Metabolic Control Analysis
— an Introduction to Sensitivity Analysis

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Outline

- Elements of Metabolic Control Analysis (MCA)
  - The flux control coefficient
  - Control coefficients and enzyme kinetics
  - Flux control coefficients in context

Two aspects of MCA

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● Outline
● Two aspects of MCA
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Elasticities
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MCA has two aspects:

1. It can be used in the planning and interpretation of experiments, to determine the degree of influence variations of a particular system component have on overall behaviours of the whole system.
2. It can be used in the analysis of metabolic models either to predict / explain experimental results on the degree of influence of a component, or it can be used to determine how sensitive are model behaviours to the specific choices for parameter values

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originated with:

- Henrik Kacser & Jim Burns (Edinburgh) and

- Reinhart Heinrich & Tom Rapoport (Berlin)

independently in 1973 (based in part on earlier work by Joe Higgins).

Kacser, H. and Burns, J. A. (1973) *Symp. Soc. Exp. Biol. 27*, 65–104. Reprinted in *Biochem. Soc. Trans. 23,* 341–366, (1995).

Heinrich, R. and Rapoport, T. A. (1974) *Eur. J. Biochem. 42*, 89–95, 97–105.

The flux–enzyme relationship

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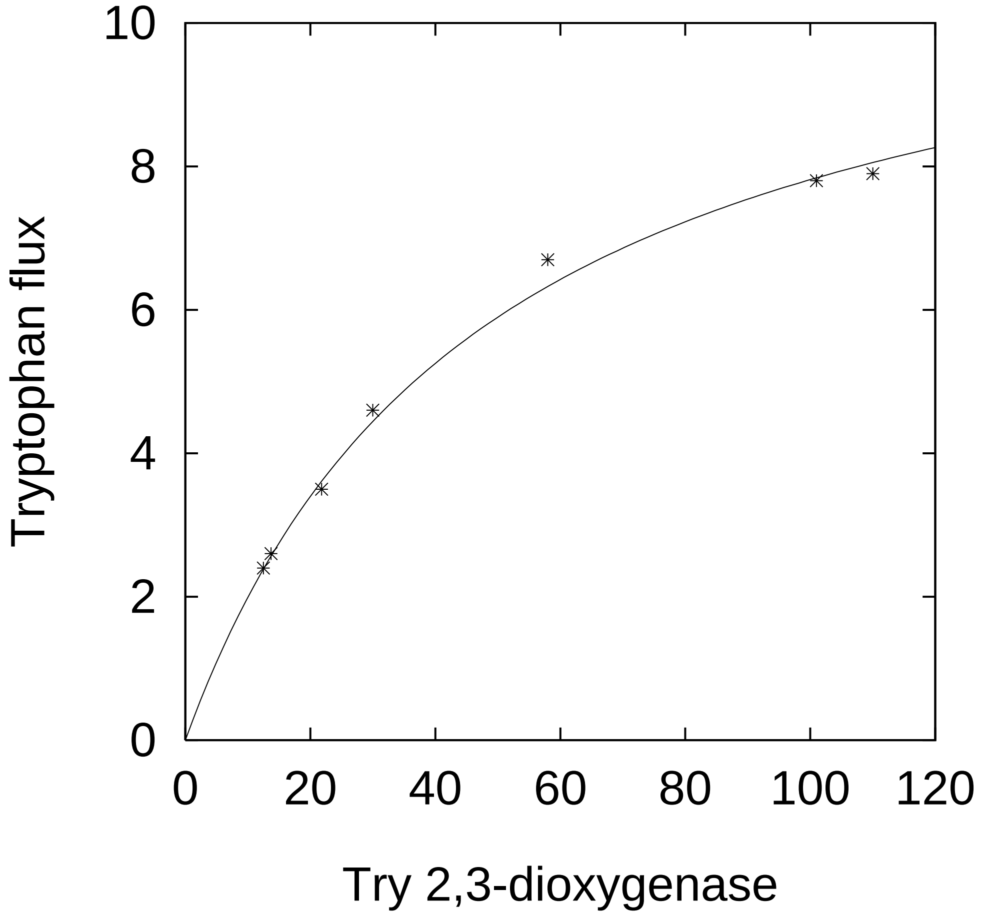

A typical example: Tryptophan 2,3–dioxygenase was adjusted by various dietary and hormonal treatments

Results of Salter et al (1986).

The flux–enzyme relationship

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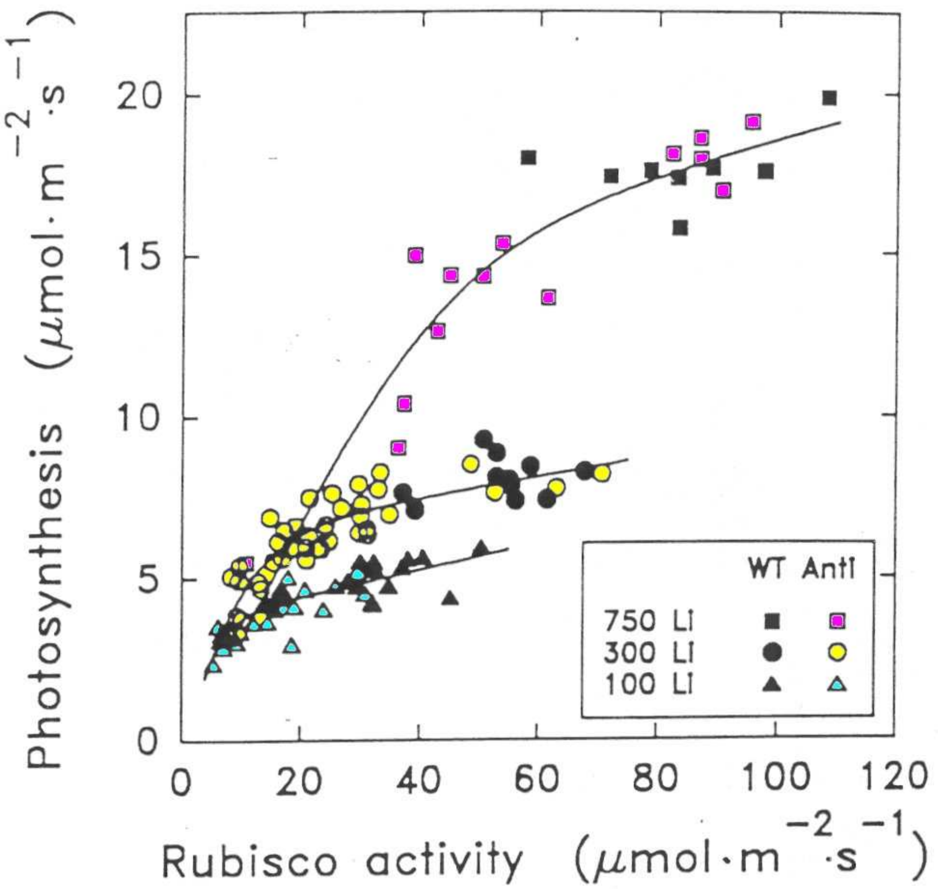

A typical example: dependence of carbon assimilation flux on rubisco levels in transgenic tobacco plants.

