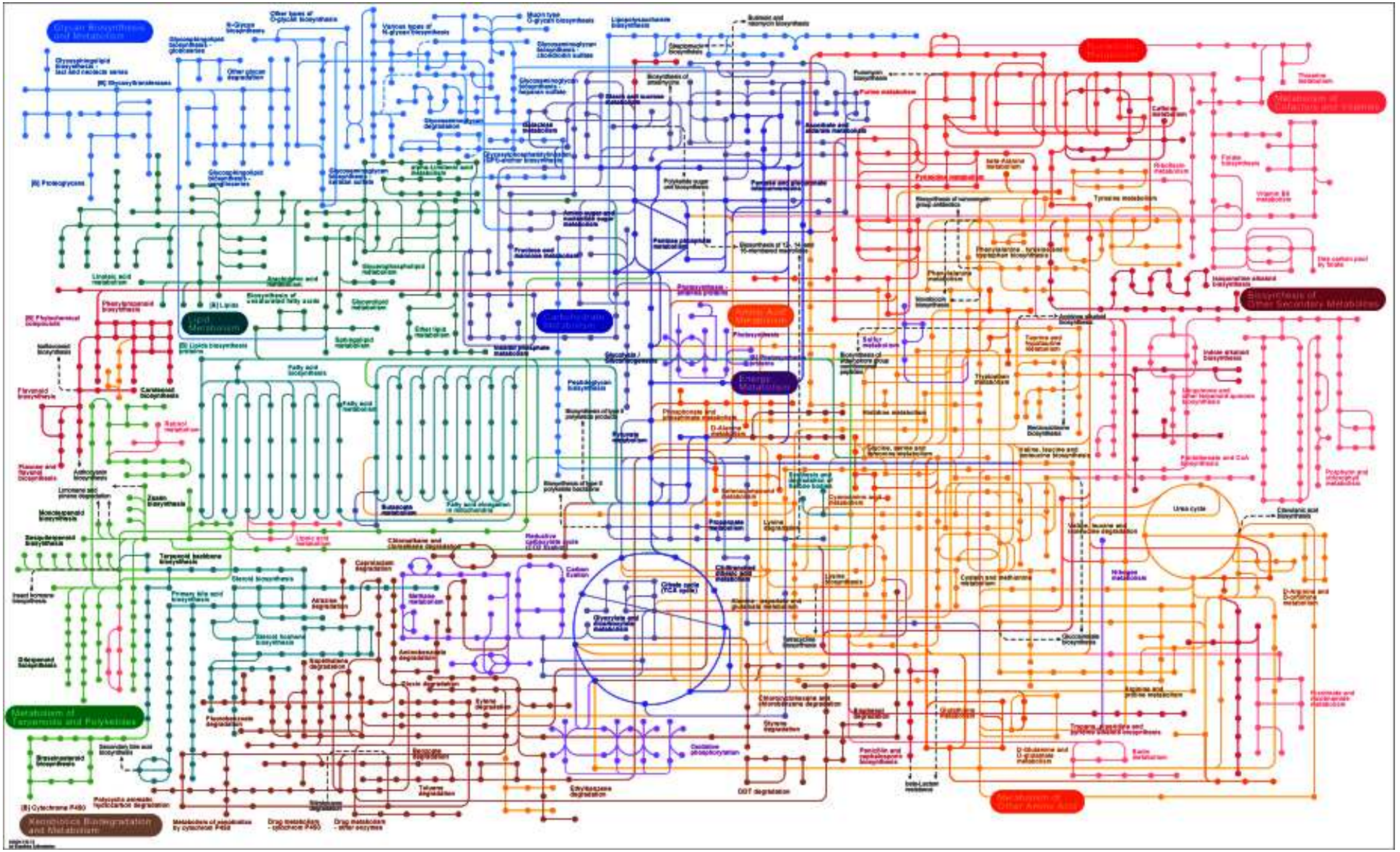
The Metabolic Network



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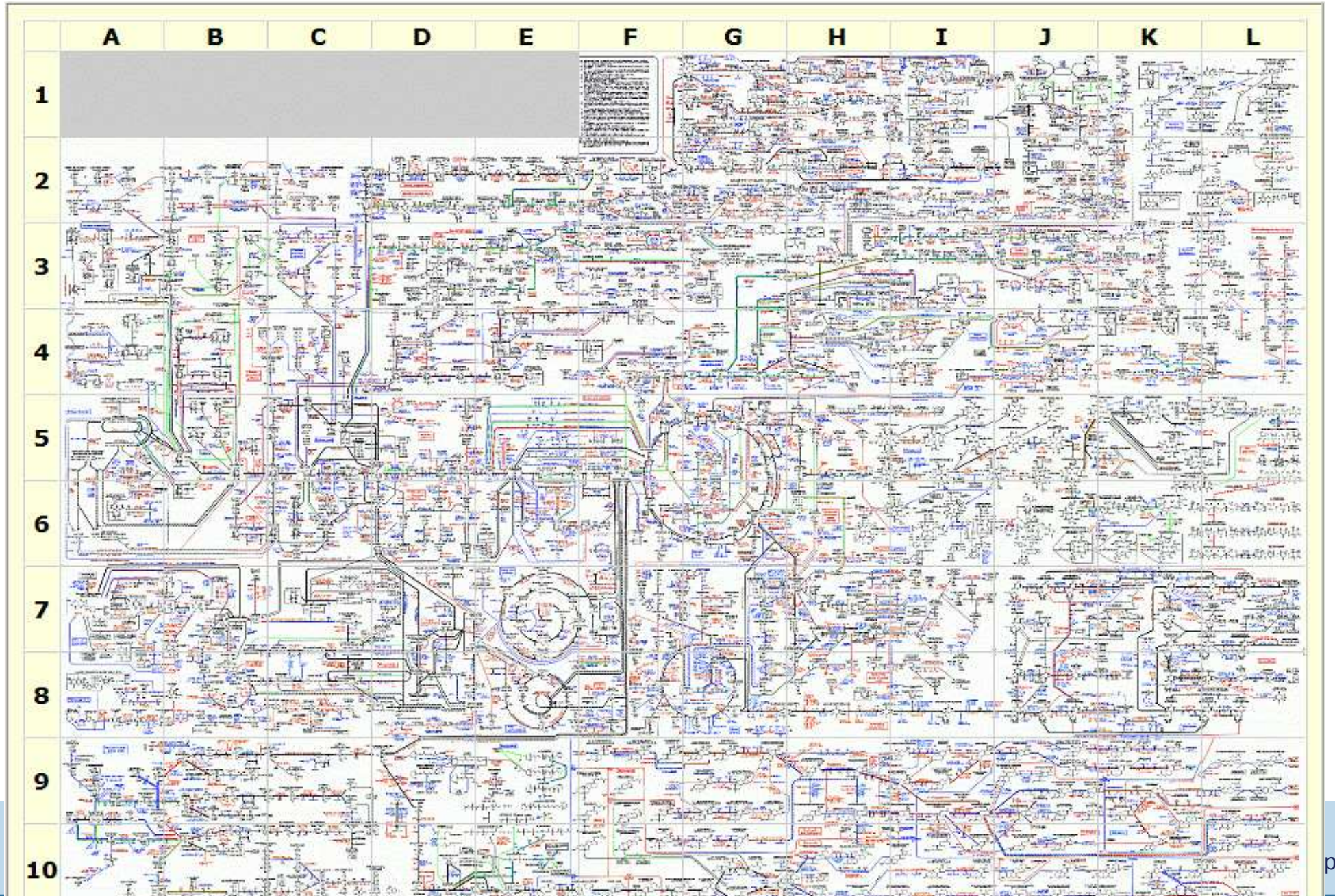
The Metabolic Network — More Detail



