Dynamic boundary conditions for metabolic networks

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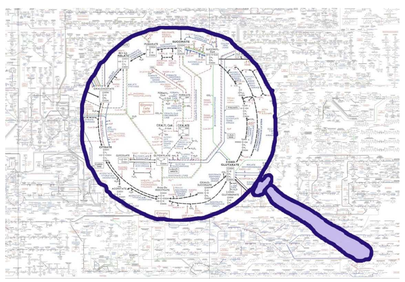
Biochemical pathways and their environment



Let us suppose we want to simulate the TCA cycle.

Can we neglect the surrounding pathways?

Assume their metabolite concentrations are fixed?

Or do we have to model the whole cell around it?

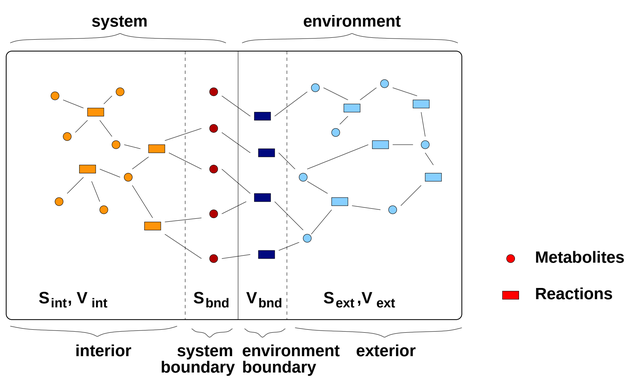
Biochemical pathways are embedded in larger networks (the "environment"). In mathematical models, external metabolites belonging to the environment are often described by fixed concentrations. In reality, the dynamics of the system affects the external metabolites, and these may act back on the system, creating a feedback loop. To capture this behaviour, the system could be enlarged. We present an alternative, namely to replace the environment model (which has to be known) by an effective model that mimicks its behaviour "as seen by the subsystem". The effective model is constructed (1) by linearising the environment model around a steady state and (2) by model reduction by balanced truncation.

Reducing the peripheral parts of metabolic models

A biochemical system follows the differential equations with

$$\dot{s}_i = \sum_l N_{il}\ v_l(s,p)$$

s_i metabolite concentrations
N: stoichiometric matrix
v_l reaction velocities
p_m kinetic parameters



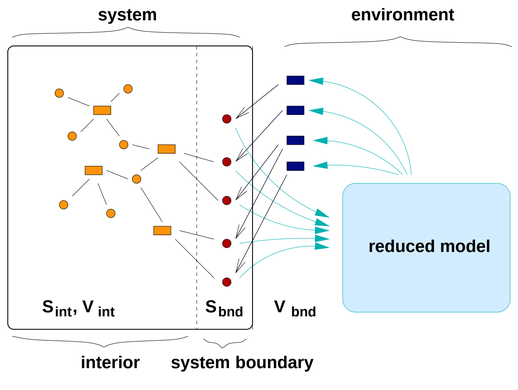
It consists of a subsystem and an environment: given $\mathbf{s}_{\mathrm{bnd}}(t)$, the environment model determines $\mathbf{v}_{\mathrm{bnd(t)}}$.

We propose to replace the environment by an effective model, which is linear and low-dimensional [2]:

- Choose reference values $\bar{\mathbf{s}}_{\mathrm{bnd}}$ leading to a steady state (concentrations $\bar{\mathbf{s}}$) of the environment.
- Linearise the environment dynamics around the reference state, setting

$$v_l(s+\Delta s, p+\Delta p) \approx v_l(\bar{\mathbf{s}},\bar{\mathbf{p}}) + \sum_k \epsilon_{lk}\ \Delta s_k + \sum_m \pi_{lm}\ \Delta p_m$$

- Apply linear model reduction to the environment. The communicating metabolites $\mathbf{u} = \Delta\mathbf{s}_{\mathrm{bnd}}$ act as the inputs, and the communicating reactions $\mathbf{y} = \Delta\mathbf{v}_{\mathrm{bnd}}$ are the outputs.