Results of Laurer et al, Planta **190** 332-345 (1993).

A specimen pathway

$$X_0 \xrightarrow{\textit{xase}} Y \xrightarrow{\textit{ydh}} Z \xrightarrow{\textit{zase}} X_1$$

X_0 is termed the *source*

X_1 is the *sink*

Y and Z are the variable metabolites that reach constant levels at steady state, when their rates of formation equal their rates of utilization.

Definition of the flux control coefficient

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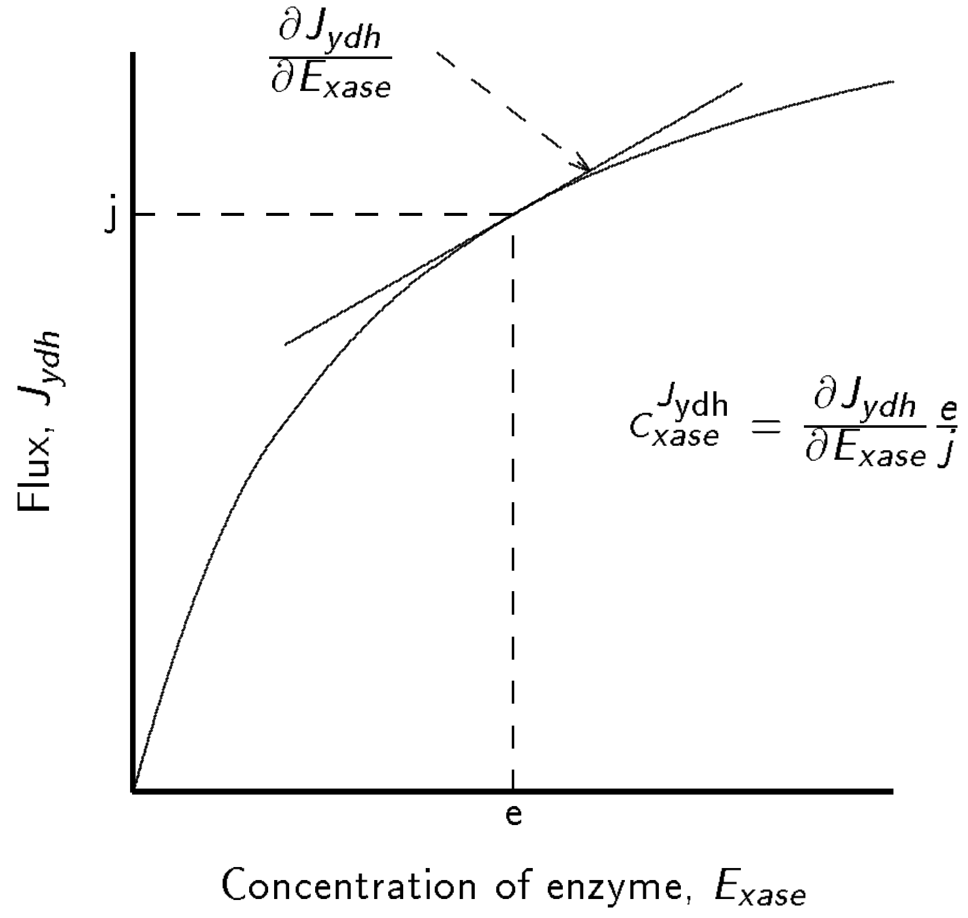
Suppose a small change, δE_{xase}, is made in the amount of enzyme E_{xase}, and that this produces a small change in the flux through the step catalyzed by *ydh*.

The flux control coefficient $C^{J_{ydh}}_{xase}$ is approximately the % change in J_{ydh} produced by a 1% change in E_{xase}.

Definition of the flux control coefficient



$$C^{J_{ydh}}_{xase} = \frac{\partial J_{ydh}}{\partial E_{xase}} \frac{e}{j}$$

Values of the flux control coefficient

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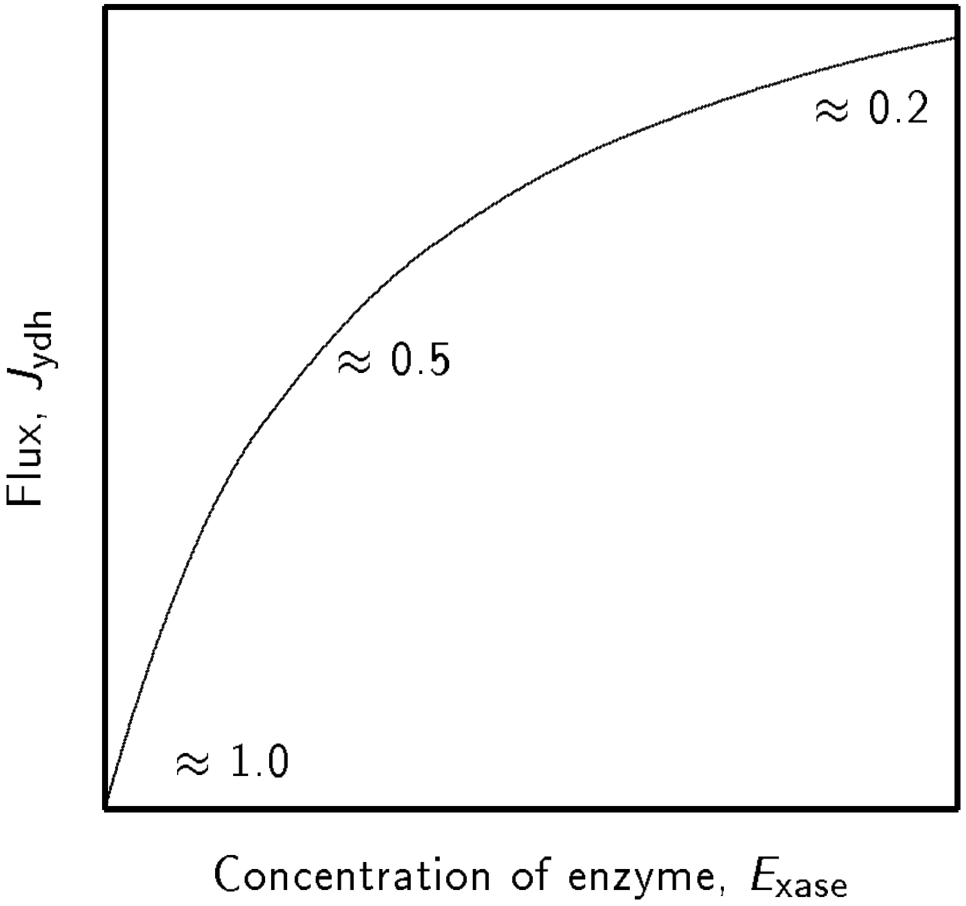