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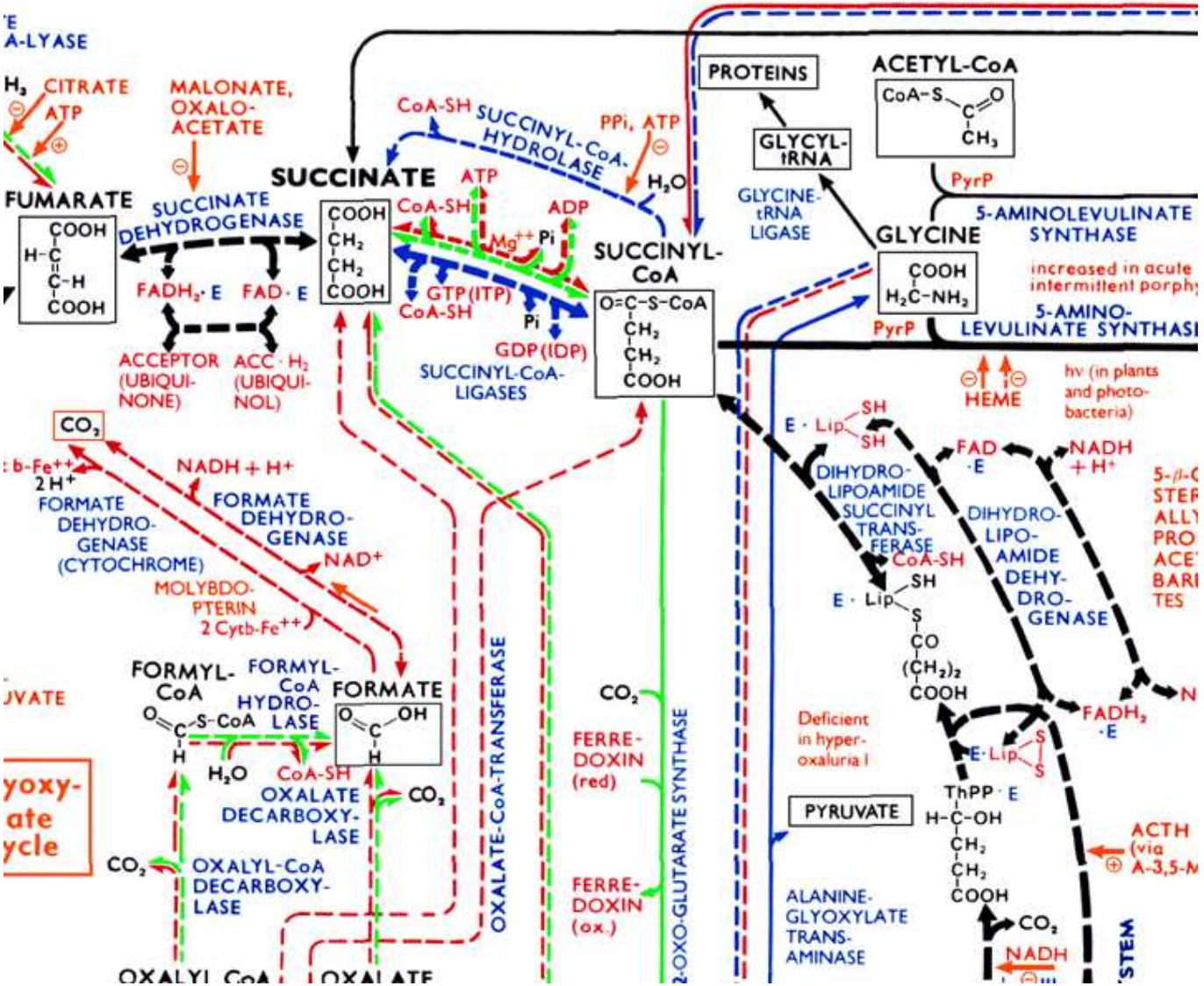
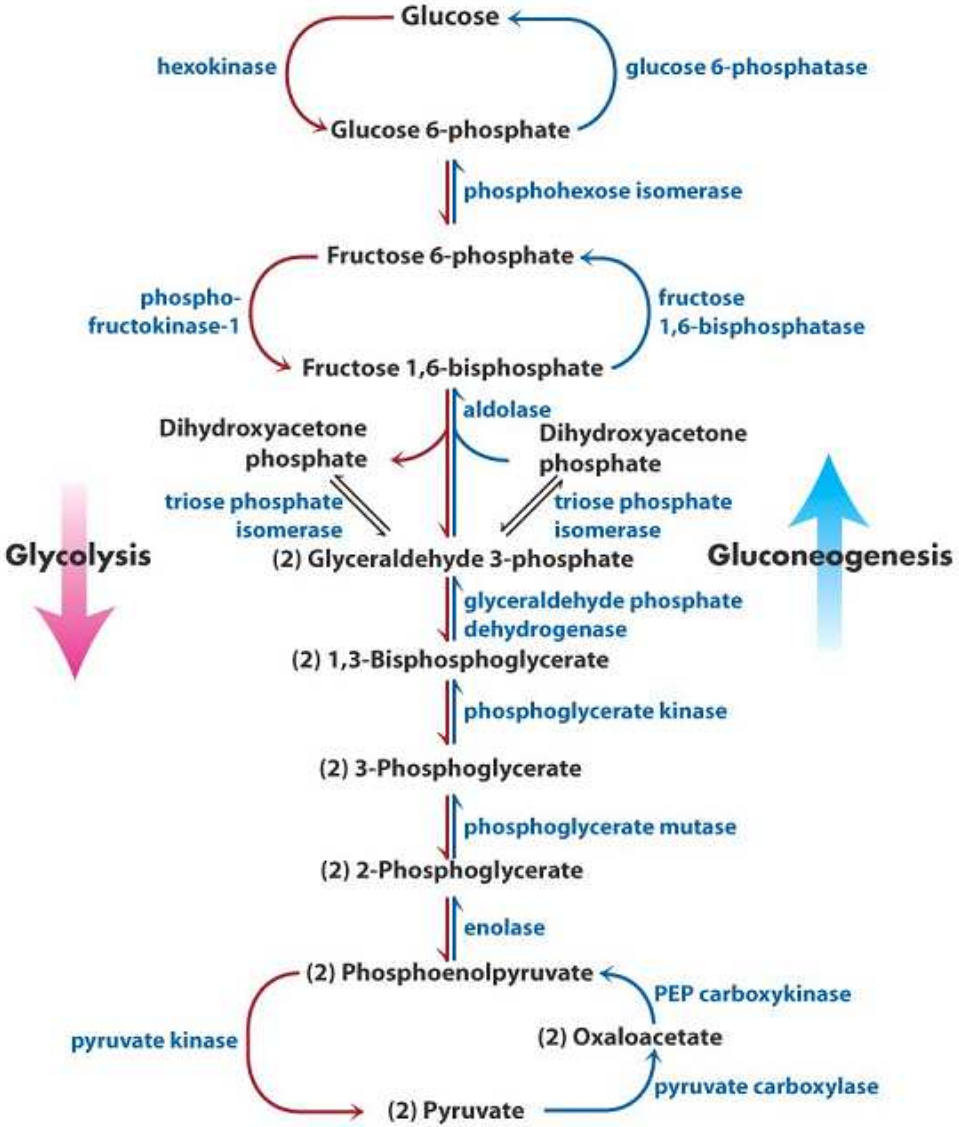
The Metabolic Network — Zoom in