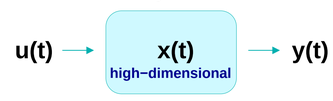
We obtain an equation system where

$$\begin{aligned}
\mathbf{u}(t) &= P\ \mathbf{s}(t) - \bar{\mathbf{s}}_{\mathrm{bnd}} \\
\dot{\mathbf{x}}(t) &= A\ \mathbf{x}(t) + B\ \mathbf{u}(t) + B_{\mathrm{p}}\Delta\mathbf{p}(t) \\
\mathbf{y}(t) &= C\ \mathbf{x}(t) + D\ \mathbf{u}(t) + D_{\mathrm{p}}\Delta\mathbf{p}(t) \\
\mathbf{v}_{\mathrm{bnd}}(t) &= \bar{\mathbf{v}}_{\mathrm{bnd}} + \mathbf{y}(t) \\
\dot{\mathbf{s}}(t) &= \mathbf{N}\ \mathbf{v}(\mathbf{s}(t),\mathbf{p}(t)) + \mathbf{N}_{\mathrm{bnd}}\ \mathbf{v}_{\mathrm{bnd}}(t)
\end{aligned}$$

$$\begin{aligned}
A &= \mathbf{N}^{\mathrm{ext}}_{\mathrm{ext}}\ \epsilon^{\mathrm{ext}}_{\mathrm{ext}} + \mathbf{N}^{\mathrm{ext}}_{\mathrm{bnd}}\ \epsilon^{\mathrm{bnd}}_{\mathrm{ext}} \\
B &= \mathbf{N}^{\mathrm{ext}}_{\mathrm{bnd}}\ \epsilon^{\mathrm{bnd}}_{\mathrm{bnd}}, \quad B_{\mathrm{p}} = \mathbf{N}^{\mathrm{ext}}_{\mathrm{bnd}}\epsilon^{\mathrm{bnd}}_{\mathrm{p}} + \mathbf{N}^{\mathrm{ext}}_{\mathrm{ext}}\epsilon^{\mathrm{ext}}_{\mathrm{p}} \\
C &= \epsilon^{\mathrm{bnd}}_{\mathrm{ext}} \\
D &= \epsilon^{\mathrm{bnd}}_{\mathrm{bnd}}, \quad D_{\mathrm{p}} = \epsilon^{\mathrm{bnd}}_{\mathrm{p}} \\
\mathbf{s}_{\mathrm{bnd}} &= P\mathbf{s}
\end{aligned}$$

Model reduction by balanced truncation

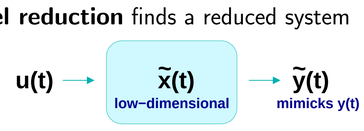
Assume a stable linear system



$$\begin{aligned}
\dot{\mathbf{x}}(t) &= A\mathbf{x}(t) + B\mathbf{u}(t) \\
\mathbf{y}(t) &= C\mathbf{x}(t) + D\mathbf{u}(t)
\end{aligned}$$

Each input time course $\mathbf{u}(t)$ yields an output time course $\mathbf{y}(t)$.

Model reduction finds a reduced system



$$\begin{aligned}
\dot{\tilde{\mathbf{x}}}(t) &= \tilde{A}\tilde{\mathbf{x}}(t) + \tilde{B}\mathbf{u}(t) \\
\tilde{\mathbf{y}}(t) &= \tilde{C}\tilde{\mathbf{x}}(t) + \tilde{D}\mathbf{u}(t)
\end{aligned}$$

with a low-dimensional $\tilde{\mathbf{x}} = T\mathbf{x}$ to approximate the output $\mathbf{y}(t)$, given $\mathbf{u}(t)$.

Balanced truncation [3]
first chooses a bijective transformation $\mathbf{x} \to \tilde{\mathbf{x}} = T\mathbf{x}$ (see box). The new variables $\tilde{x}_i$ are ordered according to their contribution to the information transfer from inputs to outputs.

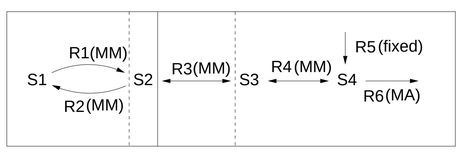
Then, $\tilde{x}_i$ for $i > r$ are neglected ("truncated"). The approximation error can be controlled by adjusting the dimensionality r of the reduced system.

