Applications of Metabolic Control Analysis

C1net Workshop 2; Day 3

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C1net gas fermentation

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Outline

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Understanding Feedback Inhibition
Metabolism and Genetics
Metabolism and Drug Action
Enzyme overexpression
Summary

MCA continued:

- Feedback inhibition
- MCA and genetics
- MCA and drug action
- Enzyme over–expression

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- Feedback inhibition and control analysis
- Feedback inhibition and control analysis
- Properties of feedback inhibition
- Supply–Demand Analysis
- Flux control and metabolite homeostasis: the link
- Flux control and metabolite homeostasis: the link

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Understanding Feedback Inhibition

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Control at Feedback–Inhibited Enzymes

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Classical biochemical theory proposed that feedback–inhibited enzymes at the start of a pathway were likely ‘rate–limiting steps’.

Early opposition to Metabolic Control Analysis centered on the prediction by the latter that such enzymes would have low control coefficients.

One example of the experimental evidence follows; others will come later.

Feedback–inhibited enzymes: ATCase

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Liu et al (1993)[1] showed that it took a 19–fold decrease in ATCase to produce a 1.8–fold decrease in growth rate attributable to pyrimidine biosynthesis. (= Approximate flux control coefficient of < 0.05.)
Nevertheless, the authors state that:

> Assuming that ATCase activity is the rate–limiting step in pyrimidine biosynthesis . . . (a situation which is highly likely because of the enzyme's position in the pathway, its pattern of regulation and the toxicity of its product) . . .

[1] C. Liu et al, *J. Bacteriol. 175*, 2363–2369 (1993).

Feedback inhibition and control analysis

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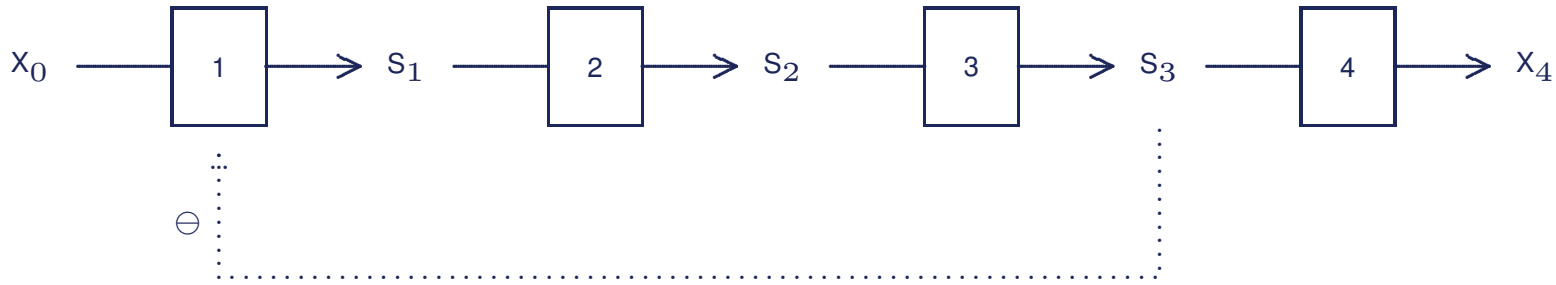

This is a generalized feedback inhibition loop, with the enzymes represented by numbered boxes. Metabolite S_3 inhibits enzyme 1.

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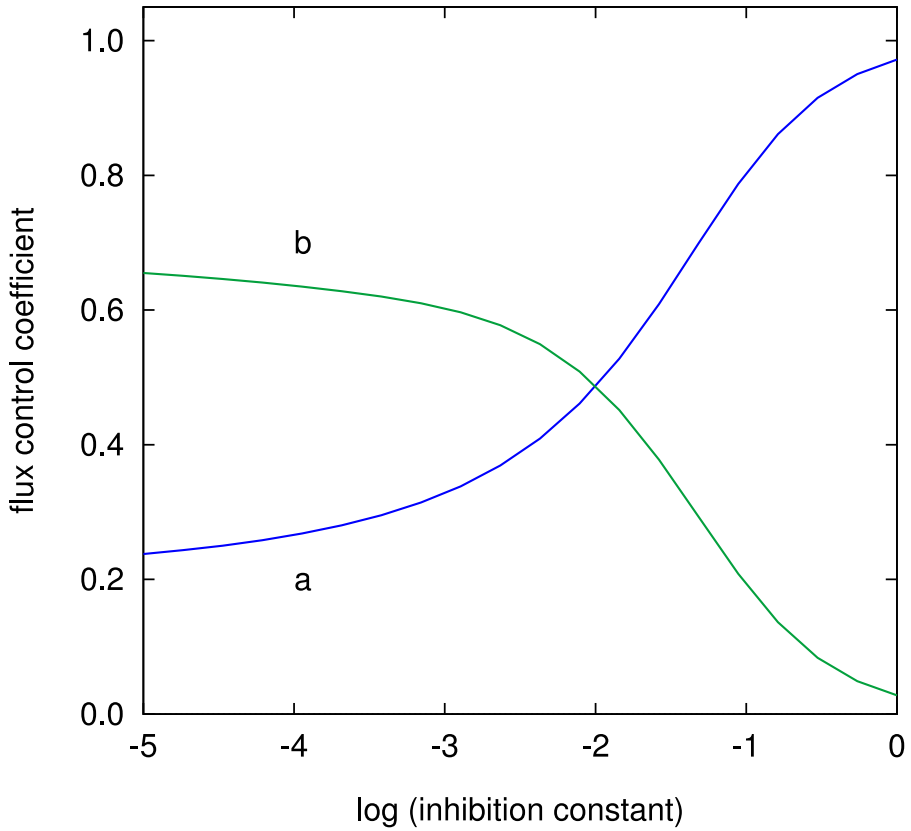
Feedback inhibition and control analysis



Feedback alters the control distribution. The flux control coefficients of enzymes 1 (curve a) and 4 (curve b) of the previous pathway are plotted against the inhibition constant for S_3 on enzyme 1 in this simulated example. The inhibition weakens from left to right.

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Properties of feedback inhibition

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1. Feedback inhibition is an antidote to the tendency of reactions at the start of a pathway to have the greater control of flux.
2. Feedback inhibition improves homoeostasis of the concentration of the feedback metabolite;increased cooperativity of the inhibition specifically enhances this effect.
3. Feedback inhibition improves the stability of pathways in that it speeds up the return to a steady state after random perturbation,

Supply–Demand Analysis

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e.g. for a linear supply–demand pathway:

$$\frac{C^S_{supply}}{C^J_{supply}} = \frac{1}{\varepsilon^{demand}_S}$$

$$\frac{C^S_{demand}}{C^J_{demand}} = \frac{1}{\varepsilon^{supply}_S}$$

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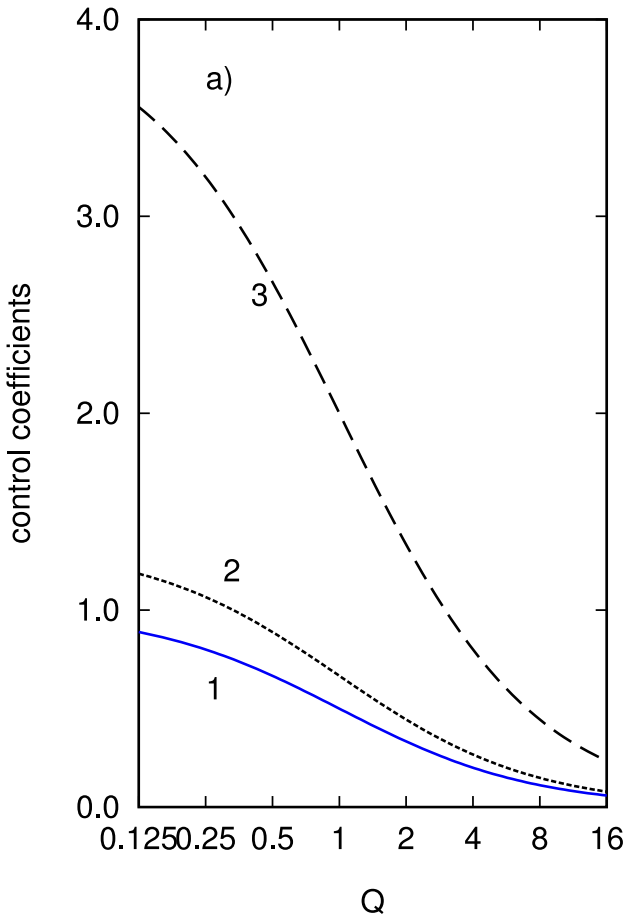

Homeostasis of metabolite concentrations is not compatible with control located in the supply reactions. (Q = $-\varepsilon_S^{supply}/\varepsilon_S^{demand}$; 1: C^J_{supply}, 2 & 3: C^S_{supply} for two values of ε_S^{demand}.)

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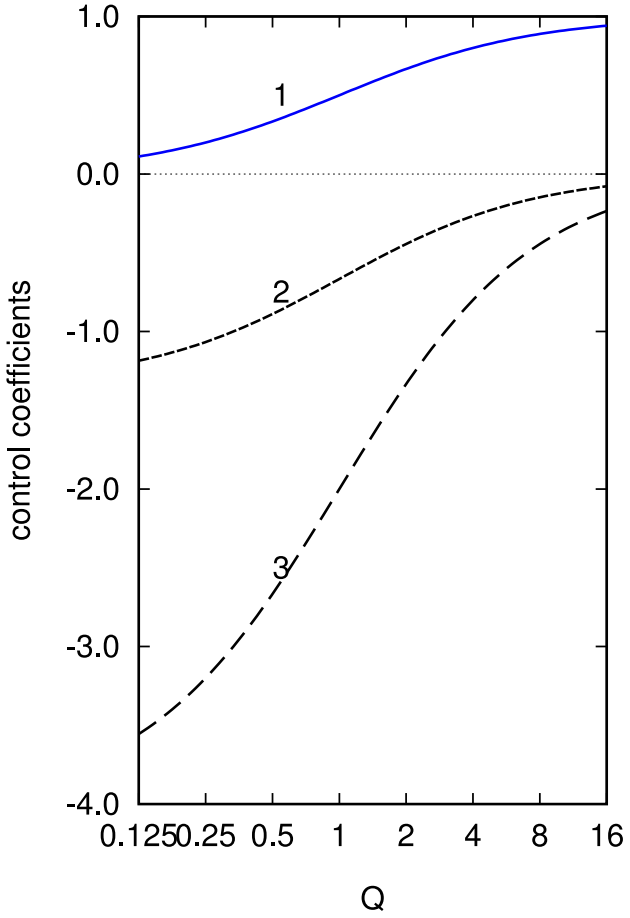

Homeostasis of metabolite concentrations is compatible with control located in the demand reactions. (Q = $-\varepsilon_S^{supply}/\varepsilon_S^{demand}$; 1: C^J_{demand}, 2 & 3: C^S_{demand} for two values of ε_S^{supply}.)