From Expasy Biochemical Pathways: http://www.expasy.ch/cgi-bin/search-biochem-index

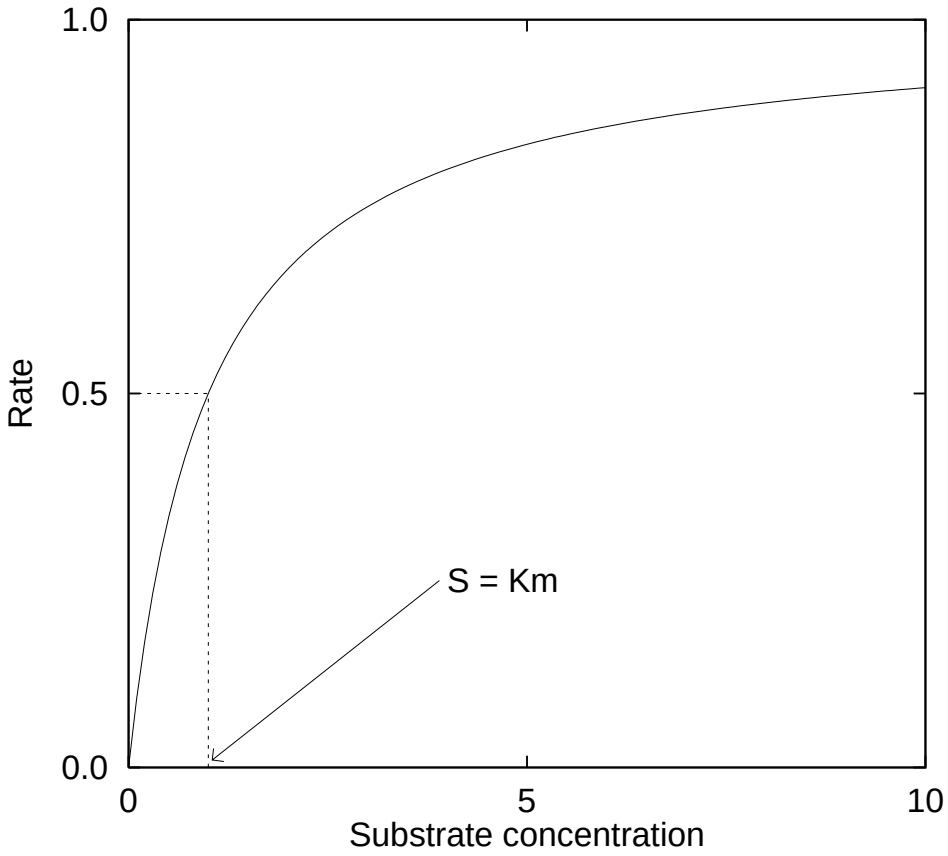
A Metabolic 'Pathway'