In balanced truncation, we choose a transformation matrix T such as to make the Gramian matrices $\mathcal{P}$ and $\mathcal{Q}$ equal and diagonal. The Gramians are determined by the Lyapunov equations

$$\begin{aligned}
A^{\mathrm{T}}\mathcal{P} + \mathcal{P}A + BB^{\mathrm{T}} &= 0 \\
A^{\mathrm{T}}\mathcal{Q} + \mathcal{Q}A + CC^{\mathrm{T}} &= 0
\end{aligned}$$

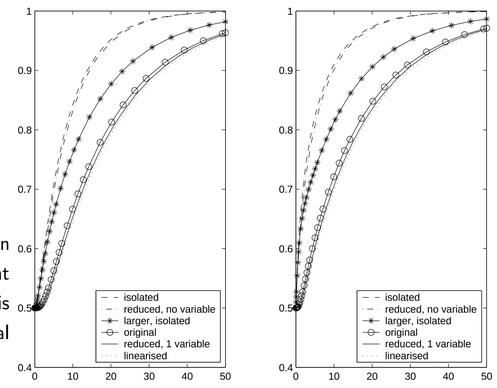
Balanced truncation software is available at http://www.tu-chemnitz.de/mathematik/industrie_technik/software/software.php

Reducing a small reaction network



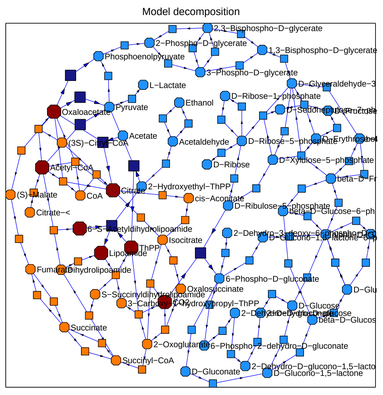
MM Michaelis-Menten kinetics
MA mass-action kinetics

Right: The graphs show time courses of s_1 (left) and s_2 (right) in arbitrary units. The lines show the original system (○) and different approximations. Model reduction with one reduced variable (-) is much more accurate than "isolated" modelling with fixed external concentrations. For simplicity, all kinetic parameters were set to 1.



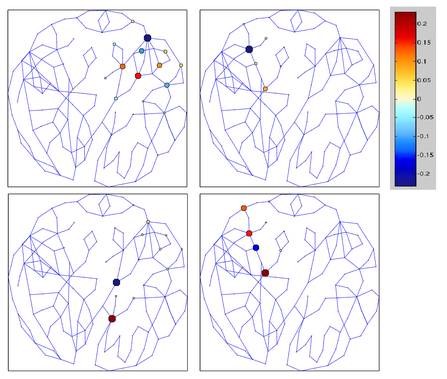
What do the reduced variables represent?

We consider a network of carbohydrate metabolism and TCA cycle (from the KEGG data base [1]). The TCA cycle has been chosen as the subsystem of interest.



The chemical reactions have been modelled by Michaelis-Menten kinetics with arbitrary parameters.

The environment concentrations can be approximated by $\Delta\mathbf{s}_{\mathrm{ext}} \approx \sum_i \tilde{x}_i\mathbf{b}_i$. A reduced variable $\tilde{x}_i$ corresponds to a pattern $\mathbf{b}_i$ of metabolite deviations.



Weights of the concentrations (colour-coded elements of $\mathbf{b}_i$) for the first 4 reduced variables

Summary

Balanced truncation highlights modes that dominate the environment's dynamics as seen from the system of interest.

Model reduction yields a practical way to improve simulations:

- More accuracy - as compared to modelling with a fixed environment
- Less computational effort - as compared to the full model
- The trade-off between accuracy and speed can be controlled by choice of dimensionality.

... and fast simulations can be vital for parameter estimation.

Requirements/drawbacks:

- The method requires a mathematical model of the environment with a stable steady state.
- Two approximations are made: linearisation and model reduction
- Conservation relations that couple subsystem and environment may be violated.

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References

[1] M. Kanehisa, S. Goto, et al. The KEGG databases at genomenet. *Nucleic Acids Res.*, 30:42–46, 2002.

[2] W. Liebermeister, U. Baur, and E. Klipp. Biochemical network models simplified by balanced truncation. *to appear in FEBS Journal*, 2005.

[3] B.C. Moore. Principal component analysis in linear systems: Controllability, observability, and model reduction. *IEEETransAC*, AC-26:17–32, 1981.