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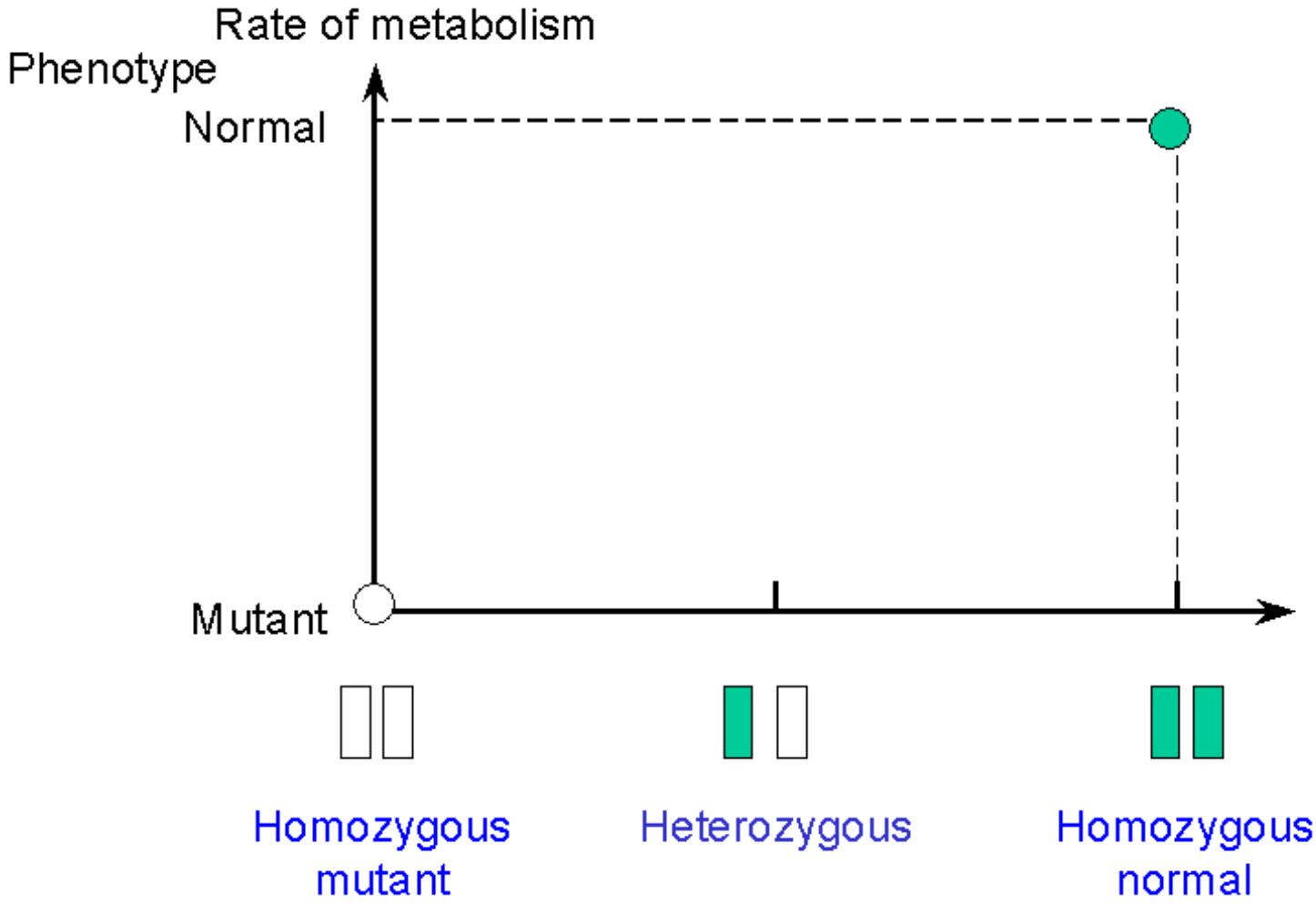

Kacser & Burns, (1981). The molecular basis of dominance. *Genetics 97*, 639-666.

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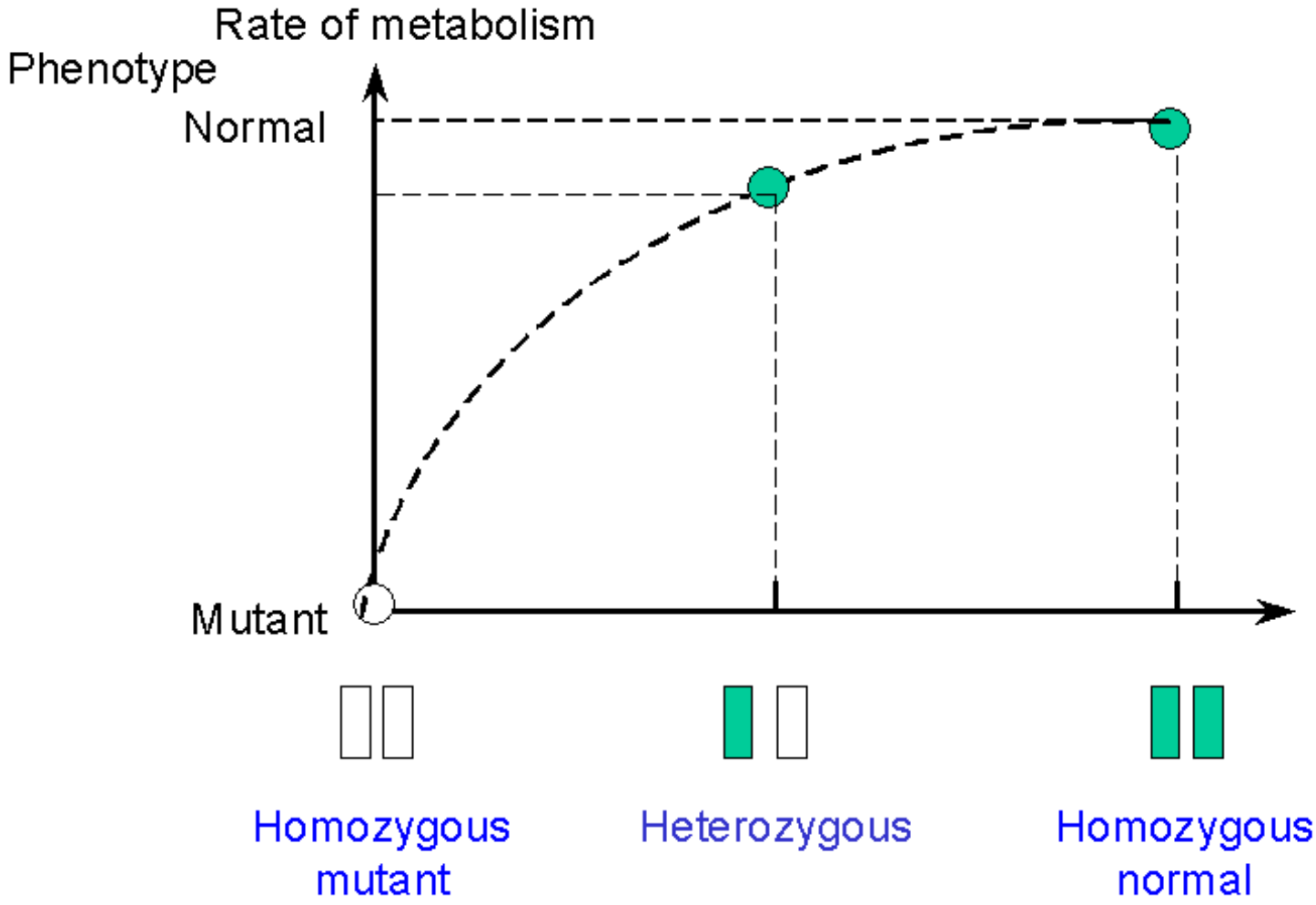