From Nelson & Cox, Lehninbger's Biochemistry, 4th ed.

Michaelis–Menten Enzyme Kinetics

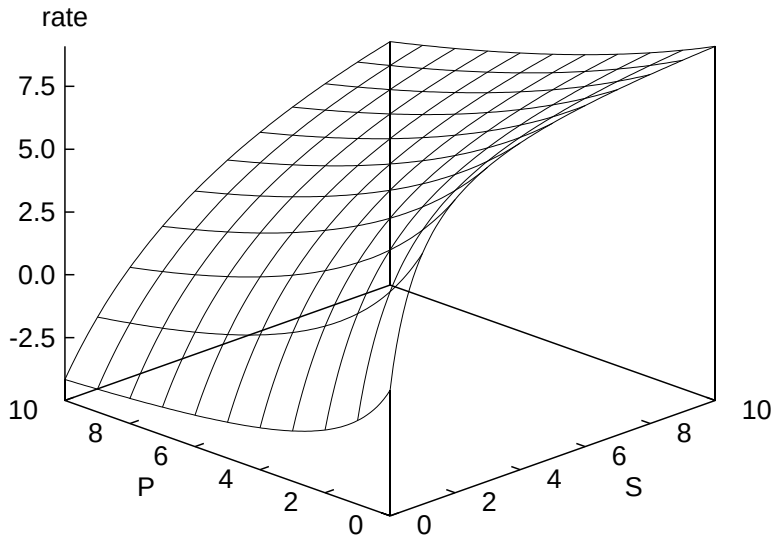
$$v = \frac{SV}{S + K_{\mathrm{m}}} \quad \text{or} \quad v = f(S)$$



The K_{m} and V have arbitarily been set to 1, where V is the *limiting rate* (or maximum velocity, V_{m}) and K_{m} is the *Michaelis constant*.

The Reversible M–M Eqn.

$$v_{net} = \frac{(V_{\mathrm{f}}/K_{\mathrm{m,S}})\,(S - P/K_{\mathrm{eq}})}{1 + S/K_{\mathrm{m,S}} + P/K_{\mathrm{m,P}}} \quad \text{or} \quad v = f(S, P)$$



Simultaneous dependence of enzyme rate on both substrate and product. The parameters have been set to: $K_{\mathrm{m,S}}$ =1; $V_{\mathrm{m,f}}$ = 10; $K_{\mathrm{m,P}} = 2$, and $K_{\mathrm{eq}} = 4$.

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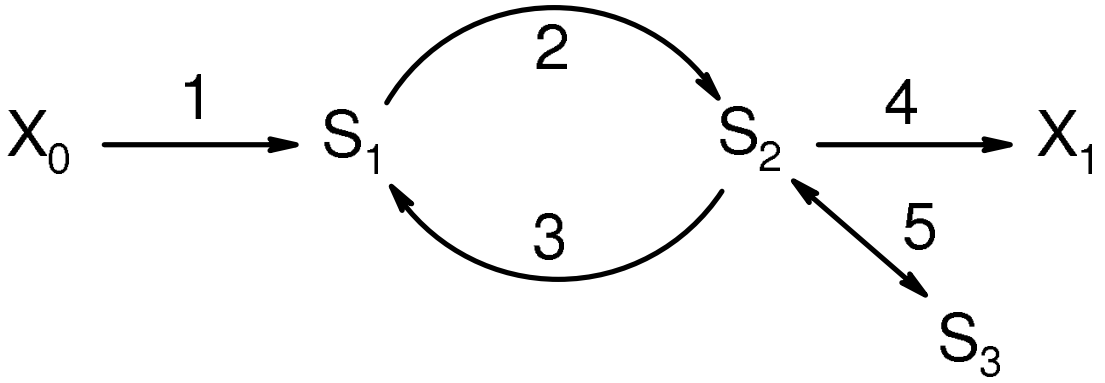
Steady state

In a metabolic network there is a flow of matter from the *source* to the *sink*. At steady state, the concentrations of the intermediates remain constant because their rates of formation exactly equal their rates of degradation. The flow through the pathway also remains constant.

If there are very slow changes in the concentrations of metabolites, or the pathway flux, because of slow changes in the source or sink, the pathway may be regarded as being in *quasi steady state* provided the time scale of the changes is very much longer than the time taken by the pathway to approach steady state.

