

International Centre for Theoretical Physics

Summer School on Design and Control of Self-Organization in Physical, Chemical, and **Biological Systems**

25 July to 5 August, 2005

Miramare-Trieste, Italy

1668/14

Metabolic Control Analysis (MCA)

Preben G. Sorensen University of Copenhagen, Denmark **International Center for Theoretical Physics 2005**

Metabolic Control Analysis

Preben Graae Sørensen Department of Chemistry University of Copenhagen

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Thermodvnamics" of a metabolic stationarv state
- \bullet "Thermodynamics" of ^a metabolic stationary state

biochemical pathways adjacent to glycolysis

Metabolic chain:

Metabo $3 \times -4 \times -5 \times$. $\ddot{}$

-
- Metabolic chain: $\frac{E}{2}$
The rate limiting step on aguilibrium step The rate limiting step of the metabolic chain must be a
non-equilibrium step
(disequilibrium ratio $\rho = \frac{\Gamma}{K_{eq}} < 1$ where Γ is the actual mass
action ratio of the product concentrations with reactant
concentrations an $\begin{aligned} \Gamma_1 \stackrel{\mathsf{E}_2}{\rightarrow} \mathsf{X}_2 \stackrel{\mathsf{E}_3}{\rightarrow} \mathsf{X}_1 \ \mathsf{A} \mathsf{B} \subset \mathsf{A} \subset \mathsf{A} \end{aligned}$ $\frac{\mathsf{E}_4}{3} \stackrel{\mathsf{E}_4}{\rightleftharpoons} \mathsf{X}_4 \stackrel{\mathsf{E}_4}{\leftarrow}$
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Higher flux by odding motobolites ofter the rate limiting o work faster i.e. having lowest limiting rate value.
- Higher flux by adding metabolites after the rate limiting step.

rate determining step

Non-equilibrium step.

Figure 4.1 Displacement of reactions from equilibrium in glycolysis in working rat heart The measurements were of metabolites in working perfused heart supplied with glucose but no insulin. Both external glucose and endogenous glycogen were being used as fuels. Equilibrium constants were corrected to measured intracellular conditions. Key: Ph, phosphorylase; Pg, phosphoglucomutase; Tr, glucose transport; He, hexokinase; GI, glucose-6-phosphate isomerase; Pf, phosphofructokinase; Pm, phosphoglycerate mutase; En, enolase; Py, pyruvate kinase. Data from Kashiwaya et al.¹²⁵

Figure from Fell. **Figure** from Fell.

rate determining step

Enzyme capacity.

Figure 4.4 Relative enzyme activities in glycolysis in working rat heart

The limiting rates (V) were all measured at pH 7.2 in the presence of 150 mM K⁺ and 5 mM Mg²⁺. They are given relative to the glycolytic flux, f_{ely} , measured for working rat hearts using glucose as a fuel. Key: Ph, phosphorylase; Pg, phosphoglucomutase; He, hexokinase; Gl, glucose-6-P isomerase; Pf, phosphofructokinase; AI, aldolase; Tr, triose phosphate isomerase; Ga, glyceraldehyde-3-phosphate dehydrogenase; Pg, phosphoglycerate kinase; Pu, phosphoglycerate mutase; En, enolase; Py, pyruvate kinase; La, lactate dehydrogenase. Data from Kashiwaya et al.¹²⁵ Figure from Fell.

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$$
X_0 \stackrel{\text{xase}}{\rightarrow} S_1 \rightarrow \dots Y \stackrel{\text{ydh}}{\rightarrow} S_6 \dots \rightarrow X_1
$$

determines the flux at reaction step ydh for a

 $\frac{1}{6}$ S₆
ction What determines the flux at reaction step ydh for a pathway
at a stationary state $[\mathcal{S}]_{ss}$? at a stationary state [S] $_{ss}$?

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determines the flux at reaction step ydh for a

- $\frac{1}{2}$ S₆
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at a stationary state $[S]_{ss}$?
Elux control coofficient and σ ^{Jydh ∂J_{ydh} [E_{xase}]} at a stationary state [S] $_{ss}$?
- Flux control coefficient C
 E_{xase} is the activity (concentration) of : - л. [F] $\mathsf{E} = \mathsf{I}$ l.