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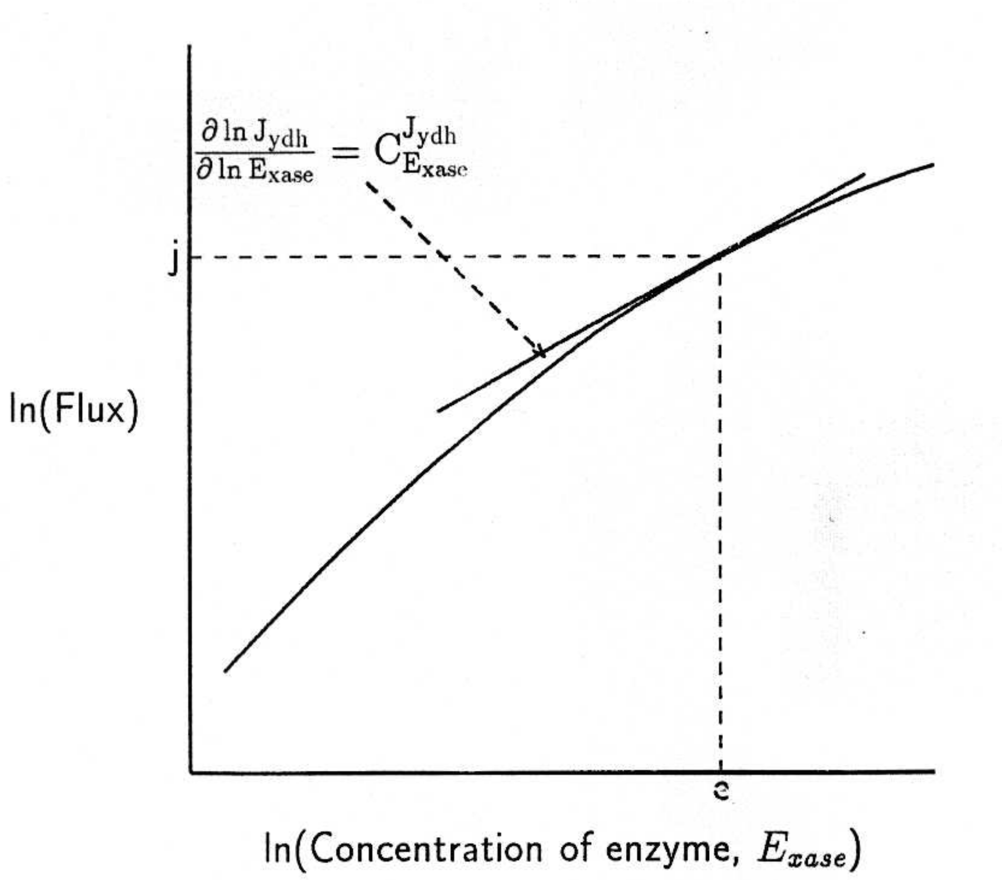
On a logarithmic plot of the curve, the flux control coefficient is the tangent to the curve.



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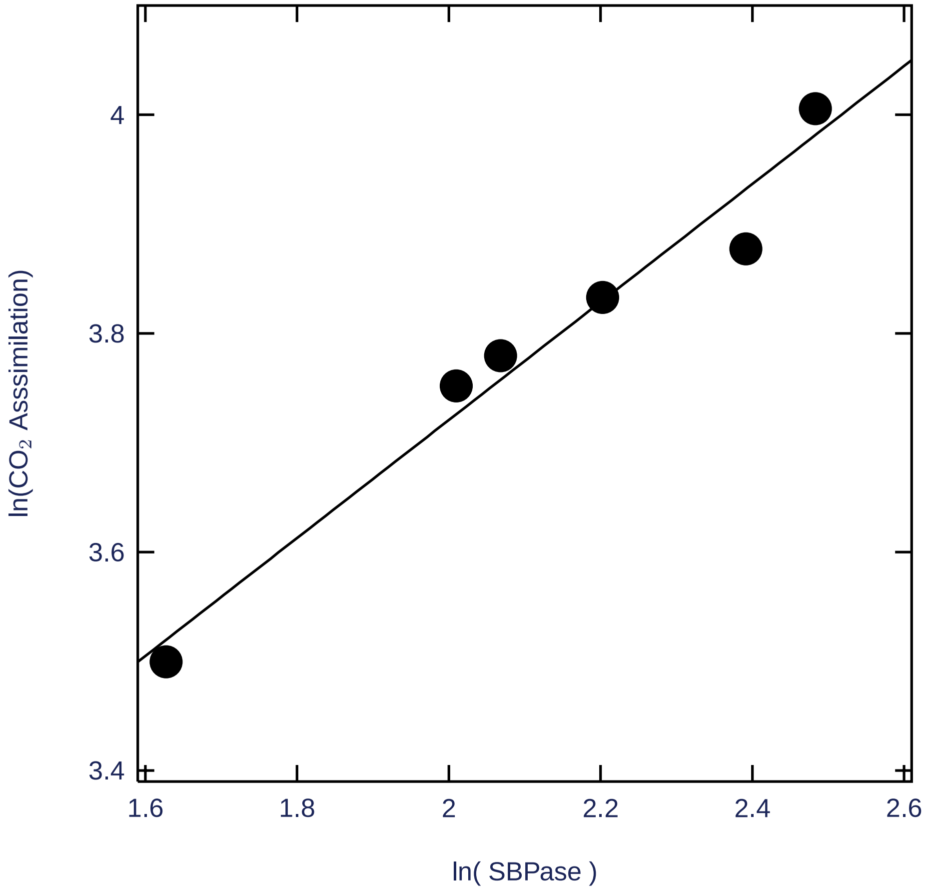
Experimental effect of reduced SBPase.



Photosynthetic rate in *N. tabacum* (tobacco) with reduced levels of SBPase. The slope of this line, and hence C^{Assim}_{SBPase}, is ≈ 0.5.

The flux summation theorem

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Flux J_{ydh} is potentially affected by all enzymes in the system, but the sum of the flux control coefficients of them all on any flux is 1:

$$\sum_{All E} C_E^{J_{ydh}} = 1$$

If a large number of enzymes affect the flux, the average value will be small

Flux control is a system property

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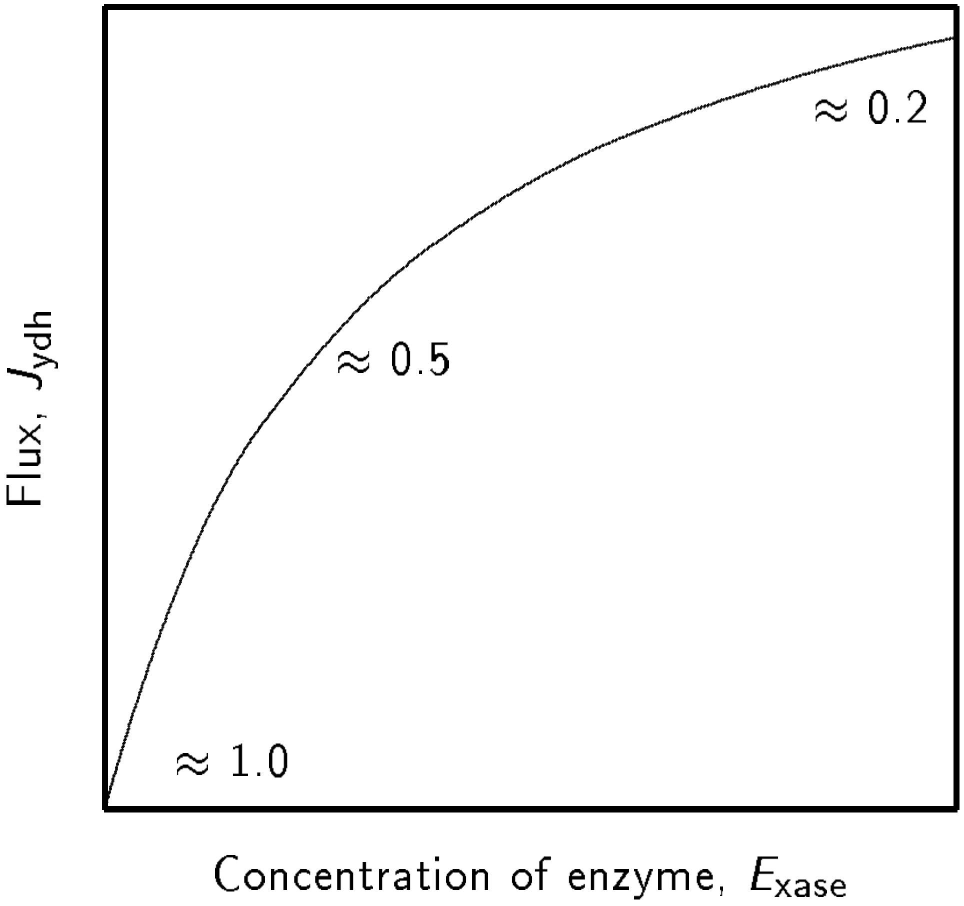

The Concentration Control Coefficent

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Suppose a small change, δE_{xase}, is made in the amount of enzyme E_{xase}, and that this produces a small change in the concentration of the metabolite, Y. The fractional changes are $\delta E_{xase}/E_{xase}$ and $\delta Y/Y$.
As δE_{xase} tends to zero, the concentration control coefficient C^Y_{xase} is given by the ratio:

$$C^Y_{xase} = \frac{\delta Y}{Y} \Bigg/ \frac{\delta E_{xase}}{E_{xase}}$$

Alternatively:

$$C^Y_{xase} = \frac{\partial Y}{\partial E_{xase}} . \frac{E_{xase}}{Y} = \frac{\partial \ln Y}{\partial \ln E_{xase}}$$

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Concentration Control Summation

Metabolite Y is potentially affected by all enzymes in the system, but the sum of the concentration control coefficients of them all on any metabolite is 0:

$$\sum_{All E} C_E^Y = 0$$

- It follows that there are necessarily both +ve and -ve control coefficients on any metabolite.
- Even in a linear pathway, there are no bounds on the value of concentration control coefficients.

Control coefficients and enzyme kinetics

Response to a change in enzyme activity

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Consider the pathway:

$$X_0 \xrightarrow{\textit{xase}} Y \xrightarrow{\textit{ydh}} Z \xrightarrow{\textit{zase}} X_1$$

Suppose that an extra amount of *ydh* is added, to increase the rate of the second step. What is the effect on the pathway?

Response to a change in enzyme activity

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$$X_0 \xrightarrow{\textit{xase}} Y \xrightarrow{\textit{ydh}} Z \xrightarrow{\textit{zase}} X_1$$

The increased amount of *ydh* tends to lower the concentration of Y. The lower Y will:

- Increase the rate of *xase* because of reduced product inhibition
- Decrease the rate of *ydh* because of lower substrate concentration

Response to a change in enzyme activity

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$$X_0 \quad \overset{\textit{xase}}{\longrightarrow} \quad Y \quad \overset{\textit{ydh}}{\longrightarrow} \quad Z \quad \overset{\textit{zase}}{\longrightarrow} \quad X_1$$

The increased amount of *ydh* tends to raise the concentration of Z. The increased Z will:

- Decrease the rate of *ydh* because of increased product inhibition
- Increase the rate of *zase* because of higher substrate concentration

Conclusion:

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- The effects of the increased amount of *ydh* involve the relative sizes of the responses of the enzymes to the pathway metabolites.

- The effects on the metabolites could tend to counteract the change in the amount of enzyme

- The effects on the metabolites could tend to change the rates of neighbouring enzymes to match the change in *ydh*

(This linkage was shown mathematically by Heinrich & Rapoport, 1974.)

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Suppose a small change, δS, is made in the amount of a metabolite S that affects the rate of the reaction, v_{ydh} catalysed by the enzyme *ydh*, producing a change δv_{ydh}. All other metabolites affecting *ydh* are kept constant at the values they have in the metabolic pathway at steady state. The fractional changes are $\delta S/S$ and $\delta v_{ydh}/v_{ydh}$.

As δS tends to zero, the elasticity coefficient ε_S^{ydh} is given by the ratio:

$$\varepsilon_S^{ydh} = \frac{\delta v_{ydh}}{v_{ydh}} \bigg/ \frac{\delta S}{S}$$

Alternatively,

$$\varepsilon_S^{ydh} = \frac{\partial v_{ydh}}{\partial S} . \frac{S}{v_{ydh}} = \frac{\partial \ln v_{ydh}}{\partial lnS}$$

Definition of the elasticity

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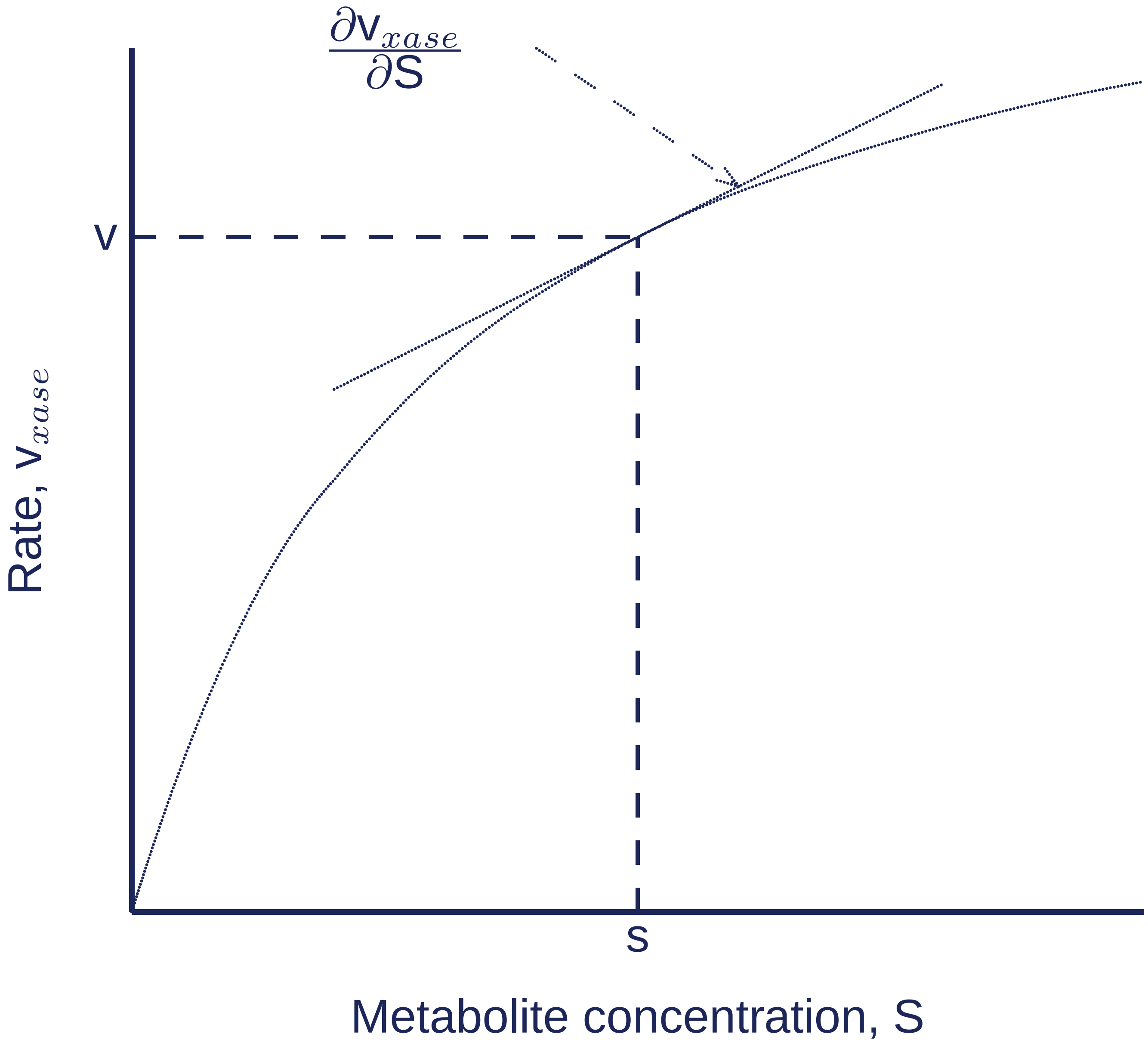