Network to Model

Consider a simple metabolic network, e.g.:



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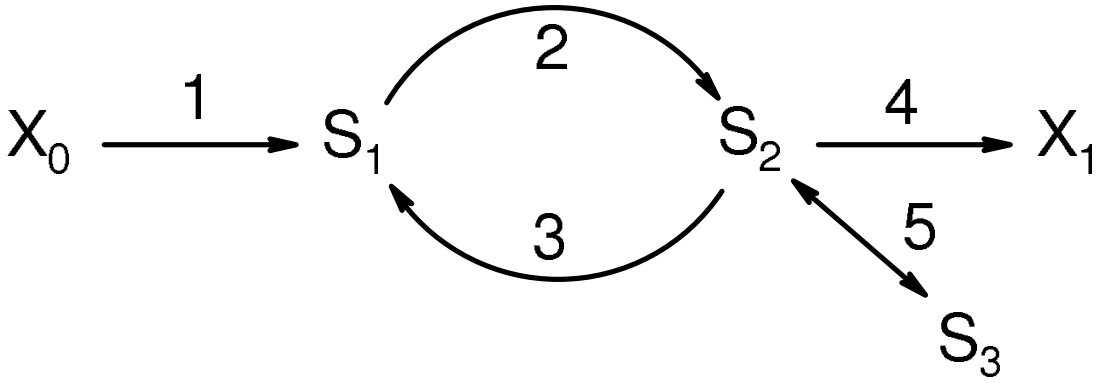

$$\begin{array}{c} S_1 \\ S_2 \\ S_3 \end{array} \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

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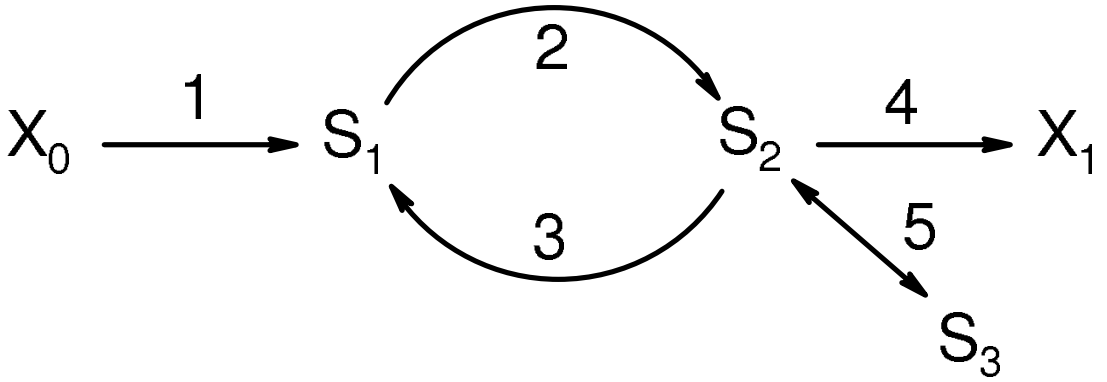
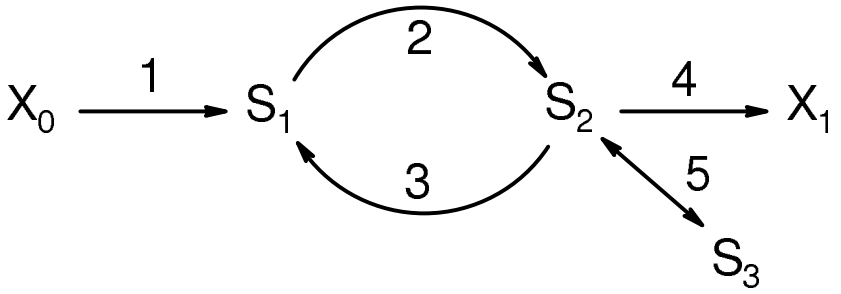


$$\begin{array}{c} \\ S_1 \\ S_2 \\ S_3 \end{array} \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

r1: X_0 -> S_1 $\sim$
r2: S_1 -> S_2 $\sim$
r3: S_2 -> S_1 $\sim$
r4: S_2 -> X_1 $\sim$
r5: S_2 -> S_3 $\sim$

Kinetics of the Metabolites



By inspection of the diagram:

$$\begin{aligned}
\frac{dS_1}{dt} &= v_1 - v_2 + v_3 \\
\frac{dS_2}{dt} &= v_2 - v_3 - v_4 - v_5 \\
\frac{dS_3}{dt} &= v_5
\end{aligned}$$

How can we generalize this?

Separation of Structure and Kinetics

The rate at which the substrate concentrations are changing is given by $\mathbf{N}.\mathbf{v}$, where $\mathbf{N}$ is the stoichiometry matrix, and $\mathbf{v}$ is a vector of enzyme kinetic functions. So for our substrate cycle network:

$$\begin{bmatrix} \frac{dS_1}{dt} \\ \frac{dS_2}{dt} \\ \frac{dS_3}{dt} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}$$

where each v_i is the rate function for enzyme i, depending on the variable metabolites and the parameters $V_{\mathrm{m,i}}$, $K_{\mathrm{m,i}}$ etc, as $f_i(\mathbf{S})$.

Integrating this set of non–linear differential equations gives a **dynamic model** of our network. The steady state is a set of non–linear simultaneous equations that can be solved for the steady state values of $\mathbf{S}$.