 λ_{xase} is the activity (concentration) of xase

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- The flux control coefficient is a network property

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- <u>Lha tluy control coatticiant is a natworl</u>
- summation is over all reactions in the cell. The flux control coefficient is a network property
Summation theorem for particular flux $\sum_{i=1}^{m} C_i^J =$ Summation theorem for particular flux $\sum_{i=1}^{m} C_i^J = 1$
summation is over all reactions in the cell.

What determines the dependence of rate on substrate?

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Elasticity coefficient $\epsilon_S^{xase} = \frac{\partial v_{xase}}{\partial [S]} \frac{[S]}{v_{xase}}$ Elasticity coefficient $\epsilon_{\mathsf{S}}^{\mathsf{x} \mathsf{a} \mathsf{s} \mathsf{e}} = \frac{\partial \mathsf{v}_{\mathsf{x} \mathsf{a}}}{\partial \mathsf{S}}$ ---. . . *I*...
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Elasticity coefficient $\epsilon_S^{xase} = \frac{\partial v_{xase}}{\partial [S]} \frac{[S]}{v_{xase}}$ $\begin{bmatrix} \mathsf{S} \mathsf{I} & \mathsf{V} \end{bmatrix}$. . .
- Elasticity coefficient $\epsilon_{\mathsf{S}}^{\mathsf{x} \mathsf{a} \mathsf{s} \mathsf{e}} = \frac{\partial \mathsf{v}_{\mathsf{x} \mathsf{a}}}{\partial |\mathsf{S}|}$
The elasticity is a property of a sir
For a Michaelis Menten enzyme The elasticity is a property of a single enzyme.
For a Michaelis Menten enzyme
 $v_{\text{Xase}} = \frac{V[S]}{K_m + [S]}$ giving $\epsilon_S^{xase} = \frac{K_m}{K_m + [S]}$ For a Michaelis Menten enzyme

$$
v_{\text{X} \text{A} \text{S} \text{B}} = \frac{V[S]}{K_m + [S]} \text{ giving } \epsilon_S^{x \text{A} \text{S} \text{B}} = \frac{K_m}{K_m + [S]}
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$$

e S $\sum_{i=1}^{m} C_i^J \epsilon_S^i = 0$
ion is over all enzymes. xase = $\frac{1}{K_m + [S]}$ giving $\epsilon_S^{\text{max}} = \frac{1}{K_m}$.
Connectivity theorem for a position summation is over all enzymes. Connectivity theorem for a particular flux J and a particular
substrate S $\sum_{i=1}^{m} C_i^J \epsilon_S^i = 0$
summation is over all enzymes. substrate S

 \bullet Reversible metabolic chain: $\frac{v_2}{1} \stackrel{V_2}{\rightleftharpoons} X_2 \stackrel{V_3}{\rightleftharpoons} X_3 \cdots X_{n-1}$ n. **Contract Contract** -

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Reversible metabolic chain: $S \stackrel{v_1}{\rightleftharpoons}$
At steady state $v_j = J$ allowing the sh At steady state $v_j = J$ allowing the short notation $C_j^J \equiv C_{\vec{E}}^J$ \overline{a}

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If E_j is only affer
C_j e_j + C_{j+1}e_j⁺¹ If E_j is only affected by X_{j-1} and X_j the connectivity theorem gives $C_j^J \epsilon_j^j + C_{j+1}^J \epsilon_j^{j+1} = 0$ $C_j^J \epsilon_j^j + C_{j+1}^J \epsilon_j^{j+1} = 0$

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From this we have $C_i^J = C_{n+1}^J \prod_{i=1}^n (-\frac{\epsilon_i^{j+1}}{N}$ $C_i^{\{1\}}\epsilon_i^{\{1\}}+C_{i+1}^{\{1\}}\epsilon_i^{\{1\}\}}=0$
- $C_j^J \epsilon_j^j + C_{j+1}^J \epsilon_j^{j+1} = 0$
From this we have C From this we have $C_j^J = C_{n+1}^J \prod_{j=1}^J$ $\int_{i=i}^{n}(-\frac{\epsilon_{i}}{i})$ į $\begin{pmatrix} -1 \ 1 \end{pmatrix}$

and the con-

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C_j^J = C_{n+1}^J \prod_{i=j}^n \left(-\frac{\epsilon_i^{i+1}}{\epsilon_i^i} \right)
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\n• and using $\sum C_j^J = 1$ we get $C_j^J = \frac{\prod_{i=j}^n \left(-\frac{\epsilon_i^{i+1}}{\epsilon_i^j} \right)}{1 + \sum_{i=1}^n \prod_{i=i}^n \left(-\frac{\epsilon_i^{i+1}}{\epsilon_i^j} \right)}$