Values of the substrate elasticity

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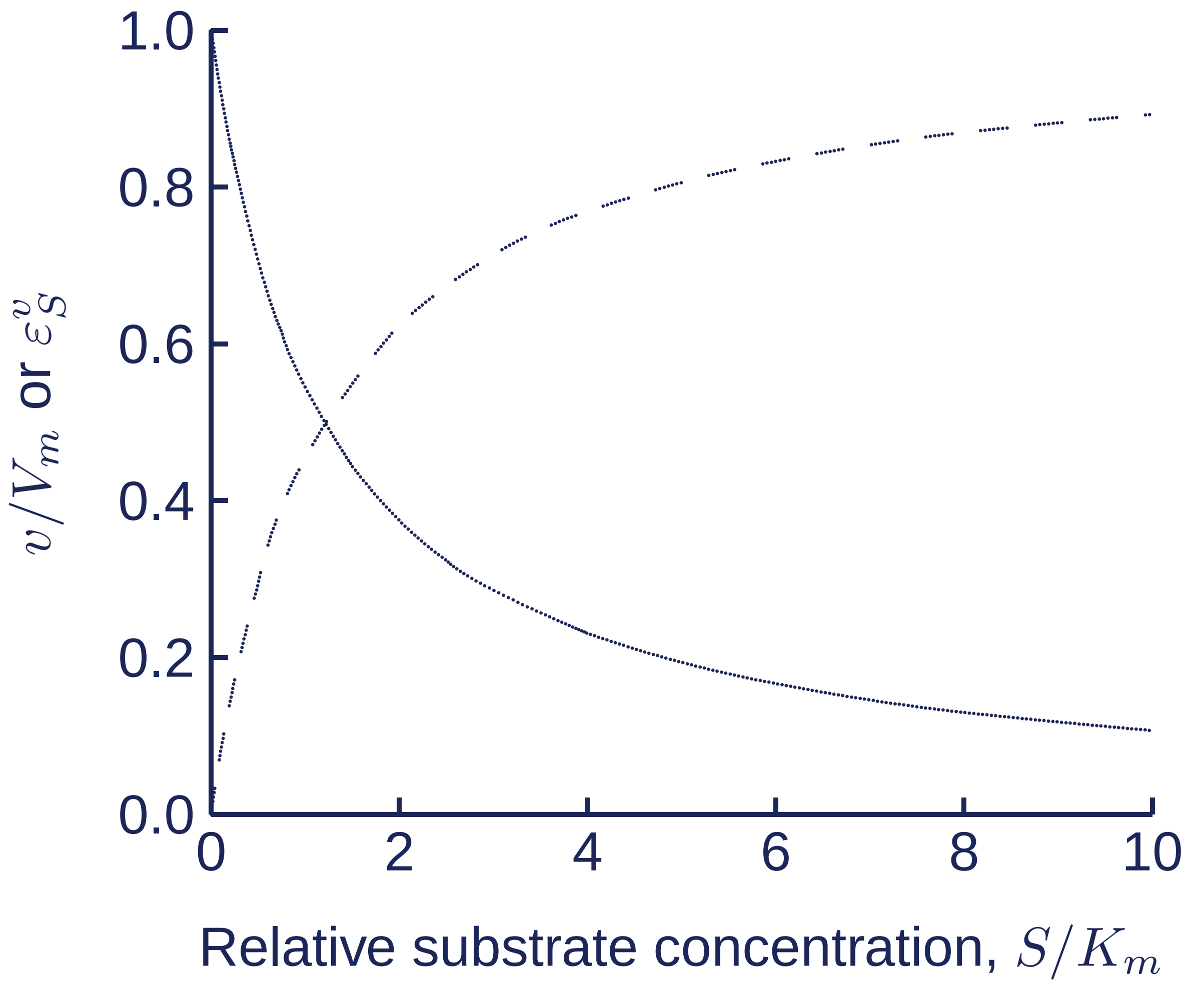

Elasticity with respect to substrate: dependence on substrate concentration for a single-substrate Michaelis–Menten enzyme.

Line, ε^v_S; dashes, fractional velocity, v/V_{max}.