Steady State Solutions

Any metabolic network at steady state satisfies the relationship $\mathbf{N}.\mathbf{v} = \mathbf{0}$, where $\mathbf{N}$ is the stoichiometry matrix, exemplified by our model network:

$$\begin{matrix} S_1 \\ S_2 \\ S_3 \end{matrix} \begin{bmatrix} 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

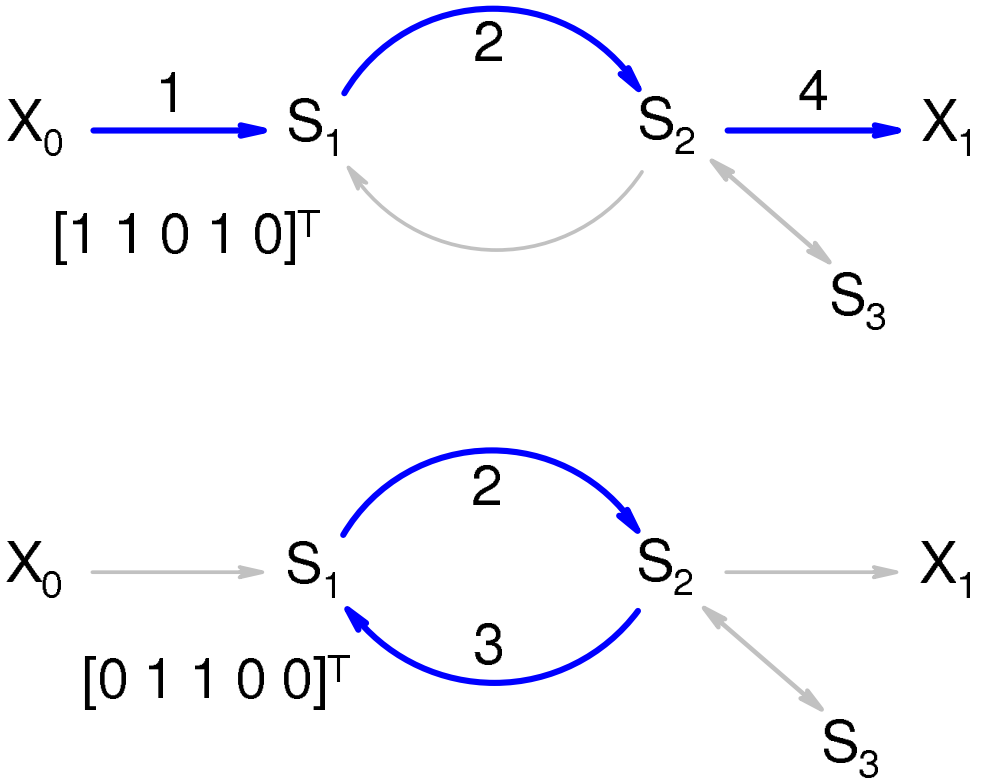
Structural Analysis: Null Space Vectors

Any observed set of velocities at steady state will be a linear combination of a set of vectors $\mathbf{K}$ referred to as a basis for the null space of the stoichiometry matrix. In this case:

$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \\ 0 & 0 \end{bmatrix}$$

The null space can be computed from the stoichiometry matrix using standard algorithms.

Null Space Vectors as Pathways



$[1 \;\; 1 \;\; 0 \;\; 1 \; 0]^T$ and $[0 \;\; 1 \;\; 1 \;\; 0 \; 0]^T$

The Null Space and Pathway Fluxes

Any feasible set of velocities at steady state is a linear combination of these null space vectors, e.g.:

$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \\ 0 & 0 \end{bmatrix}$$

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and:

$$\begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} a \\ b \end{bmatrix} = \begin{bmatrix} a \\ a+b \\ b \\ a \\ 0 \end{bmatrix} = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}$$

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$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \\ 0 & 0 \end{bmatrix} \begin{matrix} \leftarrow \text{subset} \\ \\ \\ \leftarrow \text{subset} \\ \\ \end{matrix}$$

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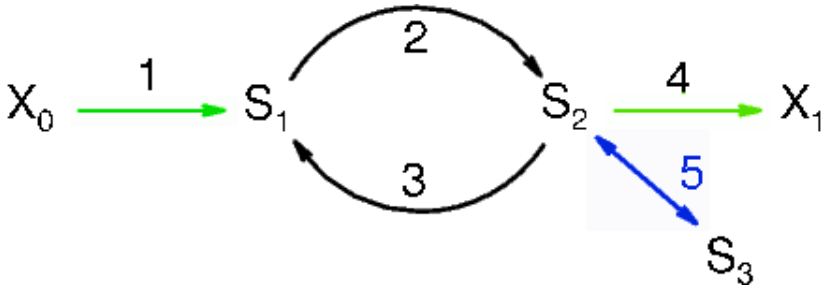
$$\mathbf{K} = \begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \\ 0 & 0 \end{bmatrix} \begin{matrix} \leftarrow \text{subset} \\ \\ \\ \leftarrow \text{subset} \\ \leftarrow \text{dead} \end{matrix}$$

and:

$$\begin{bmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \\ 1 & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} a \\ b \end{bmatrix} = \begin{bmatrix} a \\ a+b \\ b \\ a \\ 0 \end{bmatrix} = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}$$

Null Space Analysis



Reaction subset
'Dead' reaction.

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Limitations of the Null Space

Null space analysis reveals aspects of the network structure, but the set of basis vectors has shortcomings as metabolic routes:

- Is not a unique solution.
- May not respect thermodynamic direction.
- Not necessarily ’simple’.
- Can mislead about the impact of enzyme deletion.

But:

- Computation is rapid, even for genome scale networks.
- Reactions or routes shown to be ’dead’ will not be found ’live’ by any other approach.

Elementary modes analysis and linear programming (Flux Balance Analysis) have a similar basis but avoid the limitations.