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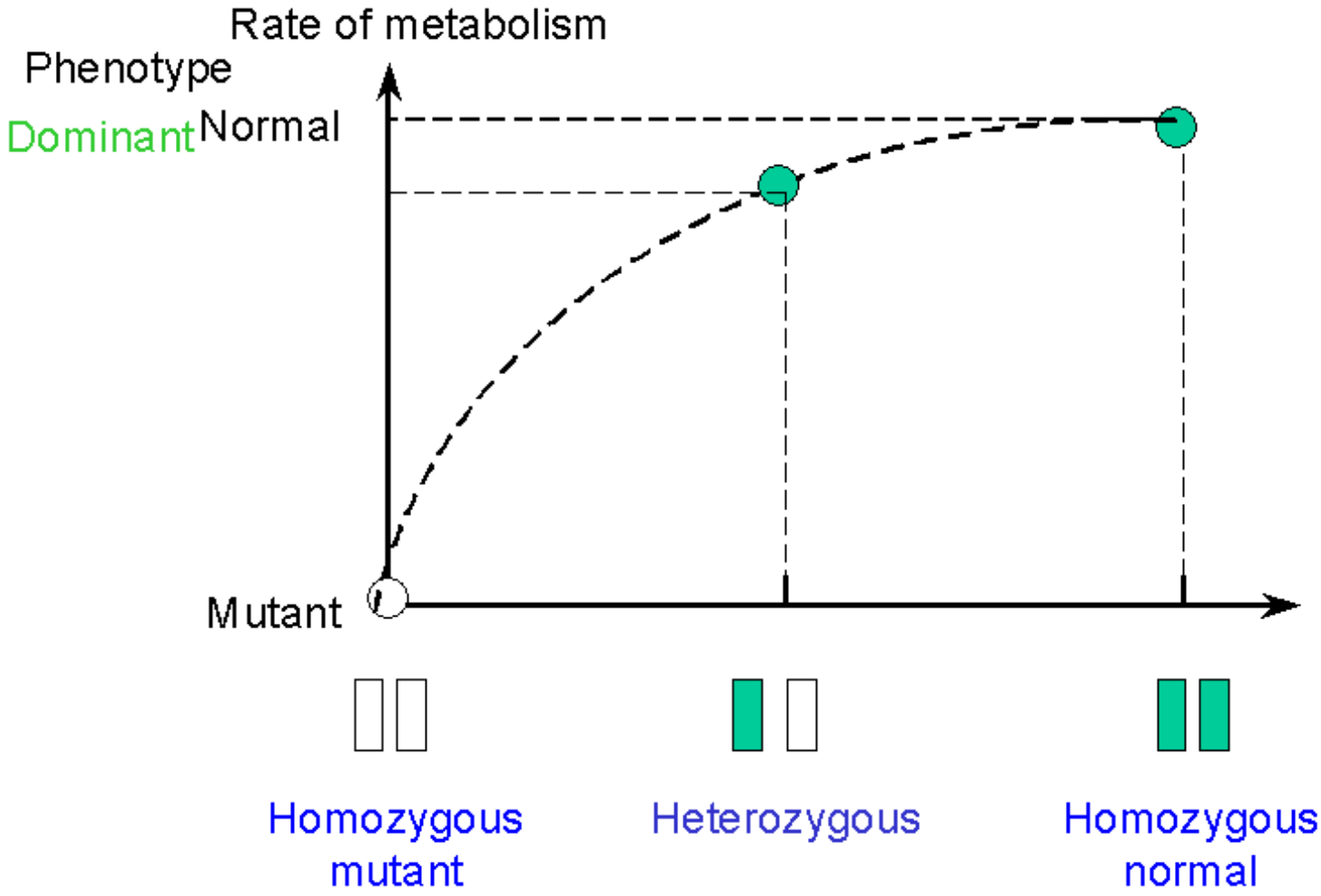

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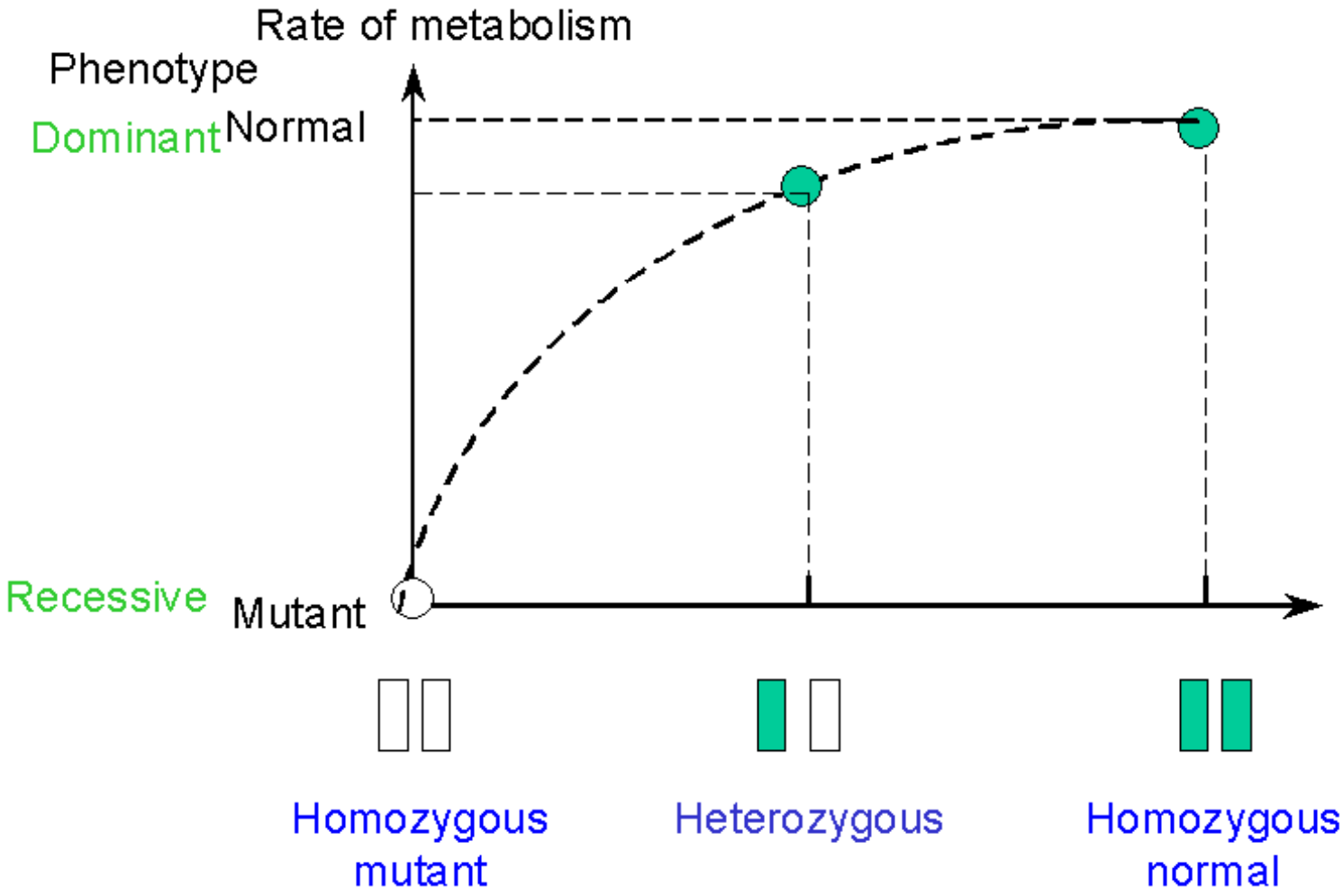

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MCA and genetics — 2

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Typically 95% of loss–of–activity mutations are recessive in terms of functional phenotype, implying that the majority of enzymes have small flux control coefficients.

Conversely, rat liver hexokinase IV (glucokinase) has a flux control coefficient of ≈ 1 on liver glycogen synthesis. In humans, MODY–2 diabetes is linked to a mutation in this enzyme and shows co–dominance (i.e. heterozygotes show an intermediate phenotype).

Hexokinase IV over–expression

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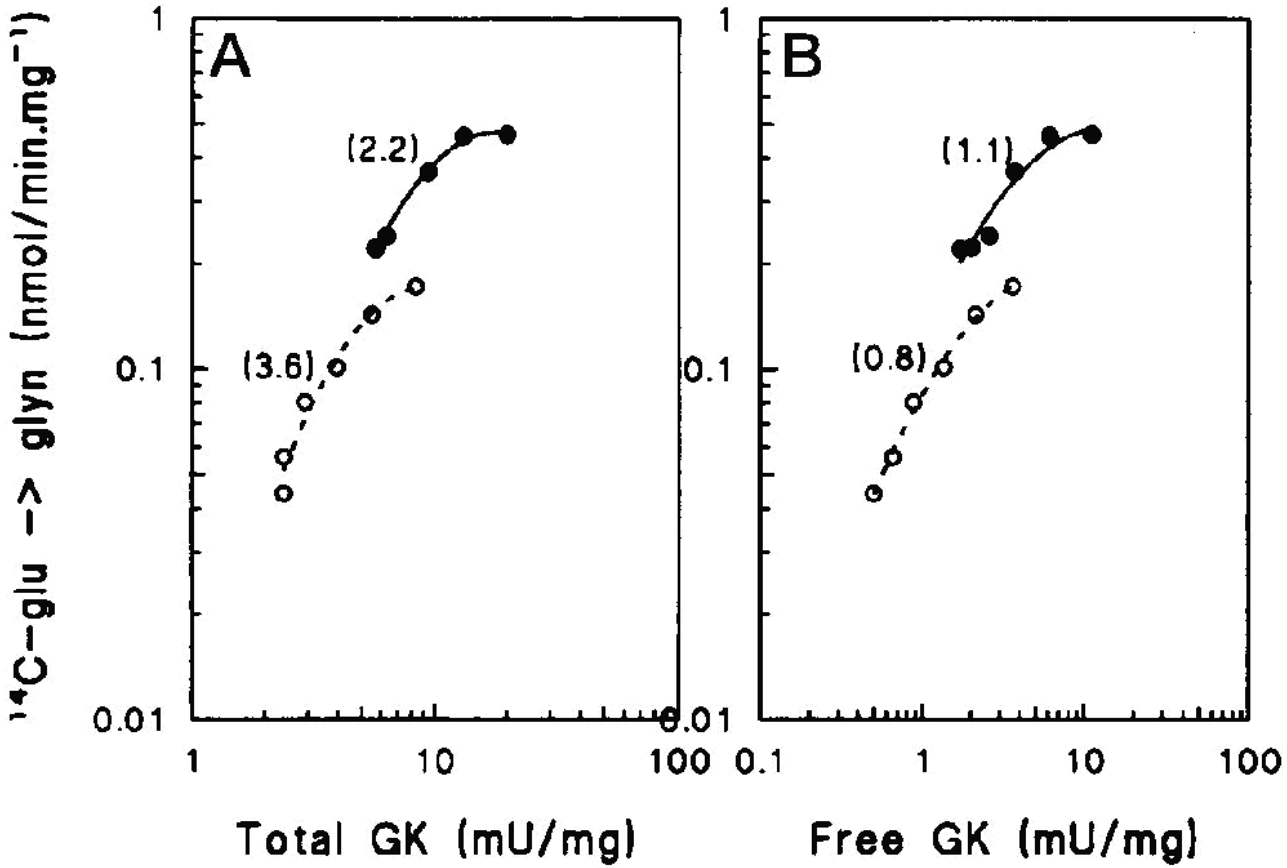

Hexokinase IV was over–expressed in hepatocytes resulting in faster glycogen synthesis from glucose (Agius et al, J. Biol. Chem. 271, 30479–30486, 1996).

