

Stability analysis of metabolic systems

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Jacobian of a metabolic system

$$d\mathbf{x}/dt = \mathbf{N} \cdot \mathbf{v}(\mathbf{x}, \mathbf{p})$$

$$\mathbf{N} = \mathbf{L} \cdot \mathbf{N}^0$$

$$d\mathbf{x}^0/dt = \mathbf{N}^0 \cdot \mathbf{v}(\mathbf{x}, \mathbf{p})$$

$$\mathfrak{J} = \mathbf{N}^0 \cdot \partial \mathbf{v} / \partial \mathbf{x} \cdot \mathbf{L}$$

Stability conditions around steady-state

Consider the eigenvalues λ_i of the Jacobian matrix

The steady-state is unstable if

$$\exists i, \operatorname{Re}(\lambda_i) > 0$$

The steady-state is exponentially stable if

$$\forall i, \operatorname{Re}(\lambda_i) < 0$$

with relaxation times $\tau_i = 1 / |\operatorname{Re}(\lambda_i)|$

and frequencies $\omega_i = \frac{|\operatorname{Im}(\lambda_i)|}{2\pi}$

Bifurcations

Consider the eigenvalues $\lambda_i(p)$ of the Jacobian matrix when parameters vary

A saddle-node bifurcation corresponds to a zero-crossing of one real eigenvalue λ_i

A Hopf bifurcation corresponds to a zero-crossing of the real parts $\text{Re}(\lambda_j)$ of one pair of conjugated eigenvalues $\text{Re}(\lambda_j) \pm 2i\pi\omega_j$

There are several other more complex bifurcation types

What makes a metabolic system stable?

Structural kinetic modeling of metabolic networks

Ralf Steuer^{*†‡}, Thilo Gross^{*§}, Joachim Selbig^{*¶}, and Bernd Blasius^{*}

Steuer *et al.* (2006), *PNAS* 103:11868-11873

Different notations:

x_i normalized by X_i (dimensionless)

v_j normalized by J_j

$$\mu_j := v_j / J_j$$

$$\Lambda_{ij} := N_{ij} J_j / X_i$$

What makes a metabolic system stable?

so that the system evolution follows:

$$d\mathbf{x} / dt = \mathbf{\Lambda} \cdot \boldsymbol{\mu}(\mathbf{x})$$

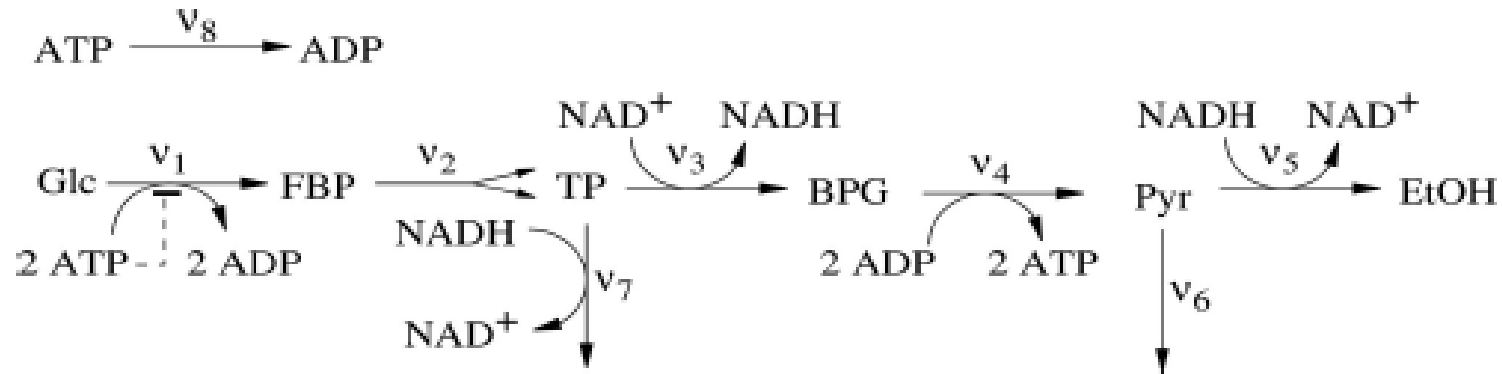
$$\mathfrak{J} = \mathbf{\Lambda} \cdot \frac{\partial \boldsymbol{\mu}}{\partial \mathbf{x}}$$

where

$$\boldsymbol{\theta} := \frac{\partial \boldsymbol{\mu}}{\partial \mathbf{x}}$$

is the matrix of normalized elasticities (usually noted $\boldsymbol{\varepsilon}$)