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\n- In case $\epsilon_j^j < 0$ (product inhib.) and $\epsilon_j^{j+1} > 0$ (substrate)
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 - $\ddot{}$ $\frac{1}{1}$
ate In case $\epsilon_j^j < 0$ (product inhib.) and $\epsilon_j^{j+1} > 0$ (substrate activ.) we have $C_j^J > 0$

- $\frac{v_2}{1} \stackrel{V_2}{\rightleftharpoons} X_2 \stackrel{V_3}{\rightleftharpoons} X_3 \cdots X_{n-1}$ n. **Contract Contract** -
- Reversible metabolic chain: $S \stackrel{v_1}{\rightleftharpoons}$
At steady state $v_j = J$ allowing the shiff E; is only affected by X_{i-1} and X_i th \overline{a}
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From this we have $C_i^J = C_{n+1}^J \prod_{i=1}^n (-\frac{\epsilon_i^{j+1}}{N}$

$$
C_j^J \epsilon_j^j + C_{j+1}^J \epsilon_j^{j+1} = 0
$$
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C_j^J = C_{n+1}^J \prod_{i=j}^n \left(-\frac{\epsilon_i^{i+1}}{\epsilon_i^i} \right)
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\n- and using $\sum C_j^J = 1$ we get $C_j^J = \frac{\prod_{i=j}^n \left(-\frac{\epsilon_i^{j+1}}{\epsilon_i^j} \right)}{1 + \sum_{i=1}^n \prod_{j=i}^n \left(-\frac{\epsilon_j^{j+1}}{\epsilon_j^j} \right)}$
\n- In case $\epsilon_j^j < 0$ (product inhib.) and $\epsilon_j^{j+1} > 0$ (substrate)
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- - $\ddot{}$ ┌)
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con: In case $\epsilon_j^j < 0$ (product inhib.) and $\epsilon_j^{j+1} > 0$ (substrate activ.) we have C_j > 0
if ϵ_j^{j+1} small (saturation) then C_{j+1} large and E_{j+1} controls flux.
- $U \sqsubset i+1$ In case $\epsilon_j^j < 0$ (product inhib.) and $\epsilon_j^{j+1} > 0$
if ϵ_j^{j+1} small (saturation) then C_{j+1}^j large and if ϵ_j^{j+1} small (saturation) then C_{j+1}^J large and E_{j+1} controls flux.

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- -In case $\epsilon_j^j < 0$ (product inhib.) and $\epsilon_j^{j+1} > 0$ (substrate activ.) we have C_j¹ > 0
if ϵ_j^{j+1} small (saturation) then C_{j¹+1} large and E_{j1+1} controls flux.
if $|\epsilon_j^j|$ small (irreversible reaction) then $\ddot{}$ ┌)
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if $|\epsilon_j^j|$ small (irreversible reaction)
- C_{j+1}^J large and E_{j+1} controls flux.

(i) then C_j^J large and E_j controls flux. if $|e_j^j|$ small (irreversible reaction) then C_j^J large and E_j controls flux.
 $\frac{1}{2}$

$$
\bullet \qquad S \stackrel{v_1}{\rightarrow} X_1 \stackrel{v_2}{\rightarrow} X_2 \stackrel{v_3}{\rightarrow} X_3 \cdots X_{n-1} \stackrel{v_n}{\rightarrow} X_n \stackrel{v_{n+1}}{\rightarrow} P
$$

$$
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$$

<u>ር</u> At steady state $v_j = J$ allowing the short notation C_j^J $\frac{1}{\cdot}$ \equiv \mathcal{A} \overline{a}

$$
\bullet \qquad S \stackrel{v_1}{\rightarrow} X_1 \stackrel{v_2}{\rightarrow} X_2 \stackrel{v_3}{\rightarrow} X_3 \cdots X_{n-1} \stackrel{v_n}{\rightarrow} X_n \stackrel{v_{n+1}}{\rightarrow} P
$$

- <u>ር</u> \overline{a} \overline{a}
- At steady state $v_j = J$ allowing the short notation C_j^J
E_j is not affected by X_j such that $\epsilon_j^j = 0$ The connect $\vec{j} \equiv$ ctivi \subseteq E_i is not affected by X_i such that $\epsilon_1^j=0$ The connectivity E_j is not affected by X_j such that $\epsilon_j^j = 0$
theorem gives $C_{j+1}^J \epsilon_j^{j+1} = 0$ such that C |
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| theorem gives $C_{j+1}^{J}e_{j}^{j+1} = 0$ such that $C_{j+1}^{J} = 0$.