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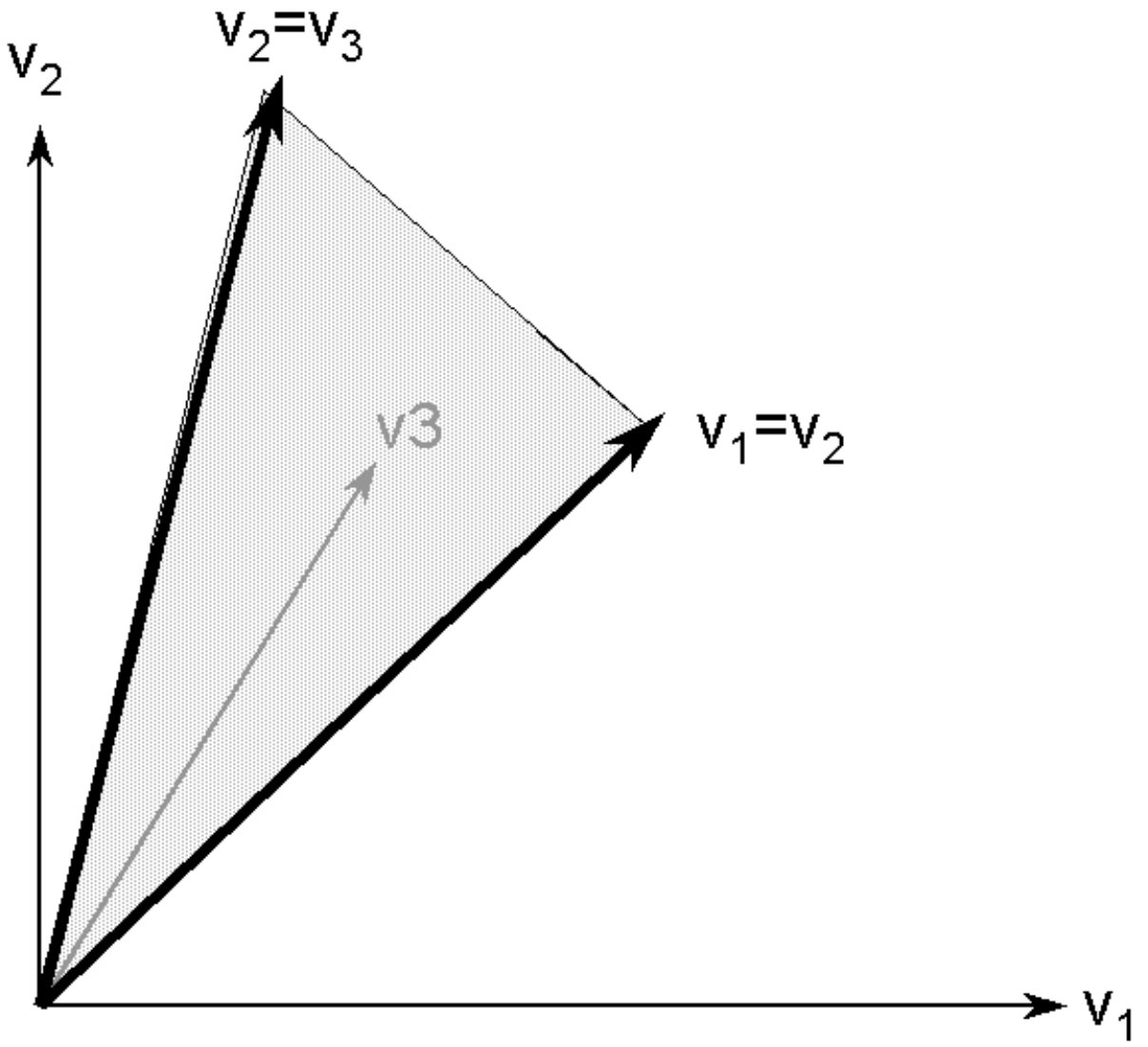
Null Space - Geometrical Interpretation



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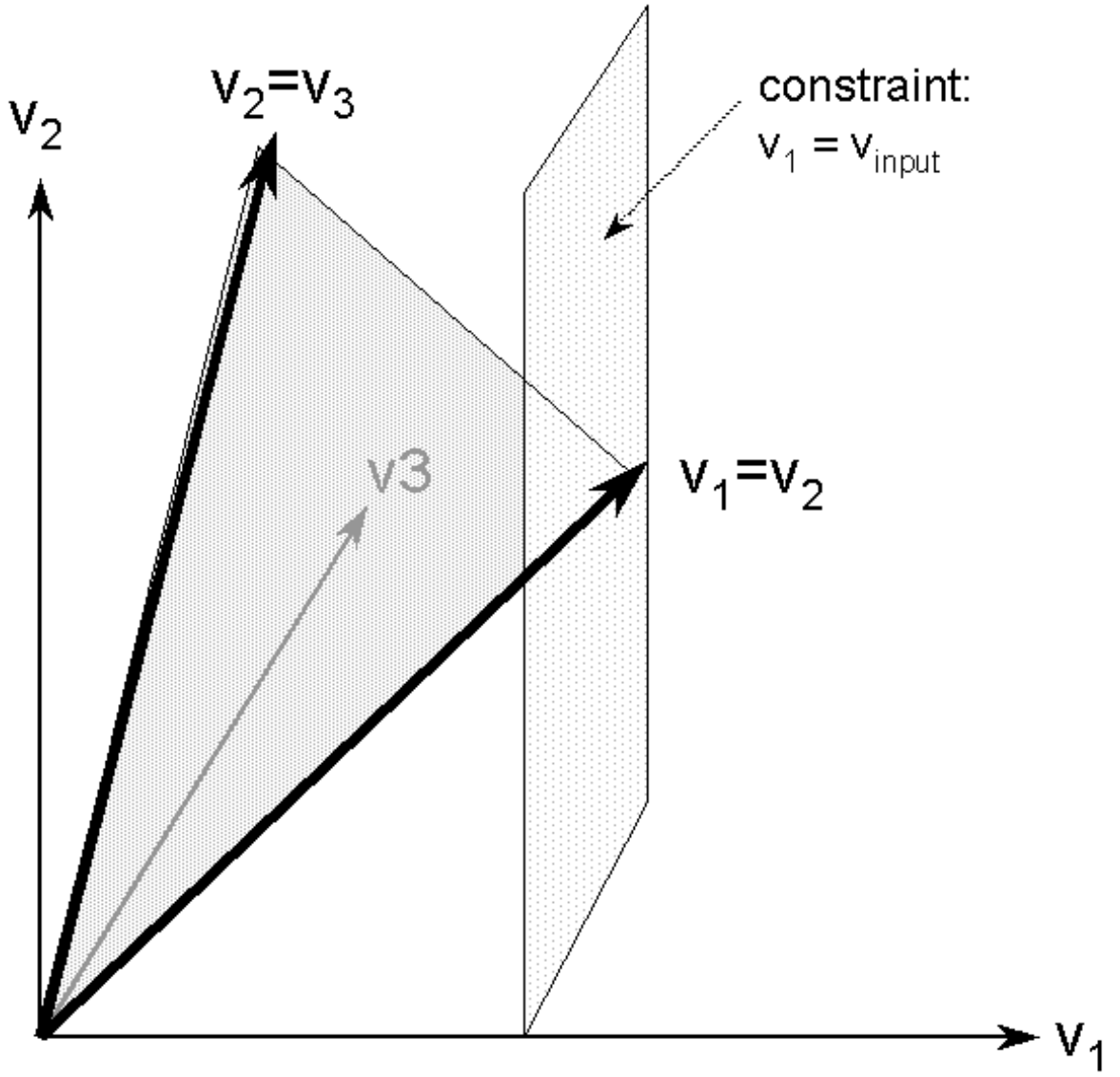
Linear Programming Solution —2