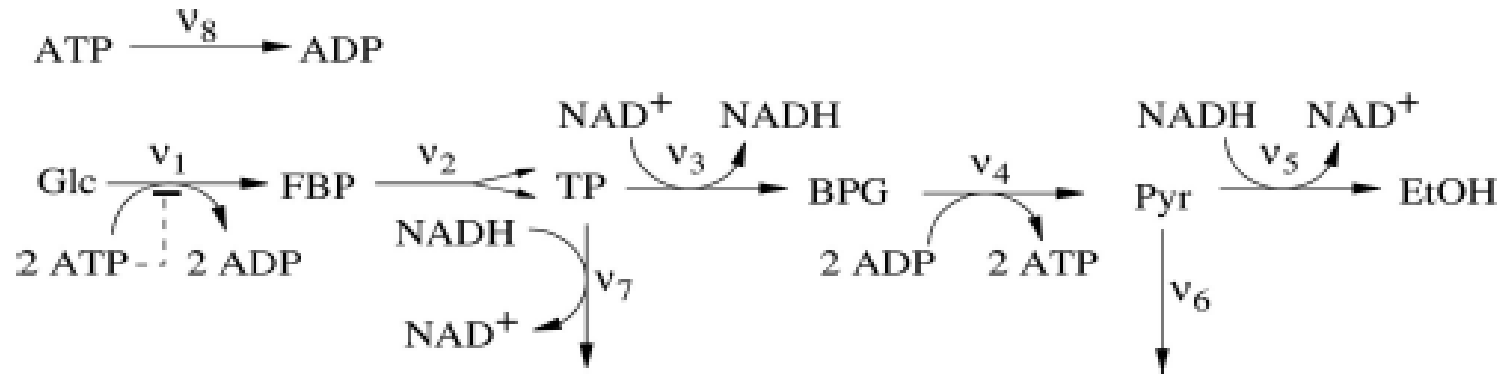
Example: simplified yeast glycolysis



with an inhibition parameter ξ for PFK by ATP:

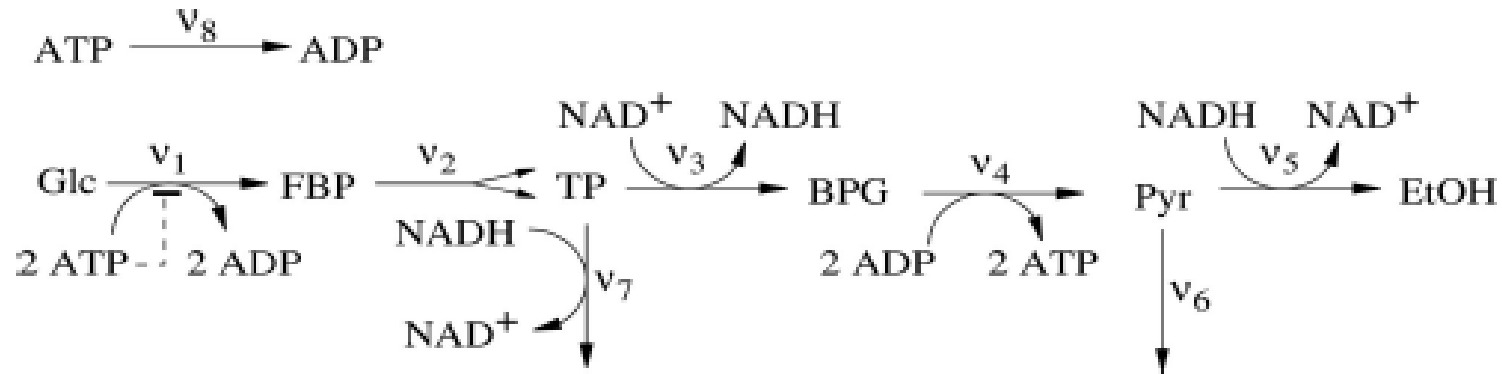
$$\theta_{ATP}^{\mu_1} = 1 - \xi$$

Stoichiometry matrix



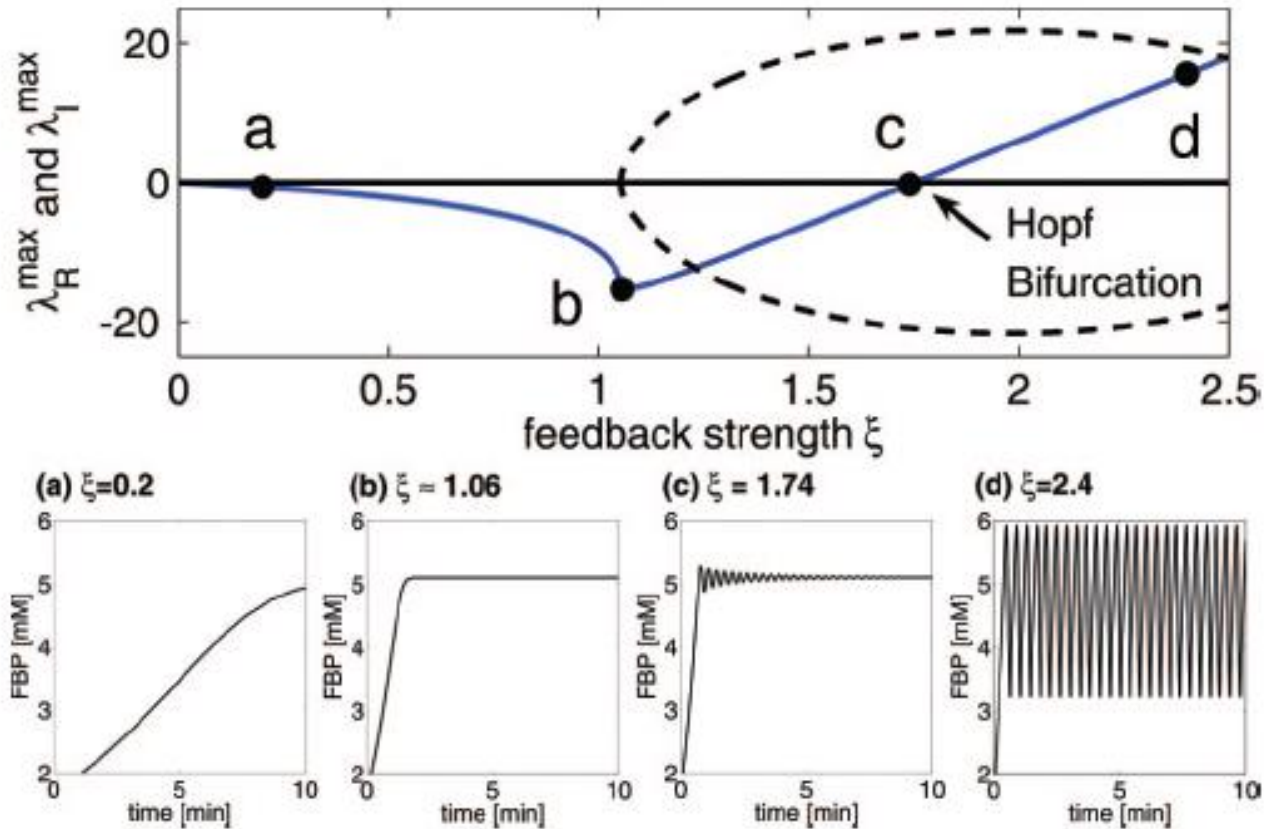
	ν_1	ν_2	ν_3	ν_4	ν_5	ν_6	ν_7	ν_8
FBP	+1	-1	0	0	0	0	0	0
TP	0	+2	-1	0	0	0	-1	0
BPG	0	0	+1	-1	0	0	0	0
Pyr/ACA	0	0	0	+1	-1	-1	0	0
ATP	-2	0	0	+2	0	0	0	-1
NADH	0	0	+1	0	-1	0	-1	0
NAD ⁺	0	0	-1	0	+1	0	+1	0
ADP	+2	0	0	-2	0	0	0	+1