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\bullet \qquad S \stackrel{v_1}{\rightarrow} X_1 \stackrel{v_2}{\rightarrow} X_2 \stackrel{v_3}{\rightarrow} X_3 \cdots X_{n-1} \stackrel{v_n}{\rightarrow} X_n \stackrel{v_{n+1}}{\rightarrow} P
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The summation theorem gives $C_1^J = 1$
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The summation theorem gives $C_{1}^{J} = 1$ such that by E₁. $\int_{j+1}^{j} = 0$
such the The summation theorem gives $C_1^J = 1$ such that all control is by E₁. by E_1 .

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\xrightarrow{v_1} X_1 \xrightarrow{v_2} X_2 \xrightarrow{v_3} X_3 \cdots X_{n-1} \xrightarrow{v_n} X_n \xrightarrow{v_{n+1}} P
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- connectivity theorem gives $C_{j+1}^{J} \epsilon_{j}^{j+1} = 0$ such that $C_{j+1}^{J} = 0$.
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The connectivity theorem gives $C_{1}^{J} \epsilon_{n}^{1} + C_{n+1}^{J} \epsilon_{n}^{n+1} = 0$ and th $\sum_{j+1}^{J}=0$
D and th $n \leq 0$
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We get $C_1^J = \frac{\epsilon_n^{n+1}}{\epsilon_n^{n+1} - \epsilon_n^1}$ and $C_{n+1}^J = -\frac{\epsilon_n^1}{\epsilon_n^{n+1} - \epsilon_n^1}$

summation theorem gives
$$
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\n• We get $C_1^J = \frac{\epsilon_n^{n+1}}{\epsilon_n^{n+1} - \epsilon_n^1}$ and $C_{n+1}^J = -\frac{\epsilon_n^1}{\epsilon_n^{n+1} - \epsilon_n^1}$

Experimental determination of flux control coefficients by
manipulation of enzyme activity. manipulation of enzyme activity.

- Experimental determination of flux control coefficients by
manipulation of enzyme activity.
4: Alteration of sono expression manipulation of enzyme activity.
- 1: Alteration of gene expression
mutant heterozygotes,gene c
2: Alteration of activity by enviro mutant heterozygotes,gene dosage,antisense RNA
	- 2: Alteration of activity by environmental means
	- 3: Titration with enzymes

rat liver homogenates C_{HK} =0.79, C_{GPI} =0.0, C_{PFK} =0.21

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- \bullet Control coefficients from elasticities

alteration of gene expression

Figure 6.2 Dependence of arginine synthesis flux in Neurospora on enzyme levels

The results are those of Flint et al.⁷⁴ with my best-fit hyperbolic curves. Most of the points were obtained by forming heterokaryons with different ratios of wild-type and mutant nuclei. In each graph, however, the point at the lowest enzyme activity is not a heterokaryon, but a partial revertant from the mutant. (a) The dependence of the flux to arginine through argininosuccinate lyase on the activity of ornithine carbamoyltransferase, both expressed as a % of wild-type levels. (b) The dependence of the same flux on the activity of argininosuccinate lyase itself.

Figure from Fell.

alteration by titration with enzymes

Figure 6.8 Dependence of glycolytic flux in a rat liver homogenate on added enzymes The enzymes added were hexokinase (\square) and phosphofructokinase (\triangle). The results are those of Torres et al.²⁴⁸ with computed best-fit rectangular hyperbolas. The leftmost point on each curve represents the original activity in the homogenate. The phosphofructokinase activity has been multiplied by a factor of 10 for display purposes. Titration with glucose-6-phosphate isomerase gave no change in flux.

Figure from Fell.