Values of the product elasticity

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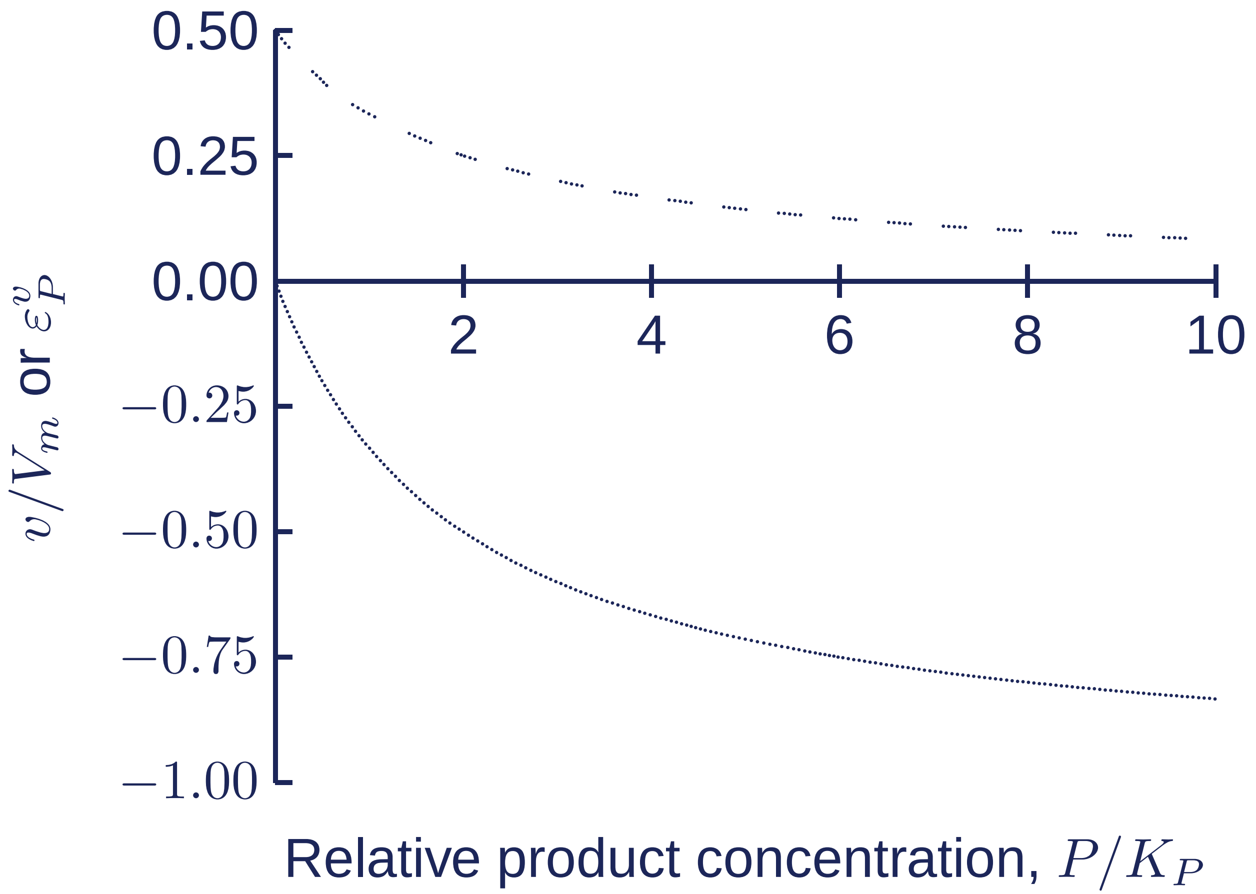

Elasticity with respect to product: dependence on product concentration for a Michaelis–Menten enzyme. — elasticity, ε^v_P;

– – – fractional velocity, v/V_{max}.

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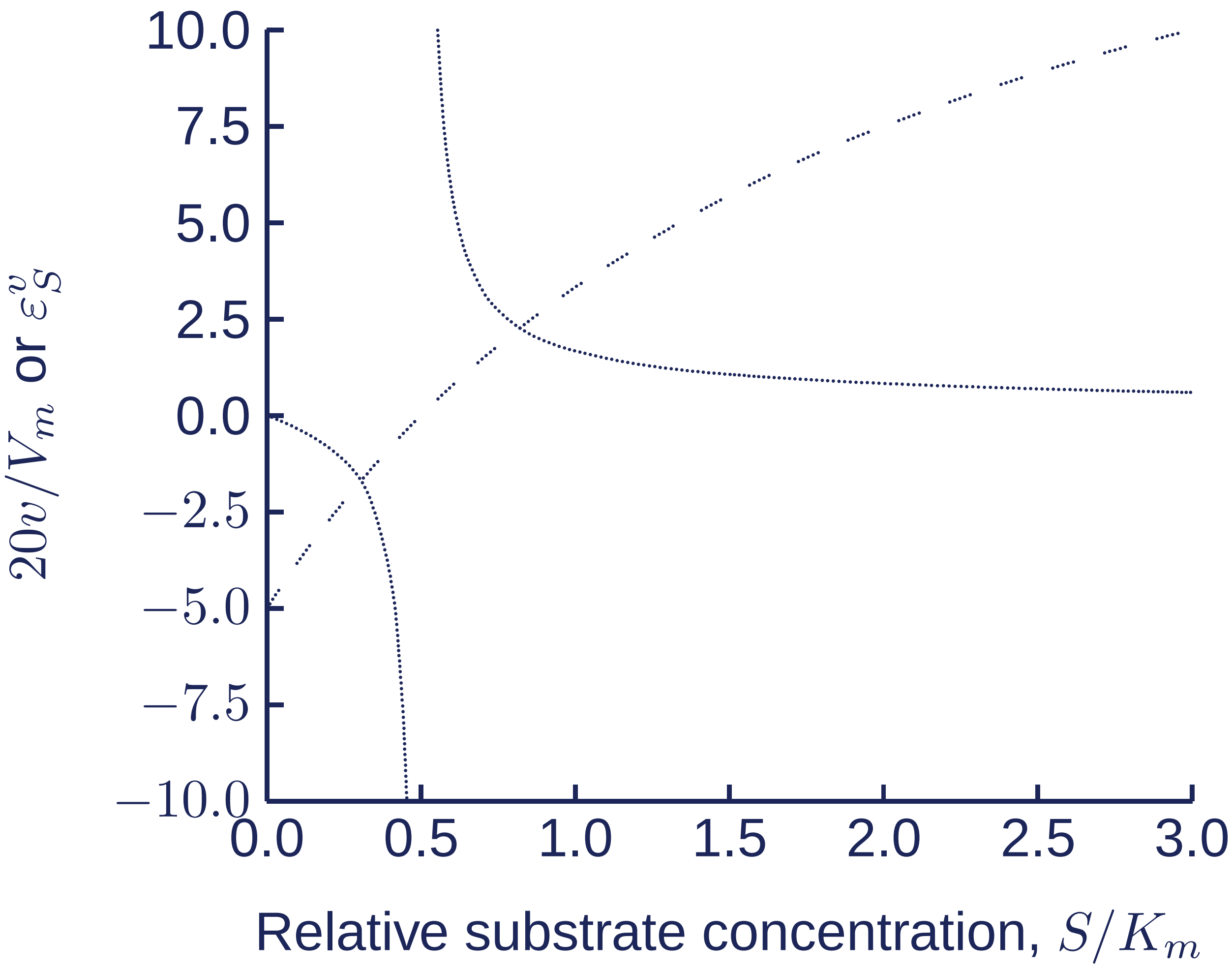

Elasticity with respect to substrate: dependence on substrate concentration for a reversible Michaelis–Menten enzyme near equilibrium. ▬ elasticity, ε^v_S; – – fractional velocity, $20 \times v/V_{max}$.