Normalized elasticity matrix



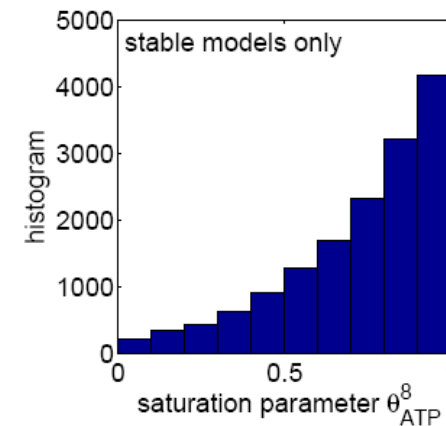
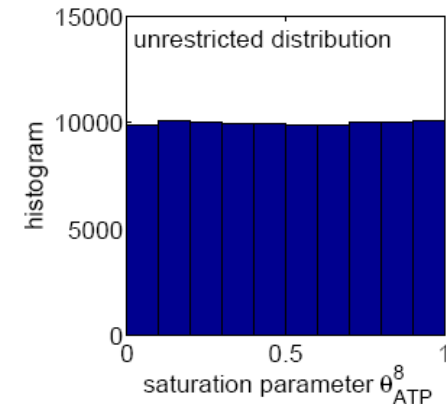
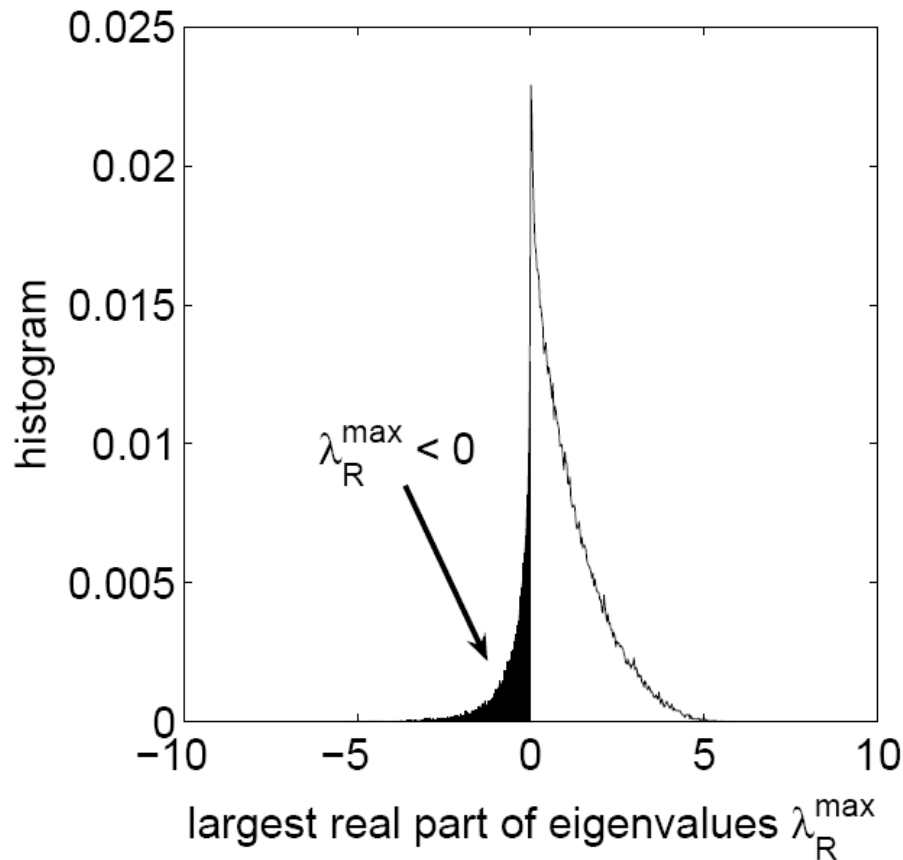
	FBP	TP	BPG	Pyr/ACA	ATP	NADH	NAD ⁺	ADP
ν_1	0	0	0	0	θ_{ATP}^1	0	0	0
ν_2	θ_{FBP}^2	0	0	0	0	0	0	0
ν_3	0	θ_{TP}^3	0	0	0	0	θ_{NAD}^3	0
ν_4	0	0	θ_{BPG}^4	0	0	0	0	θ_{ADP}^4
ν_5	0	0	0	θ_{Pyr}^5	0	θ_{NADH}^5	0	0
ν_6	0	0	0	θ_{Pyr}^6	0	0	0	0
ν_7	0	θ_{TP}^7	0	0	0	θ_{NADH}^7	0	0
ν_8	0	0	0	0	θ_{ATP}^8	0	0	0