. . . $v_e = f(2PG, PEP) = J$
Aeasure from three different experiments

 \bullet Measure from three different experiments
 $\Delta J_1 = J_1 - J_c$, $\Delta 2PG_1 = 2PG_1 - 2PG_c$, Δ
 $\Delta J_2 = J_2 - J_c$, $\Delta 2PG_2 = 2PG_2 - 2PG_c$, Δ $J_1 = J_1 - J_c$, $\Delta 2PG_1 = 2PG_1 - 2PG_c$, $\Delta PEP_1 = PEP_1 - PE$. $J_2 = J_2 - J_c$, $\Delta 2PG_2 = 2PG_2 - 2PG_c$, $\Delta PEP_2 = PEP_2 - PE$

. . . $v \rightarrow 2PG \stackrel{\text{enolase}}{\rightarrow} PEP \rightarrow ...$ $e = f(2PG, PEP) = J$

Measure from three different experiments
 $\Delta J_1 = J_1 - J_c$, $\Delta 2PG_1 = 2PG_1 - 2PG_c$, Δ
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By differentiation of J_1 , J_2 and J_3 from three diffe $J_1 = J_1 - J_c$, $\Delta 2PG_1 = 2PG_1 - 2PG_c$, $\Delta PEP_1 = PEP_1 - PE$. $J_2 = J_2 - J_c$, $\Delta 2PG_2 = 2PG_2 - 2PG_c$, $\Delta PEP_2 = PEP_2 - PE$

 $\Delta 2PG_2 = 2PG_2 - 2PG_c, ~~\Delta$

of J_1, J_2 and J_c from three diffe
 $2PG_1 + \frac{\partial v_e}{\partial r} \wedge PEP_1 \wedge J_2 \approx 0$ By differentiation of J_1 , J_2 and J_c from three different experiments we have $\Delta J_1 \approx \frac{\partial v_e}{\partial 2PG} \Delta 2PG_1 + \frac{\partial v_e}{\partial PEP} \Delta PEP_1$, $\Delta J_2 \approx \frac{\partial v_e}{\partial 2PG} \Delta 2PG_2 + \frac{\partial v_e}{\partial PEP} \Delta$ \overline{I} at ∂ $\frac{\partial v_e}{\partial r} \wedge 2PG_1 + \frac{\partial}{\partial r}$ $\frac{\partial v_e}{\partial E E} \Delta P E P_1$, $\Delta J_2 \approx \frac{\partial}{\partial \Omega}$ $\frac{\partial v_e}{\partial r} \wedge 2PG_2 + \frac{\partial}{\partial r}$ $\frac{ove}{-} \wedge PF$

. . . $v \rightarrow 2PG \stackrel{\text{enolase}}{\rightarrow} PEP \rightarrow ...$ $e = f(2PG, PEP) = J$

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Scaling these equation by division \overline{I} at ∂ $\frac{\partial v_e}{\partial r} \wedge 2PG_1 + \frac{\partial}{\partial r}$ $\frac{\partial v_e}{\partial E E} \Delta P E P_1$, $\Delta J_2 \approx \frac{\partial}{\partial \Omega}$ $\frac{\partial v_e}{\partial r} \wedge 2PG_2 + \frac{\partial}{\partial r}$ $\frac{ove}{-} \wedge PF$
- Scaling these equation by division with J_c gives $\frac{\Delta J_1}{J_c} \approx \epsilon_{2PG}^e \frac{\Delta 2PG_1}{2PG_c} + \epsilon_{PEP}^e \frac{\Delta PEP_1}{PEP_c}$ and $\frac{\Delta J_2}{J_c}$ \mathbf{r} \boldsymbol{I} $\frac{\Delta^2 P}{\Delta^2 P G} = \frac{\Delta^2 P G_1}{2P G_c} + \epsilon_{PEP}^e \frac{\Delta P E P_1}{P E P_c}$ and $\frac{\Delta J_2}{J_c} \approx \epsilon_{2PG}^e \frac{\Delta 2 P G_2}{2P G_c} + \epsilon_{PEP}^e \frac{\Delta P E P_2}{P E P_c}$

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By differentiation of J_1 , J_2 and J_3 from three diffe $J_1 = J_1 - J_c$, $\Delta 2PG_1 = 2PG_1 - 2PG_c$, $\Delta PEP_1 = PEP_1 - PE$. $J_2 = J_2 - J_c$, $\Delta 2PG_2 = 2PG_2 - 2PG_c$, $\Delta PEP_2 = PEP_2 - PE$

