Stability analysis of metabolic systems

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Jacobian of a differential system

Let us consider a system of ordinary differential equations (ODEs)

$$d\mathbf{x}/dt = \mathbf{f}(\mathbf{x})$$

We define its Jacobian matrix as the matrix of its partial derivatives

$$\mathfrak{J} := \partial\mathbf{f}/\partial\mathbf{x}$$

which is a square matrix

System evolution around steady-state

Let us now consider the system around a steady-state $\mathbf{X}$

$$d\mathbf{x}/dt\ (\mathbf{X}) = \mathbf{f}(\mathbf{X}) = \mathbf{0}$$

In the vicinity of $\mathbf{X}$ we may use the first order approximation

$$d\mathbf{x}/dt \sim \mathfrak{J} \cdot [\ \mathbf{x} - \mathbf{X}\ ]$$

which integrates into

$$\mathbf{x} - \mathbf{X} = \exp(\mathfrak{J}t) \cdot [\ \mathbf{x}(0) - \mathbf{X}\ ]$$

using the matrix exponential

$$\exp(\mathfrak{J}t) := \sum_{k=0}^{\infty} \frac{1}{k!} \mathfrak{J}^k t^k$$

Stability conditions around steady-state

Consider the eigenvalues λ_i of the Jacobian matrix

The steady-state is unstable if
$\exists i, \mathrm{Re}(\lambda_i) > 0$

The steady-state is exponentially stable if
$\forall i, \mathrm{Re}(\lambda_i) < 0$
with relaxation times $\tau_i = 1/|\mathrm{Re}(\lambda_i)|$
and frequencies $\omega_i = \frac{|\mathrm{Im}(\lambda_i)|}{2\pi}$

Bifurcations

Consider the eigenvalues $\lambda_i(\mathrm{p})$ 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 $\mathrm{Re}(\lambda_j)$ of one pair of conjugated eigenvalues
$\mathrm{Re}(\lambda_j) \pm 2i\pi\omega_j$
There are several other more complex bifurcation types

Jacobian of a metabolic system

From the evolution equation

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

we derive the Jacobian

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

Jacobian of a metabolic system

However this Jacobian is singular if **N** has not maximal rank.
It is then useful to reduce the system to independent variables:

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

with

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

$$\partial\mathbf{x}/\partial\mathbf{x}^0 = \mathbf{L}$$

and we derive the Jacobian

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

that must be definite negative for the system to be stable

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:

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

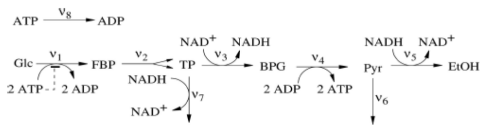
$$\mathfrak{J} = \mathbf{\Lambda} \cdot \frac{\partial \boldsymbol{\mu}}{\partial \mathbf{x}}$$

where

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

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

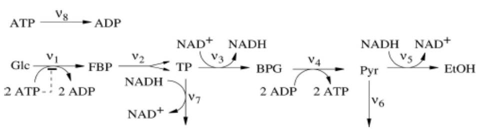
Example: simplified yeast glycolysis



with an inhibition parameter ξ for PFK by ATP:

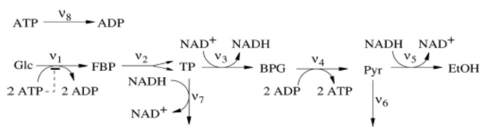
$$\theta_{ATP}^{\mu_1} = 1 - \xi$$

Stoichiometry matrix



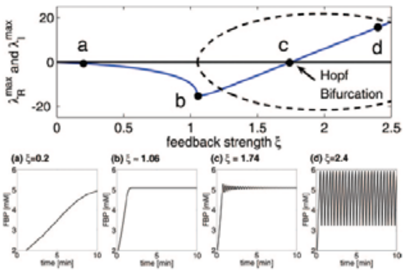
	ν_1	ν_2	ν_3	ν_4	ν_5	ν_6	ν_7	ν_8
FBP	+1	-1	0	0	0	0	0	0
TP	0	+2	-1	0	0	0	-1	0
BPG	0	0	+1	-1	0	0	0	0
Pyr/ACA	0	0	0	+1	-1	-1	0	0
ATP	-2	0	0	+2	0	0	0	-1
NADH	0	0	+1	0	-1	0	-1	0
NAD^+	0	0	-1	0	+1	0	+1	0
ADP	+2	0	0	-2	0	0	0	+1

Normalized elasticity matrix



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

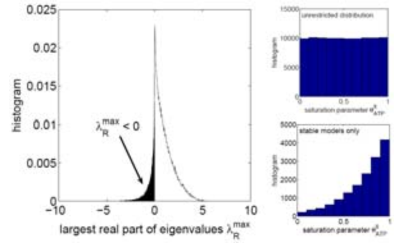
Effect of ATP feedback on stability



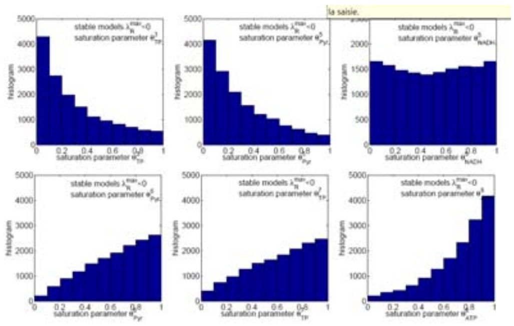
Stabilization and saturation

Random sampling of parameters:

destabilization by saturation of ATP consumption



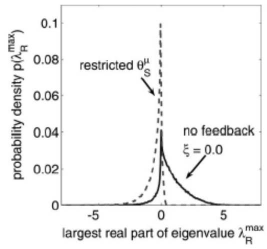
Stabilization and saturation



Stabilization and saturation

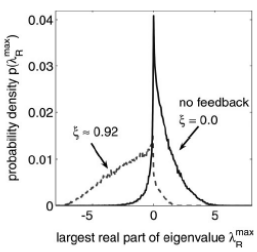
Random sampling of parameters

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



Stabilization by feedback

Random sampling of parameters



Destabilization by feedback