Relaxation and stability of metabolic systems

Daniel Kahn
Laboratoire d'Ecologie Microbienne
Lyon 1 University
& INRA MIA Department

Daniel.Kahn@univ-lyon1.fr

Jacobian of a differential system

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

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

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

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

which is a square matrix

System evolution around steady-state

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

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

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

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

which integrates into

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

using the matrix exponential

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

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 $\omega_i = \dfrac{|\mathrm{Im}(\lambda_i)|}{2\pi}$

Jacobian of a metabolic system

From the evolution equation

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

we derive the Jacobian

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

Jacobian of a metabolic system

However this Jacobian is singular if $\mathbf{N}$ has not maximal rank.

It is then useful to reduce the system to independent variables:

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

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

and we derive the Jacobian

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

that must be definite negative
for the system to be asymptotically stable

Shifting between steady-states

Starting from a steady-state $\mathbf{X}_1$, what happens if we perturb the rates $\mathbf{v}$ with a small change in parameters $\delta\mathbf{p}$?

$$\frac{d\mathbf{x}^0}{dt} \sim \Im.\left(\mathbf{x}^0(t) - \mathbf{X}_2^0\right)$$

where $\mathbf{X}_2$ is the new steady-state.

$$\begin{cases} \dfrac{d\mathbf{x}^0}{dt} = \mathbf{N}^0.\mathbf{v}(\mathbf{x}, \mathbf{p} + \delta\mathbf{p}) \\[2mm] \dfrac{d\mathbf{x}^0}{dt}(0) = \mathbf{N}^0.\dfrac{\partial\mathbf{v}}{\partial\mathbf{p}}.\delta\mathbf{p} = \mathbf{N}^0.\delta\mathbf{v} \\[2mm] \mathbf{x}^0(0) = \mathbf{X}_1^0 \end{cases}$$

Shifting between steady-states

which integrates into:

$$\mathbf{x}^0(t) - \mathbf{X}_1^0 = -\left(\mathbf{I} - \exp \Im t\right)\Im^{-1}.\mathbf{N}^0.\delta\mathbf{v}$$

$\Im$ being definitive negative for the steady-state to be stable:

$$\delta\mathbf{x} \underset{t\to\infty}{\to} \delta\mathbf{X} = \mathbf{L}\left(\mathbf{X}_2^0 - \mathbf{X}_1^0\right) = -\mathbf{L}.\Im^{-1}.\mathbf{N}^0.\delta\mathbf{v}$$

$$\delta\mathbf{J} = \frac{\partial\mathbf{v}}{\partial\mathbf{x}}\delta\mathbf{X} + \frac{\partial\mathbf{v}}{\partial\mathbf{p}}\delta\mathbf{p} = \left(\mathbf{I} - \frac{\partial\mathbf{v}}{\partial\mathbf{x}}\mathbf{L}.\Im^{-1}.\mathbf{N}^0\right).\delta\mathbf{v}$$

These relationships express the changes in steady-state concentrations $\mathbf{X}$ and fluxes $\mathbf{J}$ in response to a change in the enzyme rates $\delta\mathbf{v}$