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of J_1, J_2 and J_c from three diffe
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 $\Delta J_1 \approx \frac{\partial v_e}{\partial 2PG} \Delta 2PG_1 + \frac{\partial v_e}{\partial PEP} \Delta PEP_1$, $\Delta J_2 \approx \frac{\partial v_e}{\partial 2PG_2} \Delta 2PG_2 + \frac{\partial v_e}{\partial PEP_1} \Delta$

Scaling these equation by division \overline{I} at ∂ $\frac{\partial v_e}{\partial r} \wedge 2PG_1 + \frac{\partial}{\partial r}$ $\frac{\partial v_e}{\partial E E} \Delta P E P_1$, $\Delta J_2 \approx \frac{\partial}{\partial \Omega}$ $\frac{\partial v_e}{\partial r} \wedge 2PG_2 + \frac{\partial}{\partial r}$ $\frac{ove}{-} \wedge PF$
- Scaling these equation by division with J_c gives
 $\frac{\Delta J_1}{J_c} \approx \epsilon_{2PG}^e \frac{\Delta 2PG_1}{2PG_c} + \epsilon_{PEP}^e \frac{\Delta PEP_1}{PEP_c}$ and $\frac{\Delta J_2}{J_c}$

These equation can now be solved for the two e \mathbf{r} \boldsymbol{I} $\frac{1}{2} \approx \epsilon_{2PG}^e \frac{\Delta 2I}{2PG_c} + \epsilon_{PEP}^e$
ese equation can now be s $\frac{\Delta 2PG_1}{2PG_c} + \epsilon_{PEP}^e \frac{\Delta PEP_1}{PEP_c}$ and $\frac{\Delta J_2}{J_c} \approx \epsilon_{2PG}^e \frac{\Delta 2PG_2}{2PG_c} + \epsilon_{PEP}^e \frac{\Delta PEP_2}{PEP_c}$
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- These equation can now be solved for the two elasticities ϵ^e_{2PG} and ϵ^e_{PEP}

- $\frac{1}{\sqrt{t}} = \sum_{r}$ recies s ֚֡֕ 's rVr
	- Kinetic equations: $\frac{dc}{dt}$
 c_s is concentration of spe $\mathbf{s}_\mathbf{s}$ is concentration of species s is the stoichiometric matrix $\mathbf r$ is the rate of reaction r

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- The stationary states are the null space of ν in R
 $\sum_{r} \nu_{s,r} v_r^{ss} = 0$ $_{r}$ $\nu_{s,r}$ v $_{r}^{ss} = 0$

- Kinetic equations: $\frac{dc}{dt}$
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	- $\frac{d}{ds}$ is concentration of species s
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 $\sum_{r} \nu_{s,r} v_r^{ss} = 0$
- $v_{s,r}v_{r}^{\text{ss}}=0$
e null space
reme curren r $\frac{\nu}{e}$ n
en The null space is a convex cone in R bounded by
extreme currents. extreme currents.

Two extreme currents in ^a 3 dimensional rate space

network for "glycolysis" in flow reactor

Intracellular reactionsExtracellular reactionsTransport across cellular membrane

ODE model at metabolome level

20 variables

24 reactions

60 parameters

Extreme currents for glycolysis at Hopf point.

control of extreme currents

control of extreme currents \overline{a} $\mathbf{E}_{\mathsf{g}|y\mathsf{c}}$ 1.8 1.6 1.4 1.2 \blacksquare 0.8 0.6 0.4 0.2 $\mathbf 0$ IpPEP Aca-flow consum GIc-flow GIC-tr H PGI
PFK **ALD GAPDH** P_K PDC **ADH** EtOH-tr pGlyc Glyc-tr Aca-tr lacto CN-flow stor $\overline{\mathsf{A}}$ K EtOH-flow Glyc-flow \overline{P}

control of extreme currents

control of extreme currents

control of flux at Hopf point

• Flux control coefficients describe the influence of Flux control coefficients describe the influence of
genetic manipulation on metabolic flux at a
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genetic manipulation on metabolic flux at a
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- Redirection of flux requires simultaneous changes
in many enzyme activities in many enzyme activities
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On long timescales changes in metabolite biological system.
- On long timescales changes in metabolite On long timescales changes in metabolite
concentrations feed back on gene express concentrations feed back on gene expression.

Fell David Fell, Understanding the Control of Metabolism Portland Press, London 2003.