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Example: Oxidative Phosphorylation

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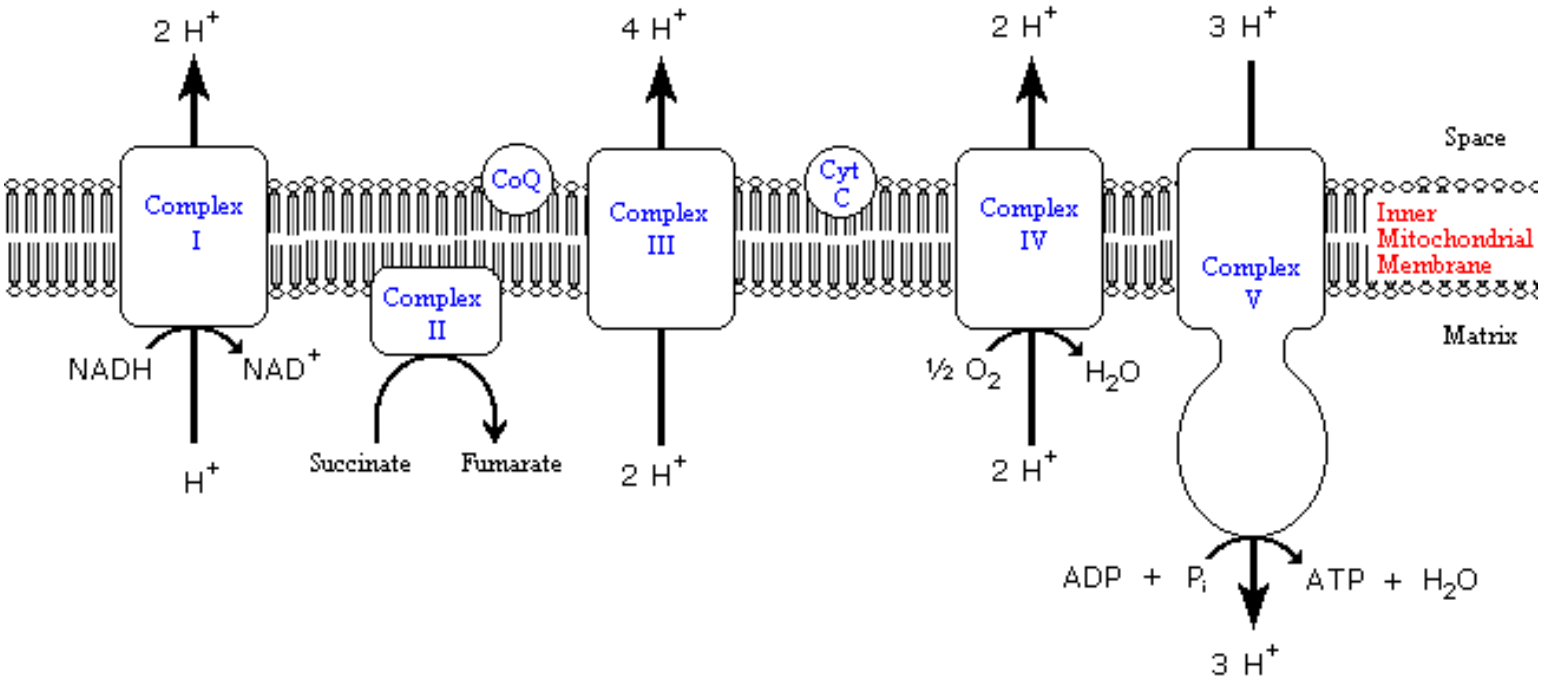

From "Metabolic pathways of Biochemistry":
http://www.gwu.edu/ mpb/index.html

Inhibitor Titration

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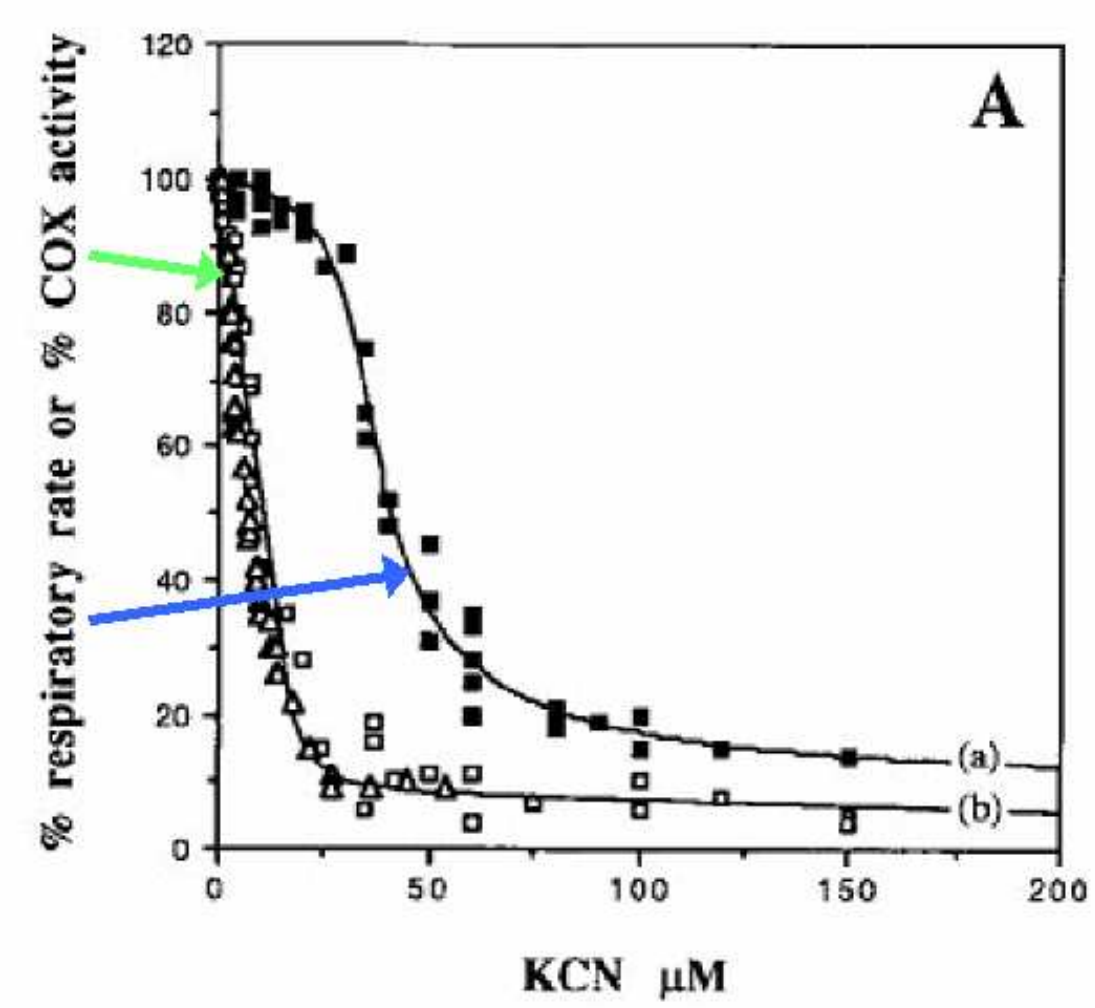

From: Rossignol et al, (1999) J Biol Chem, 274, 33426–33432.

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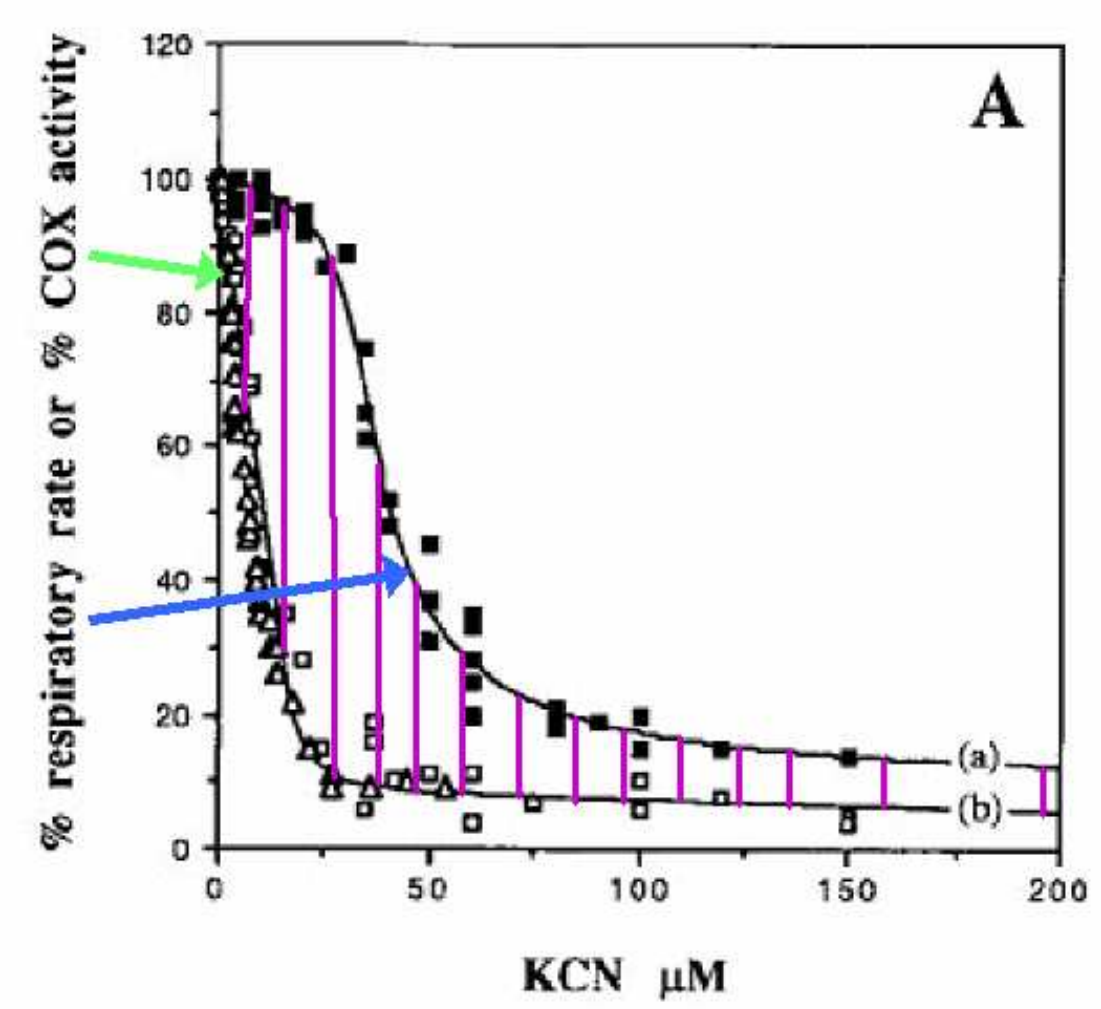