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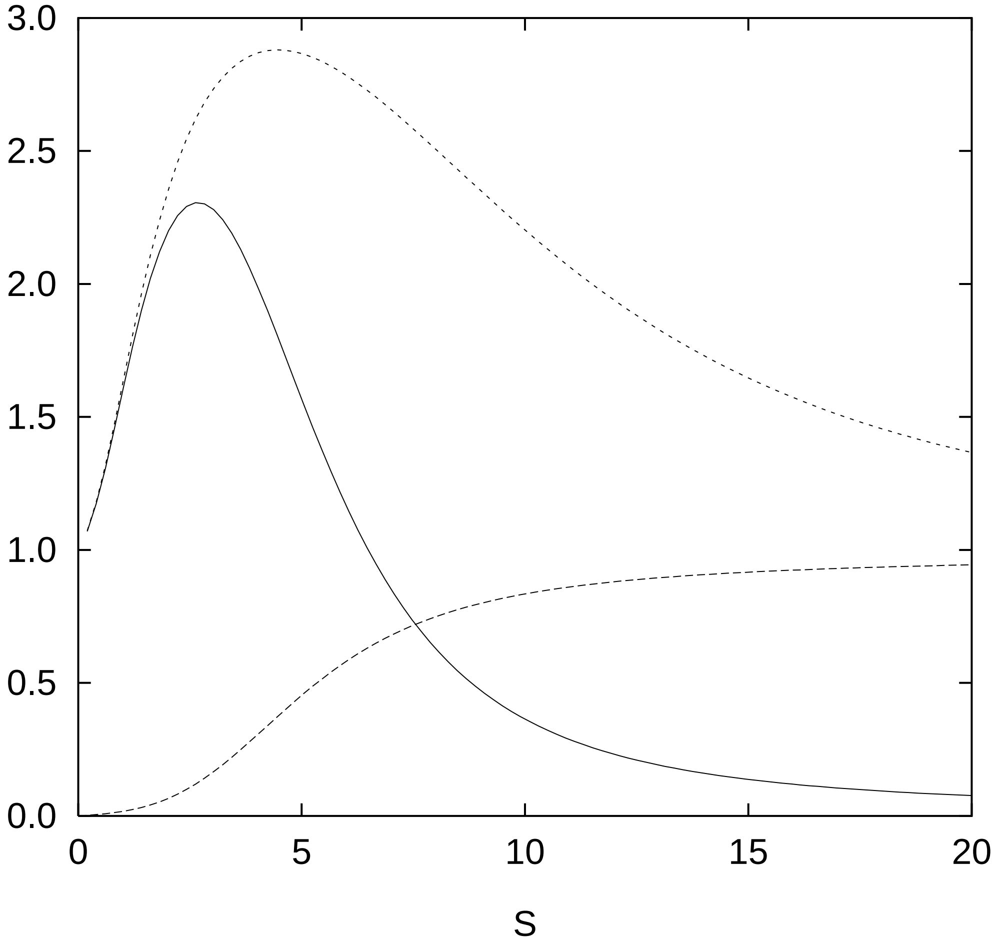

Elasticity of an allosteric enzyme

The curves show the Hill coefficient, the elasticity and the fractional saturation.

Elasticities from enzyme kinetics

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$$\varepsilon^v_S = \frac{1}{1-\rho} - \frac{S/K_{m,S}}{1 + S/K_{m,S} + P/K_{m,P}}$$

$$= \frac{1}{1-\rho} - \frac{v_f}{V_{m,f}}$$

where $\rho = \Gamma/K_{eq}$, and for the reaction:

$$S \rightleftharpoons P$$

Γ, the mass action ratio, is defined as:

$$\Gamma = \frac{[P]}{[S]}$$

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Connectivity theorem

The connectivity theorem

Consider the pathway:

$$X_0 \xrightarrow{\textit{xase}} Y \xrightarrow{\textit{ydh}} X_1$$

The *connectivity theorem* (Kacser & Burns, 1973) states the following relationships between the flux control coefficients and elasticities for this pathway:

$$C^J_{xase}\varepsilon^{xase}_Y + C^J_{ydh}\varepsilon^{ydh}_Y = 0$$

or

$$\frac{C^J_{xase}}{C^J_{ydh}} = -\frac{\varepsilon^{ydh}_Y}{\varepsilon^{xase}_Y}$$

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For a larger pathway, where Y affects more than two enzymes (*in any manner whatsoever*), the complete form of the connectivity relationship is:

$$\sum_{All E} C^J_E \varepsilon^E_Y = 0$$

Furthermore, there is a connectivity relationship for every metabolite in the pathway.

Summation and connectivity

$$X_0 \xrightarrow{\textit{xase}} Y \xrightarrow{\textit{ydh}} X_1$$

$$\begin{aligned} C^J_{xase} &+ C^J_{ydh} &= 1 \\ C^J_{xase}\varepsilon^{xase}_Y &+ C^J_{ydh}\varepsilon^{ydh}_Y &= 0 \end{aligned}$$

From this it follows that, if the elasticities are known:

$$C^J_{xase} = \frac{\varepsilon^{ydh}_Y}{\varepsilon^{ydh}_Y - \varepsilon^{xase}_Y} \; ; \; C^J_{ydh} = \frac{-\varepsilon^{xase}_Y}{\varepsilon^{ydh}_Y - \varepsilon^{xase}_Y}$$

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If the elasticities of all the enzymes in a pathway to all the metabolites in a pathway are known, it is possible to calculate the flux control coefficients.

The concentration connectivity theorem

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Problems

Consider the pathway:

$$X_0 \quad \xrightarrow{\textit{xase}} \quad Y \quad \xrightarrow{\textit{ydh}} \quad X_1$$

The *concentration connectivity theorem* states the following relationships between the flux control coefficients and elasticities for this pathway:

$$C^Y_{xase}\varepsilon^{xase}_Y + C^Y_{ydh}\varepsilon^{ydh}_Y = -1$$

HOWEVER for the control coefficients on a *different* metabolite Z:

$$C^Z_{xase}\varepsilon^{xase}_Y + C^Z_{ydh}\varepsilon^{ydh}_Y = 0$$

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Problems

For a larger pathway, where Y affects more than two enzymes (*in any manner whatsoever*), the complete forms of the concentration connectivity relationships are:

$$\sum_{All\,E} C^{Y}_{E}\,\varepsilon^{E}_{Y} = -1$$

and

$$\sum_{All\,E} C^{Z}_{E}\varepsilon^{E}_{Y} = 0$$

Concentration summation and connectivity

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$$X_0 \quad \overset{xase}{\longrightarrow} \quad Y \quad \overset{ydh}{\longrightarrow} \quad X_1$$

$$\begin{array}{lcccr} C^Y_{xase} & + & C^Y_{ydh} & = & 0 \\ C^Y_{xase}\varepsilon^{xase}_Y & + & C^Y_{ydh}\varepsilon^{ydh}_Y & = & -1 \end{array}$$

From this it follows that, if the elasticities are known:

$$C^Y_{xase} = \frac{1}{\varepsilon^{ydh}_Y - \varepsilon^{xase}_Y} \; ; \; C^Y_{ydh} = \frac{-1}{\varepsilon^{ydh}_Y - \varepsilon^{xase}_Y}$$