Effect of ATP feedback on stability



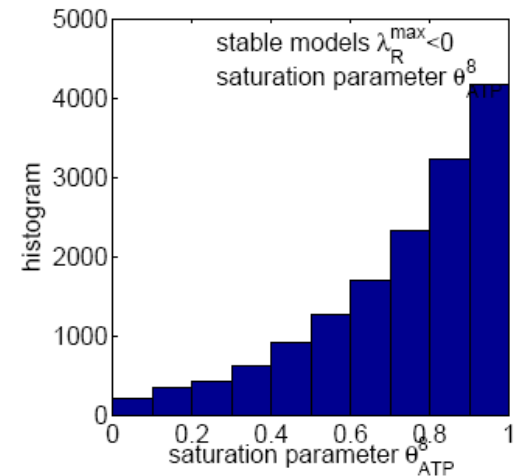
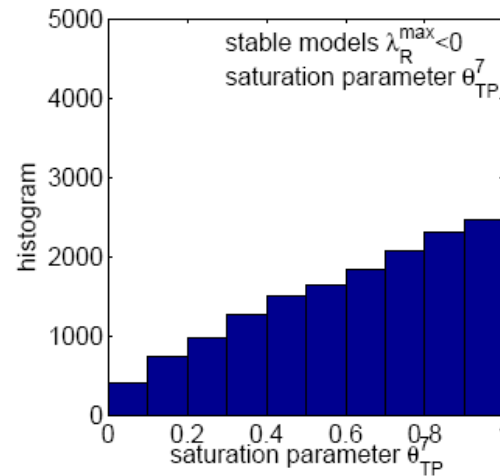
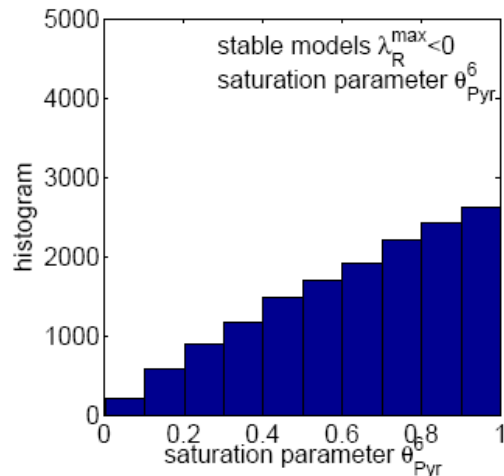
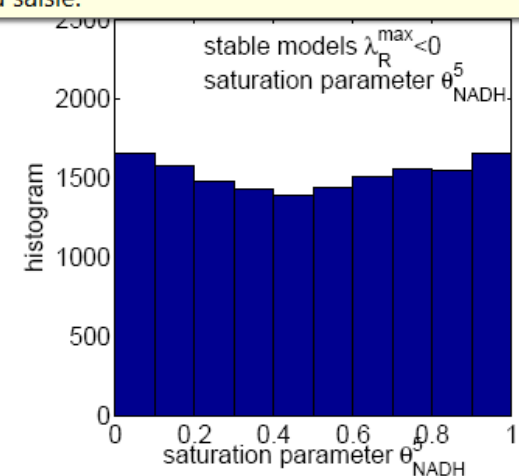
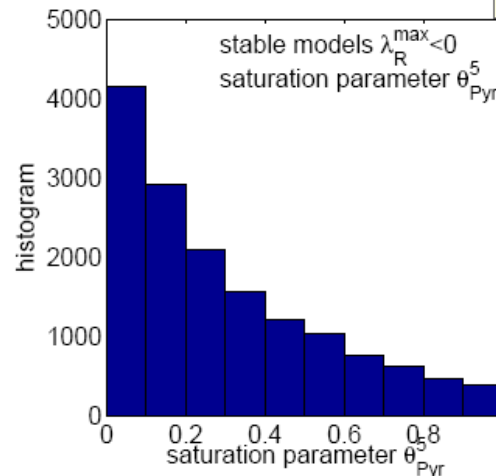
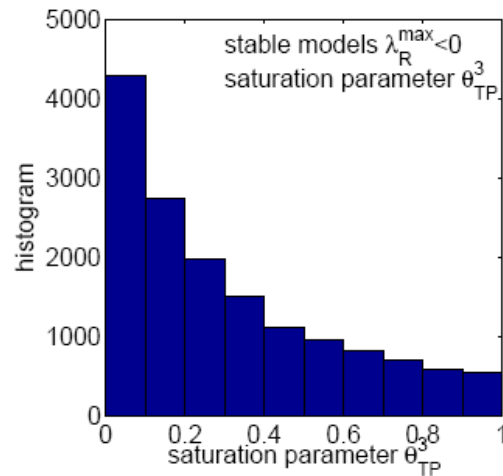
Stabilization and saturation