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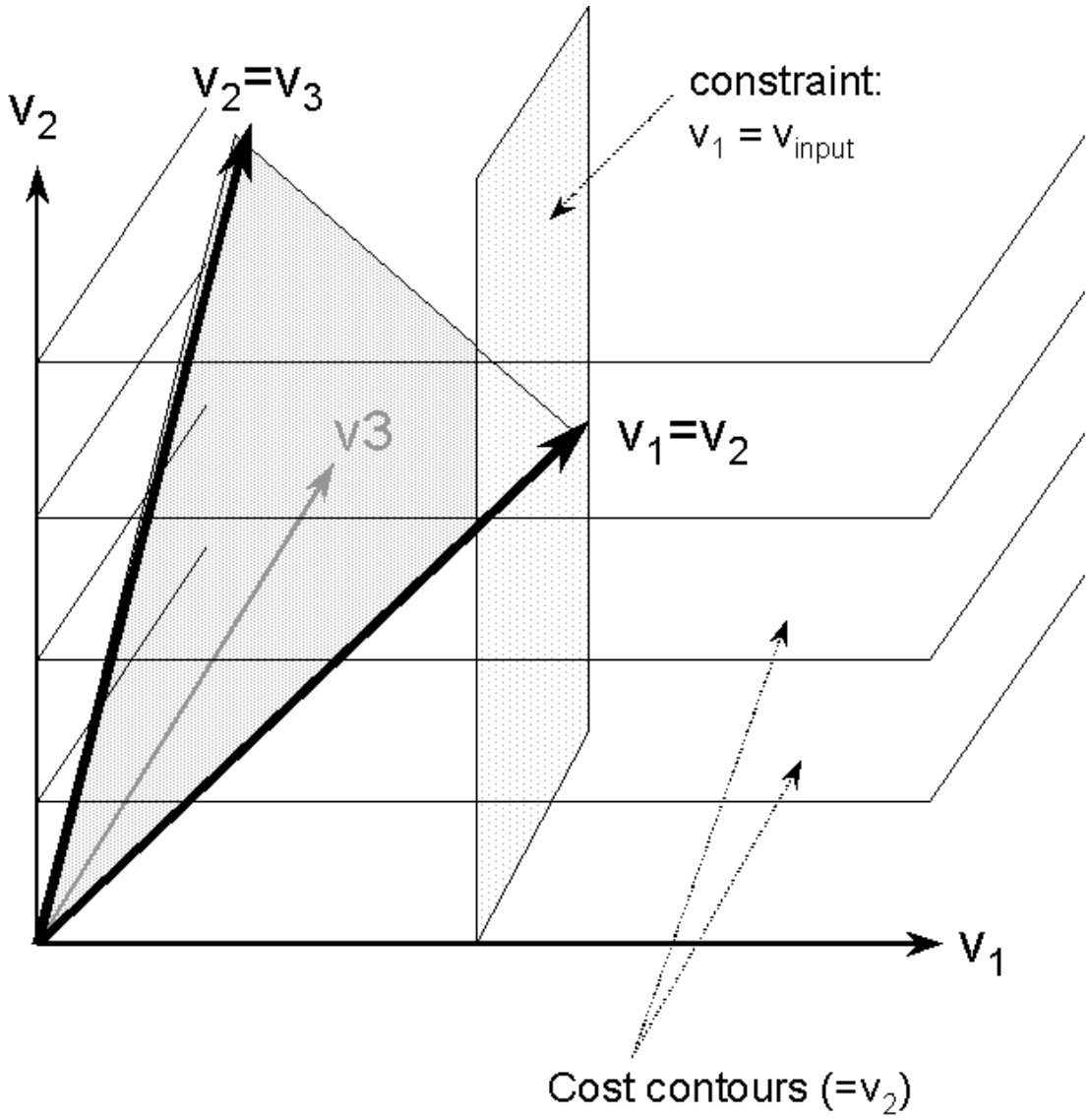
Linear Programming Solution —3



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Advantages of Structural Analysis

- Knowledge is more complete for network structure than for enzyme kinetics.

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- Structural models underlie kinetic models, and other techniques such as Metabolic Flux Analysis and Metabolic Control Analysis.