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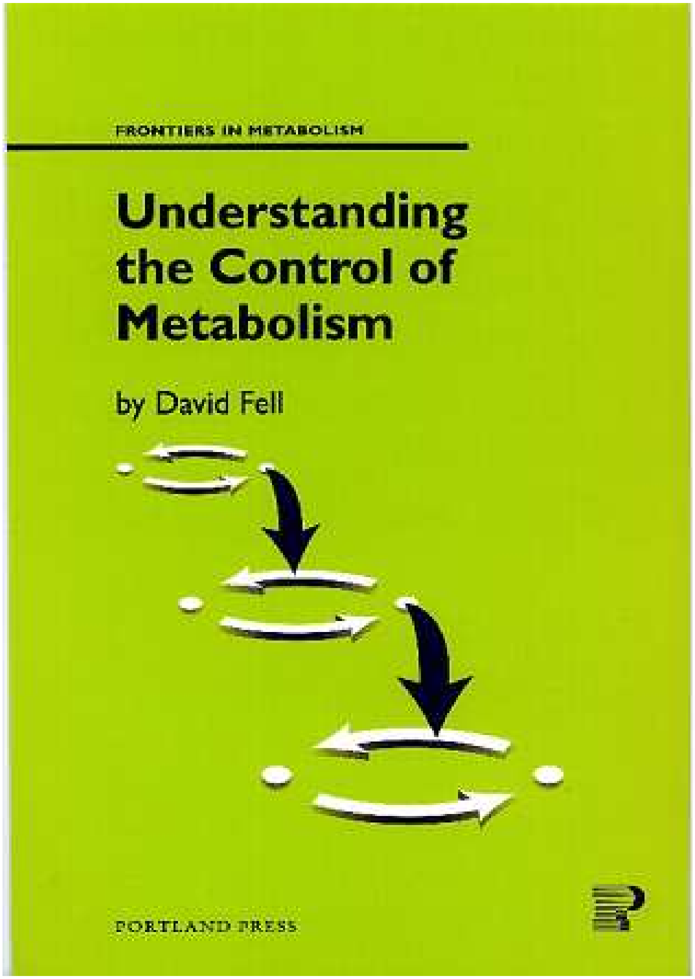
Read all about it!

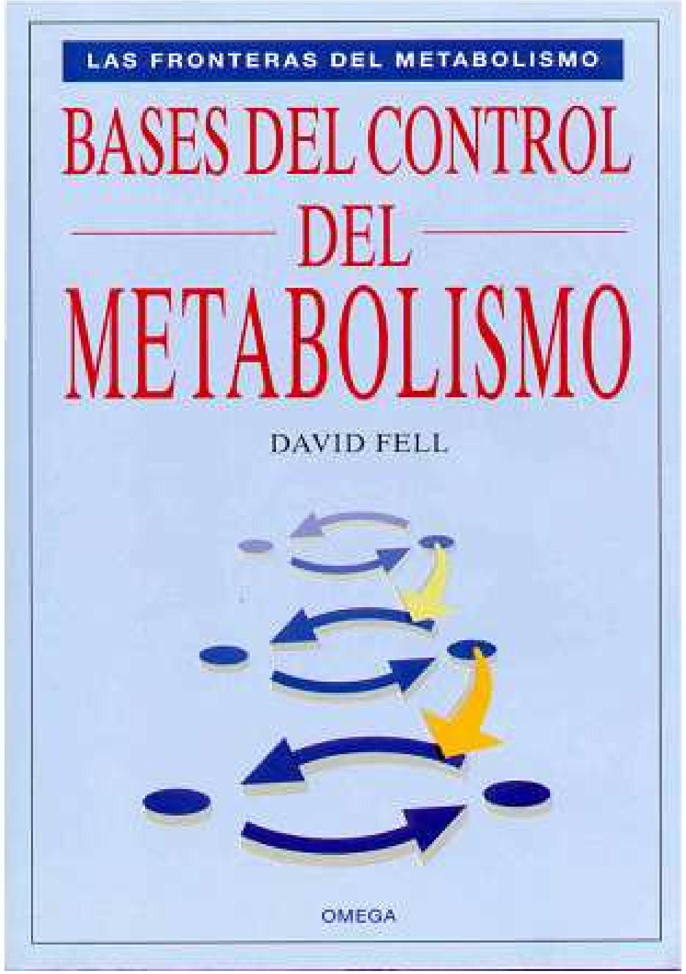


FRONTIERS IN METABOLISM

Understanding the Control of Metabolism

by David Fell

PORTLAND PRESS



LAS FRONTERAS DEL METABOLISMO

BASES DEL CONTROL DEL METABOLISMO

DAVID FELL

OMEGA

Problems 1

1. Suppose an enzyme in a pathway follows Michaelis-Menten kinetics with V_m = 100 units and K_m = 0.05mM:

   $$v = \frac{[S]V_m}{[S] + K_m}$$

   What is the elasticity of the enzyme with respect to its substrate (a) at a substrate concentration of 0.025mM; (b) at a substrate concentration of 0.3mM? (Hint: a non-mathematical way of doing this is to determine the slope of the $\ln v$ against $\ln[S]$ curve at the two concentrations Calculate v at 90%, 95%, 100%, 105% and 110% of the required substrate concentration; plot these values as $\ln v$ against $\ln[S]$ and determine the slope at 100%.) (Mathematical answers, eg via differentiation of the rate law, also accepted.)
2. In the serine biosynthesis pathway:

   $$\text{3-phosphoglycerate} \xrightarrow{1} \text{phosphoserine} \xrightarrow{2} \text{serine}$$

   the elasticity of the first step, ε^1_{pser}, is -1.43 in the liver of rabbits on a normal low protein diet. (The first step is actually catalysed by two enzymes, but the elasticity is the ’combined’ elasticity for them both, so they can be treated as a single step.) The elasticity of the second step, ε^2_{pser}, is 0.041. What are the flux control coefficients, C^J_1 and C^J_2, of the two steps?

Problems 2

1. The enzyme fumarase catalyzes the reaction:

   $$\text{fumarate} \rightleftharpoons \text{malate}$$

   Its rate of reaction is decsribed by the reveresible Michaelis–Menten equation:

   $$v = \frac{V_m\left([fum] - \frac{[mal]}{K_{eq}}\right)}{K_{fum} + [fum] + \frac{K_{fum}[mal]}{K_{mal}}}$$

   where $V_m = 20\mu$mol.min^{-1}, K_{fum} = 0.9mM, K_{mal} = 1.2mM and K_{eq} = 11. What are the elasticities of the enzyme with respect to fumarate and malate at [fum] = 0.4mM and [mal] = 0.5mM? (Hint: a non-mathematical way of doing this is to determine the slope of the $\ln v$ against $\ln[fum]$ curve at the concentrations specified. Calculate v at 90%, 95%, 100%, 105% and 110% of the fumarate substrate concentration; plot these values as $\ln v$ against $\ln[fumarate]$ and determine the slope at 100%. Repeat for malate.) (Mathematical answers, eg via differentiation of the rate law, also accepted.)

2. Consider the glycolytic pathway, particularly the successive enzymes phosphofructokinase and aldolase:

   $$\cdots \text{Fru-6-P} \xrightarrow{PFK} \text{Fru-1,6bisP} \xrightarrow{Ald} \text{DHAP + GAP} \cdots$$

   The elasticity of phosphofructokinase (PFK) with respect to fru-1,6-bisP, ε^{PFK}_{FBP}, is -0.01, whilst that of aldolase to the same metabolite ε^{ald}_{FBP}, is 2.5 in a particular cell. What is the ratio of the flux control coefficients of these two enzymes on glycolysis? What is the flux control coefficient of aldolase if ε^{PFK}_{FBP} is 0?