Random sampling of parameters



Stabilization and saturation

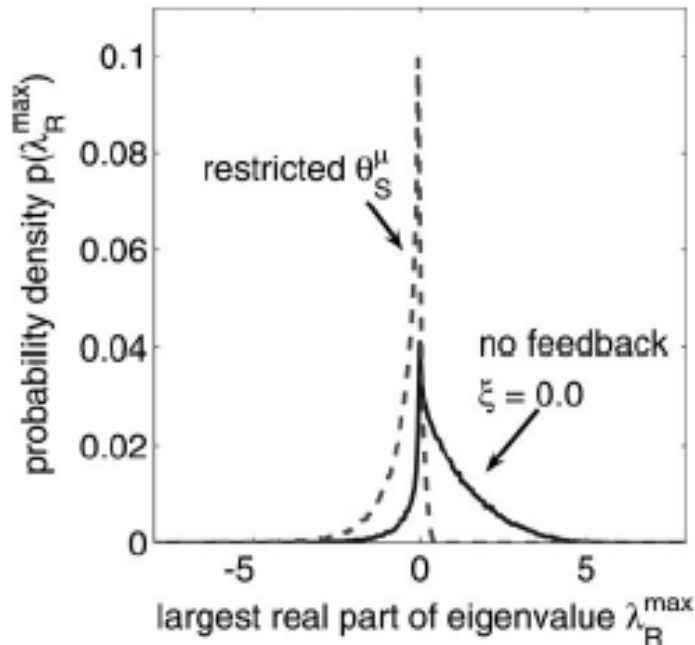
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Stabilization and saturation

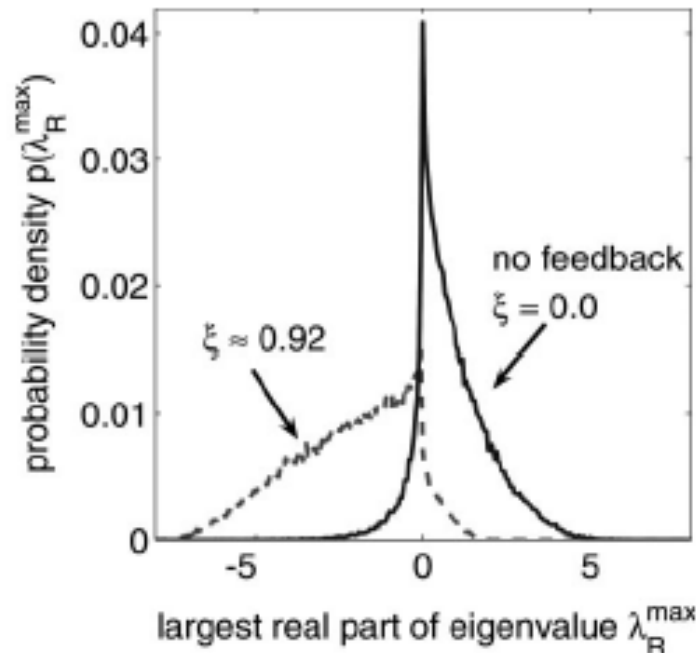
Random sampling of parameters

Constraining $\theta_{ATP}^{\mu_8} = \theta_{Pyr}^{\mu_6} = \theta_{TP}^{\mu_7} = 0.9$



Stabilization by feedback

Random sampling of parameters



Destabilization by feedback