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Flux v. Degree of Inhibition

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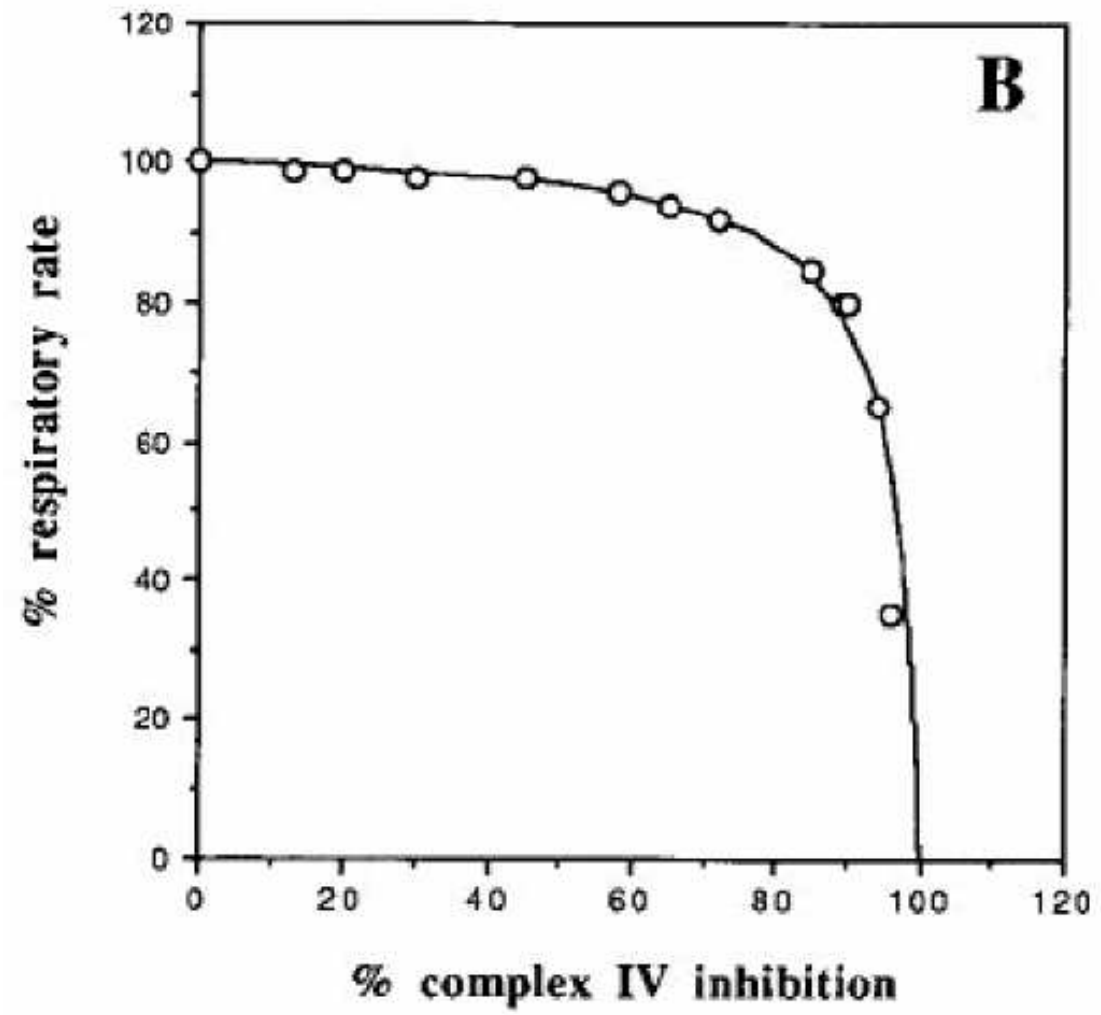

Inhibitor Titrations and Control Coefficients

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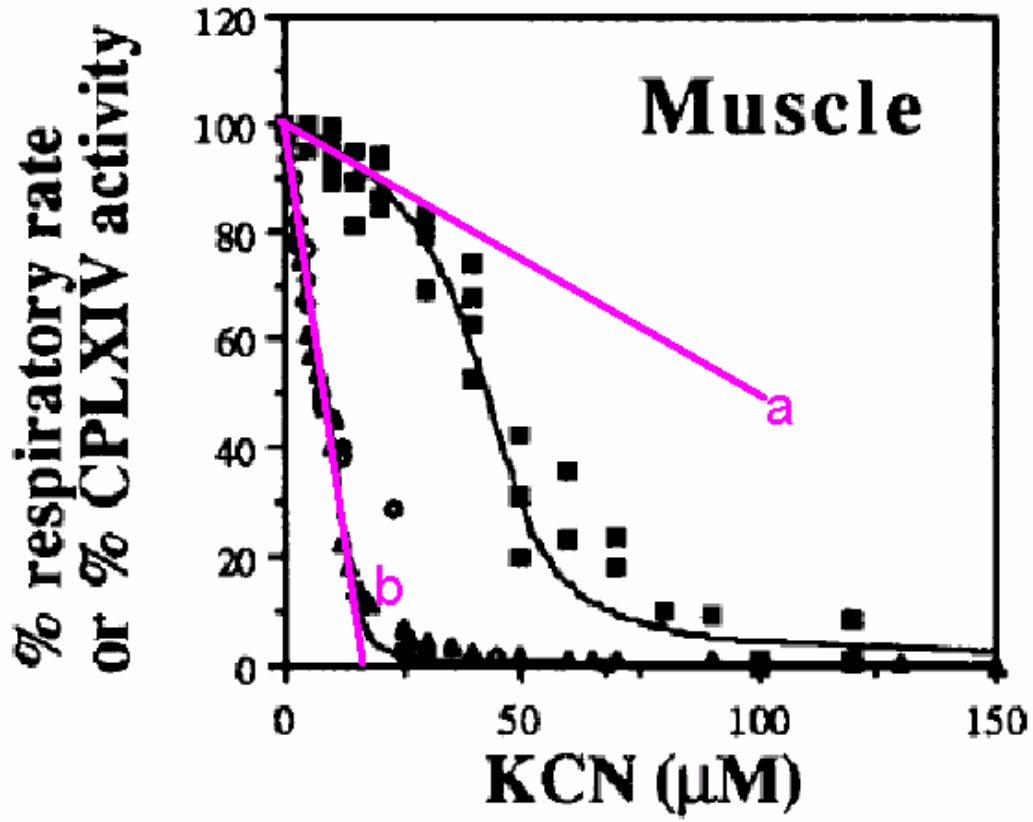

$$C^{J_{resp}}_{CmplxIV} = \frac{\text{slope a}}{\text{slope b}} = 0.2$$

From: Rossignol et al, (2000) Biochem J, 347, 45-53.

MCA and Drug Action

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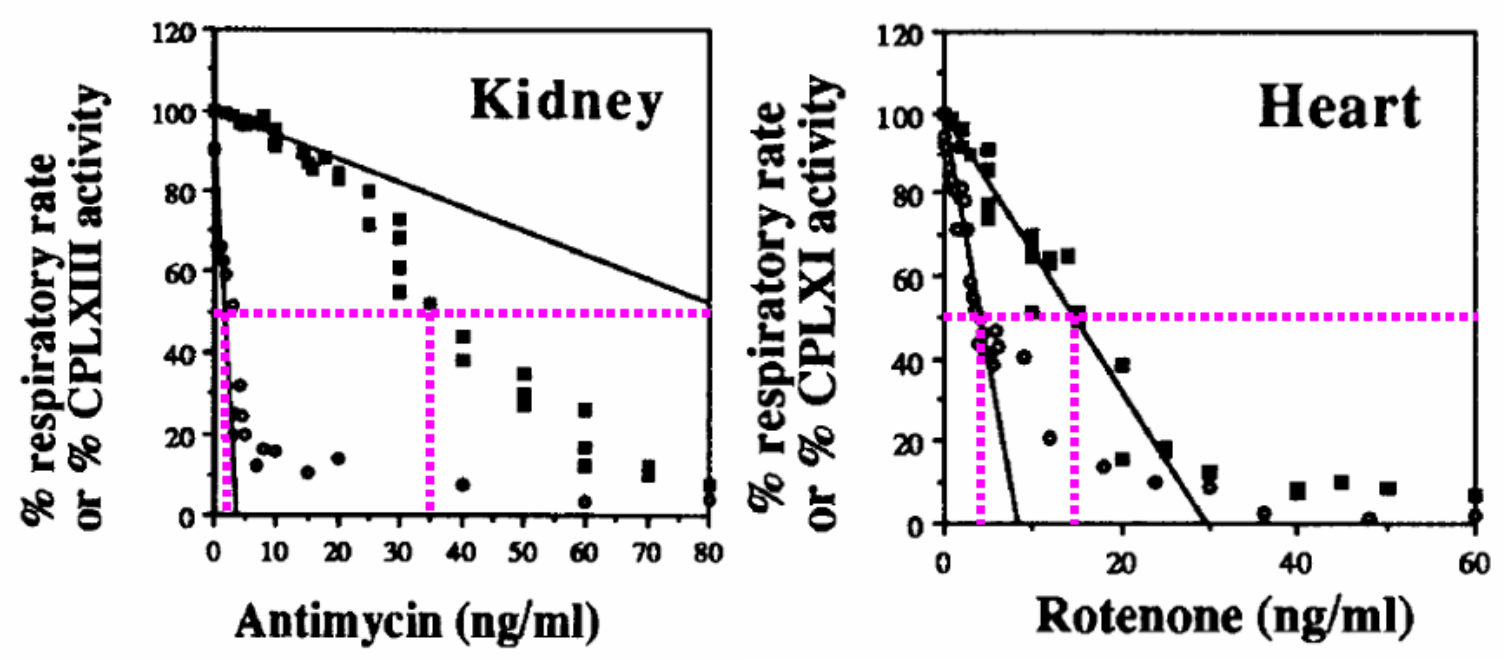

$C^{J_{resp}}_{CmplxIII}$ = 0.02

$C^{J_{resp}}_{CmplxI}$ = 0.26

(Results of Jean-Pierre Mazat's group, Bordeaux.)

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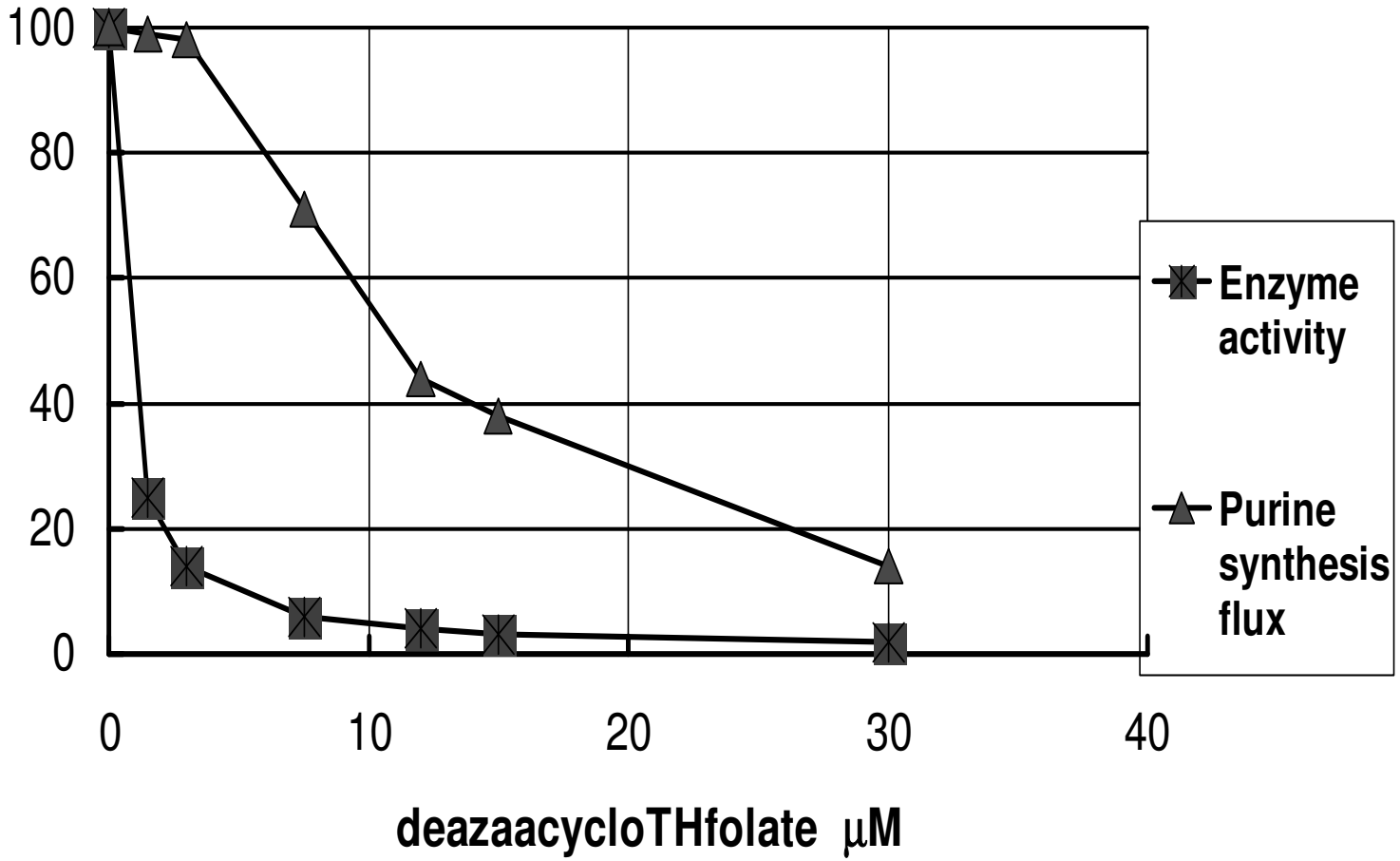
The action of a candidate drug on GAR transformylase in purine synthesis in human leukaemia T cells.



$C_{GART}^{J_{purine}} = 0.01$ (Results of Pogson's group, Wellcome.)

Transketolase as a drug target

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Transketolase, in the pentose phosphate pathway has a requirement for thiamine as a cofactor. Cancer patients are often thiamine–deficient.

But transketolase has a control coefficient on growth of 0.9 in thiamine-depleted cells, so added thiamine drives nucleic acid synthesis and cancer growth.

Restoring normal thiamine levels increases cancer growth up to 164%. However, transketolase is therefore a potential target for cancer therapy .

Begona, C-A et al. Eur. J. Biochem 268 (2001) 4177-4182.

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Summary

(Rankin Small & Henrik Kacser, 1993)

The factor f by which the pathway flux will increase for an r fold increase in the amount of enzyme activity in a linear pathway is:

$$f = \frac{1}{1 - \frac{r-1}{r} C_E^J}$$

where C_E^J is the flux control coefficient of the enzyme E on the pathway flux, J.

Limitations on the flux response

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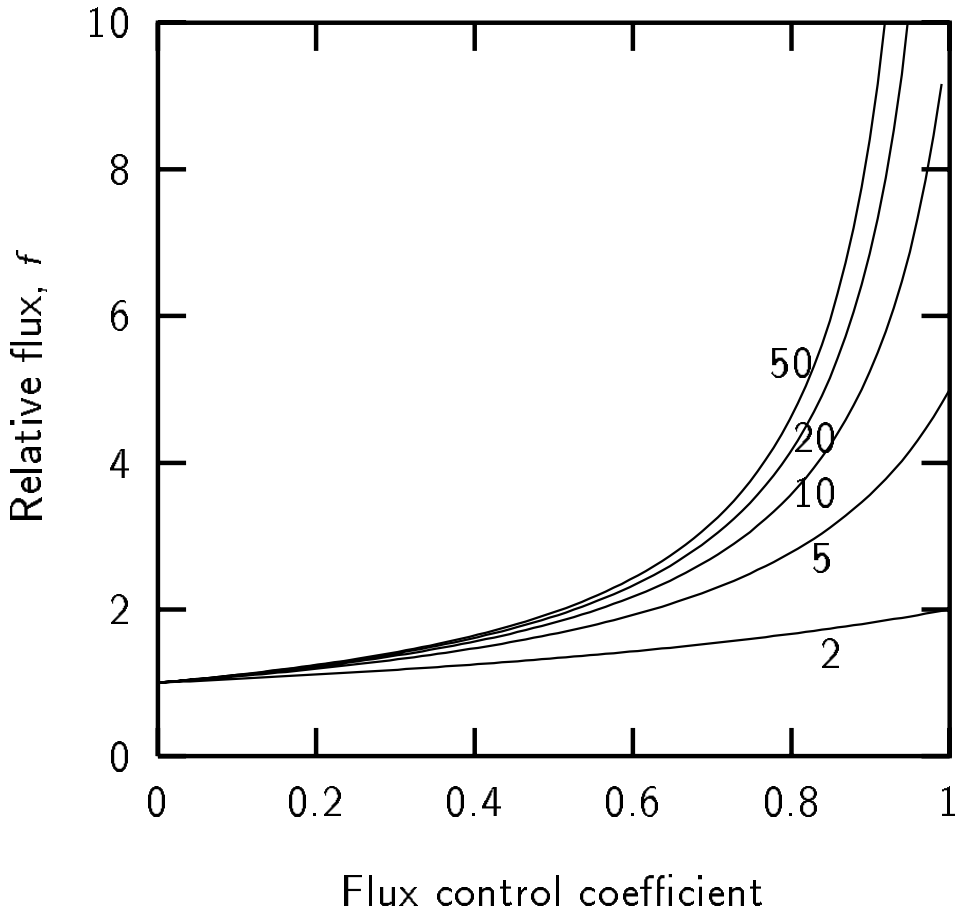

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Yeast Anaerobic Glycolysis

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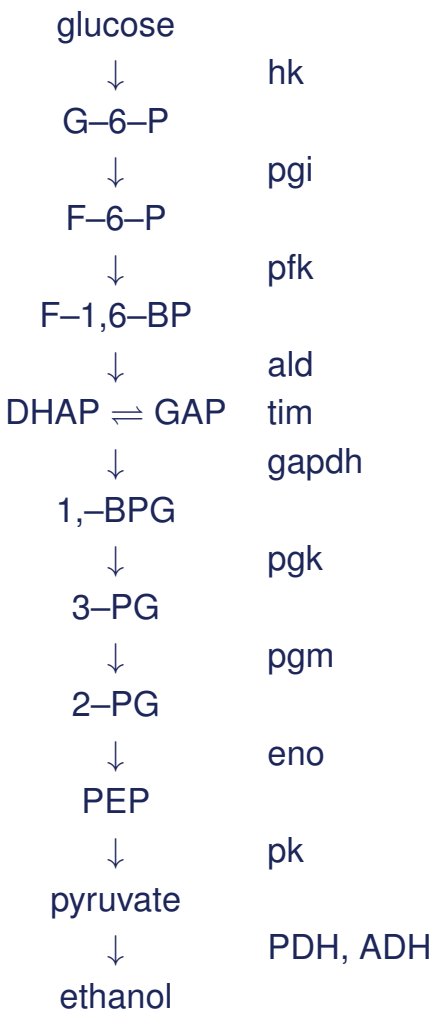

Engineering yeast ethanol production

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Over–production of glycolytic enzymes on multicopy plasmids

Enzyme	(x WT)	EtOH flux (x WT)
HK	13.9	1.07
GPI	11.3	0.91
PFK	3.7	1.02
PGK	7.5	0.97
PGM	12.2	1.07
PK	8.6	1.07
PD	3.7	0.85
ADH	4.8	0.89
PFK + PK	5.6+1.3	1.07
PD + ADH	3.7 + 5.9	0.94

Schaaff et al, *Yeast 5*, 285–290 (1989)

Control at Feedback–Inhibited Enzymes

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The result for PFK suggests that its flux control coefficient is low. In addition, complementation of *pfk-* mutants with a non–allosteric enzyme from *D. discoideum* gave the same growth as wild–type.[1]

No flux change was obtained with 30–fold amplification of the PEP–inhibited enzyme of potato tubers.[2]

This is consistent with predictions from control analysis. Kacser & Burns (1973) showed that feedback would transfer flux control downstream to steps utilising the feedback metabolite.

[1] A. M. Estévez et al, FEBS Lett, 374, 100–104, (1995). [2] M. Burrell et al, *Planta, 194*, 95–101 (1994); S. Thomas et al, *Biochem. J. 322*, 119–127 (1997).

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Potato Tuber Glycolysis from Starch

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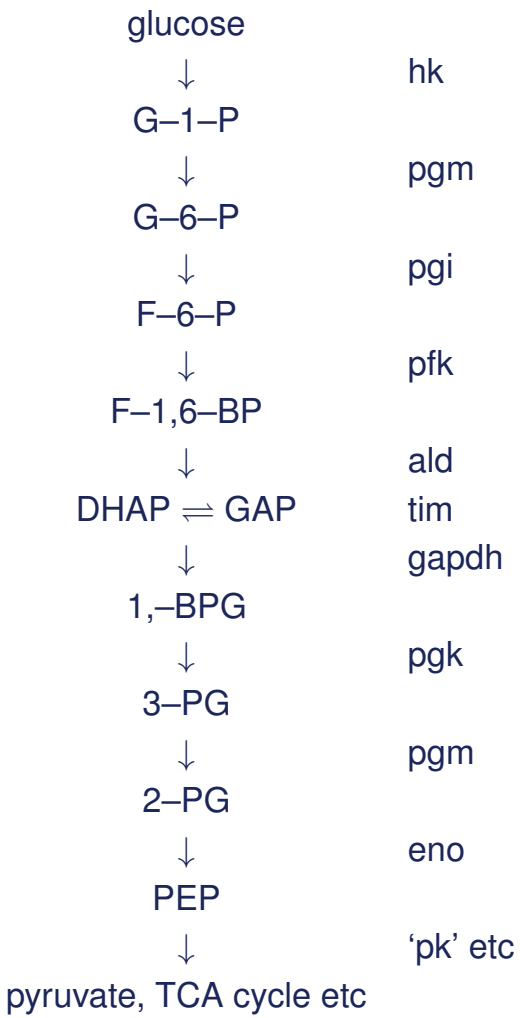

Over–expressing PFK in potato tubers

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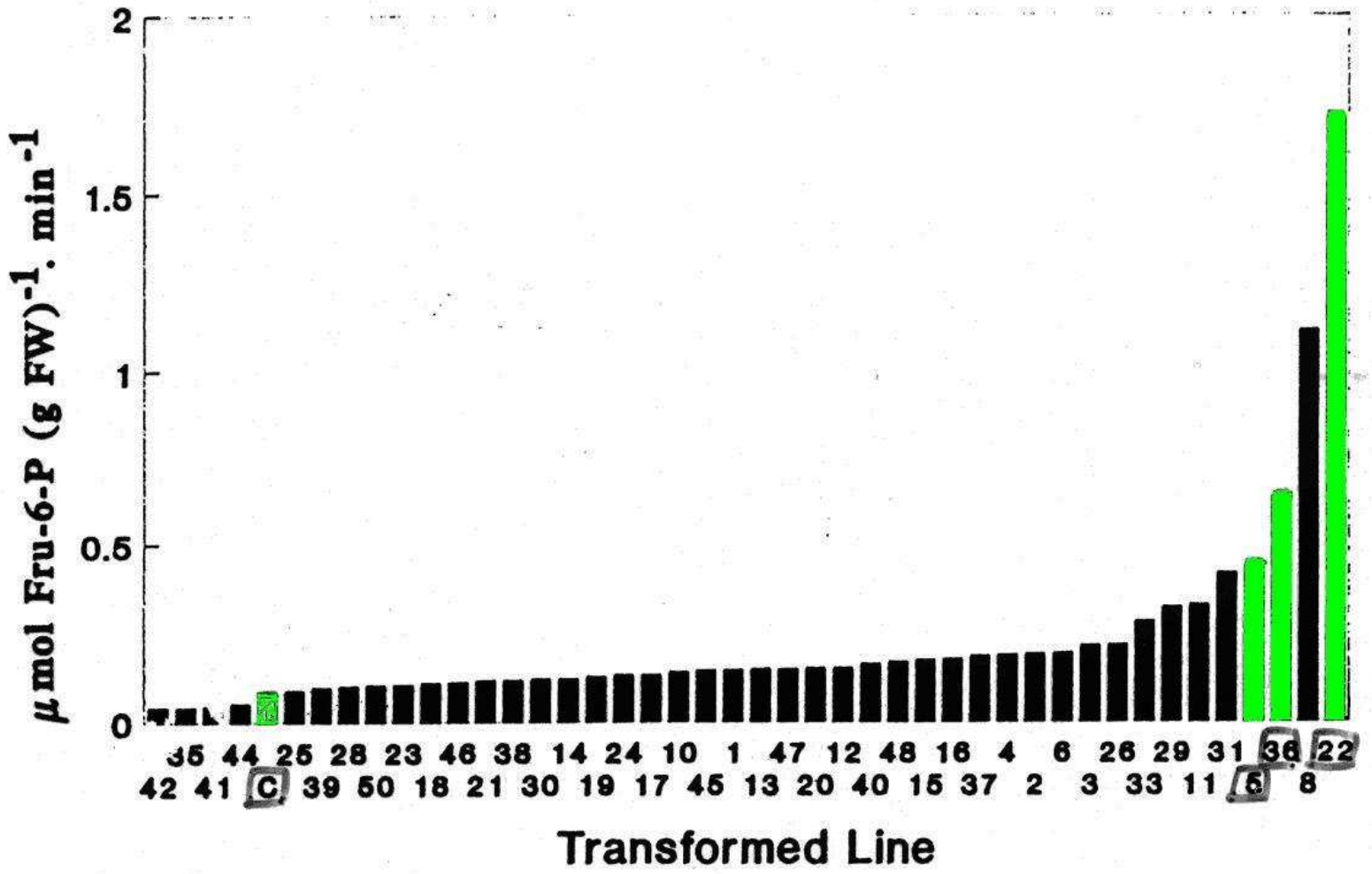

Burrell et al (1994) *Planta, 194,* 95-101.

Metabolite changes in transgenics

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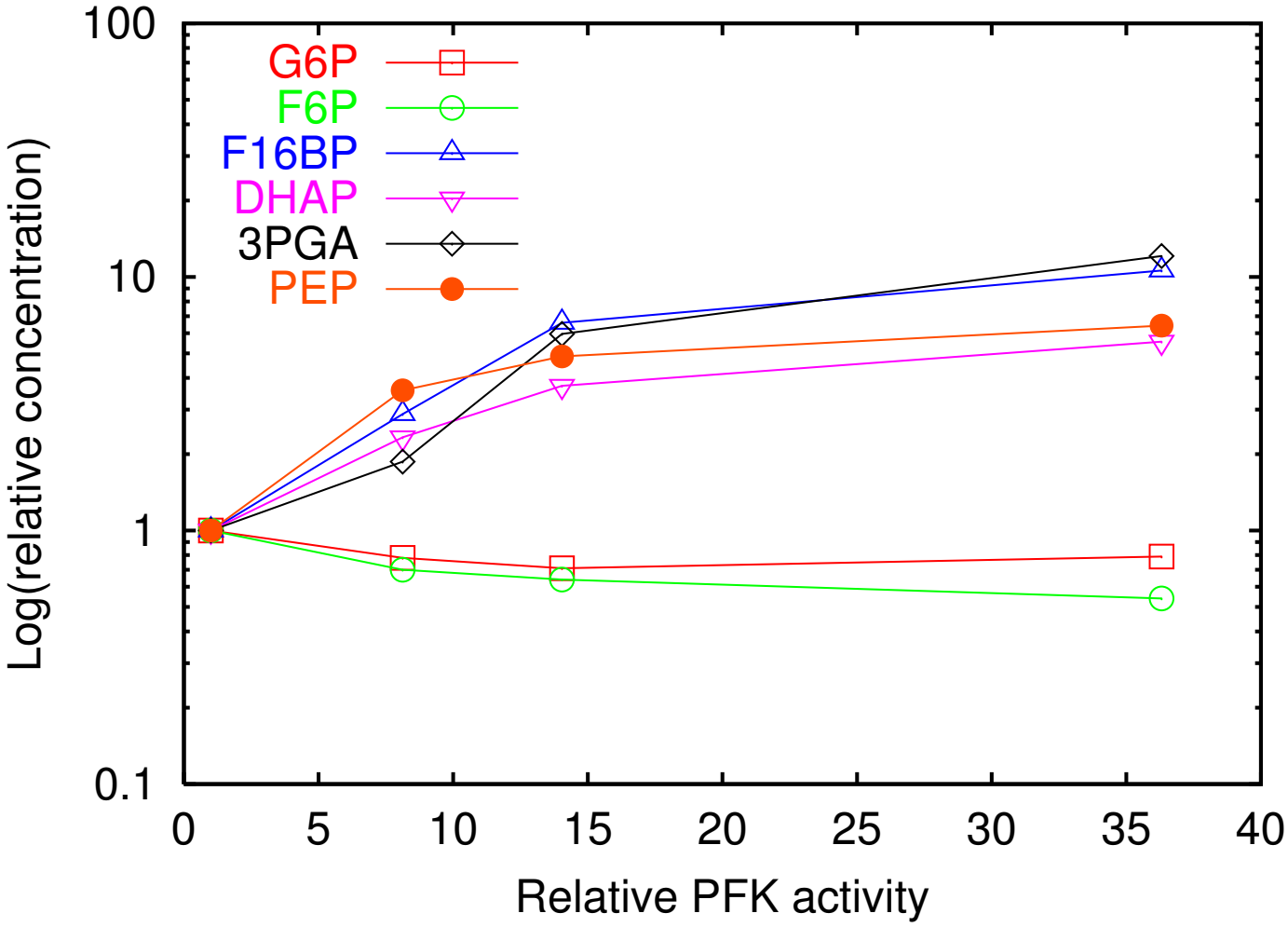

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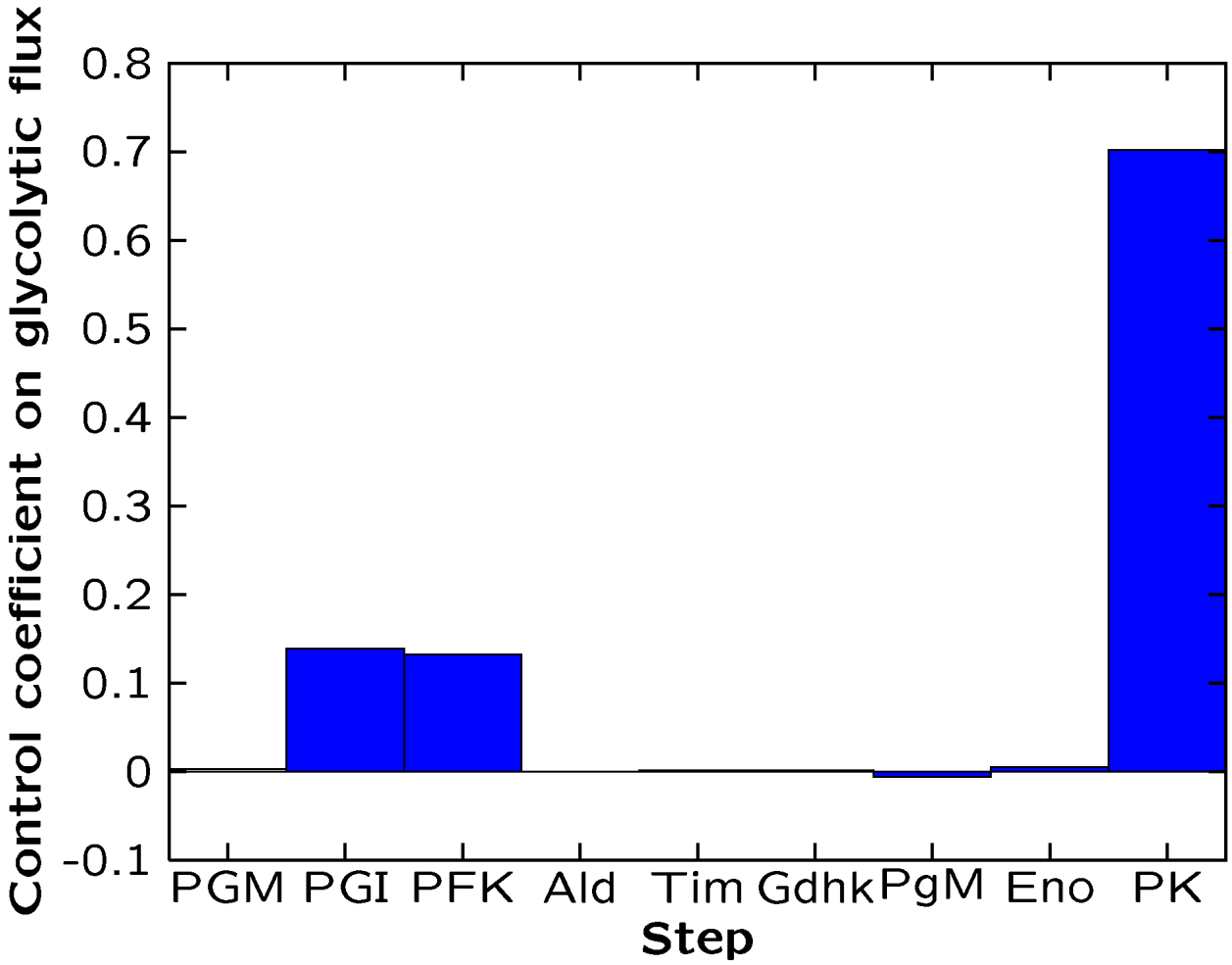

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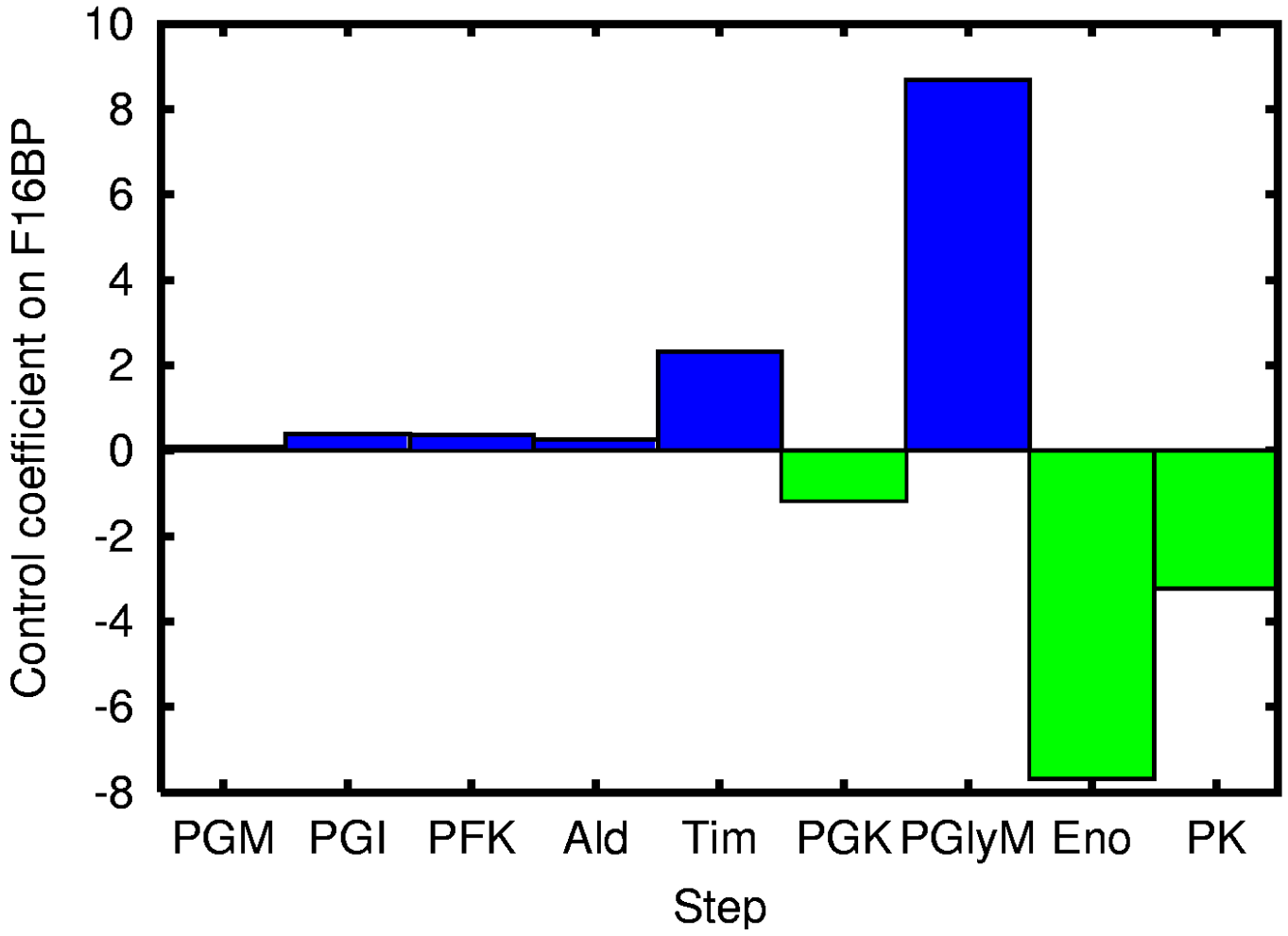

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- The variability of flux control coefficients is central to understanding the effects of mutations and drugs.
- Enzymes experiencing feedback inhibition have low flux control coefficients.
- Metabolite homeostasis is the dominant function of many control mechanisms, including feedback inhibition.
- It's hard to increase metabolic flux by activating/overexpressing a single enzyme.

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