rijksuniversiteit
groningen

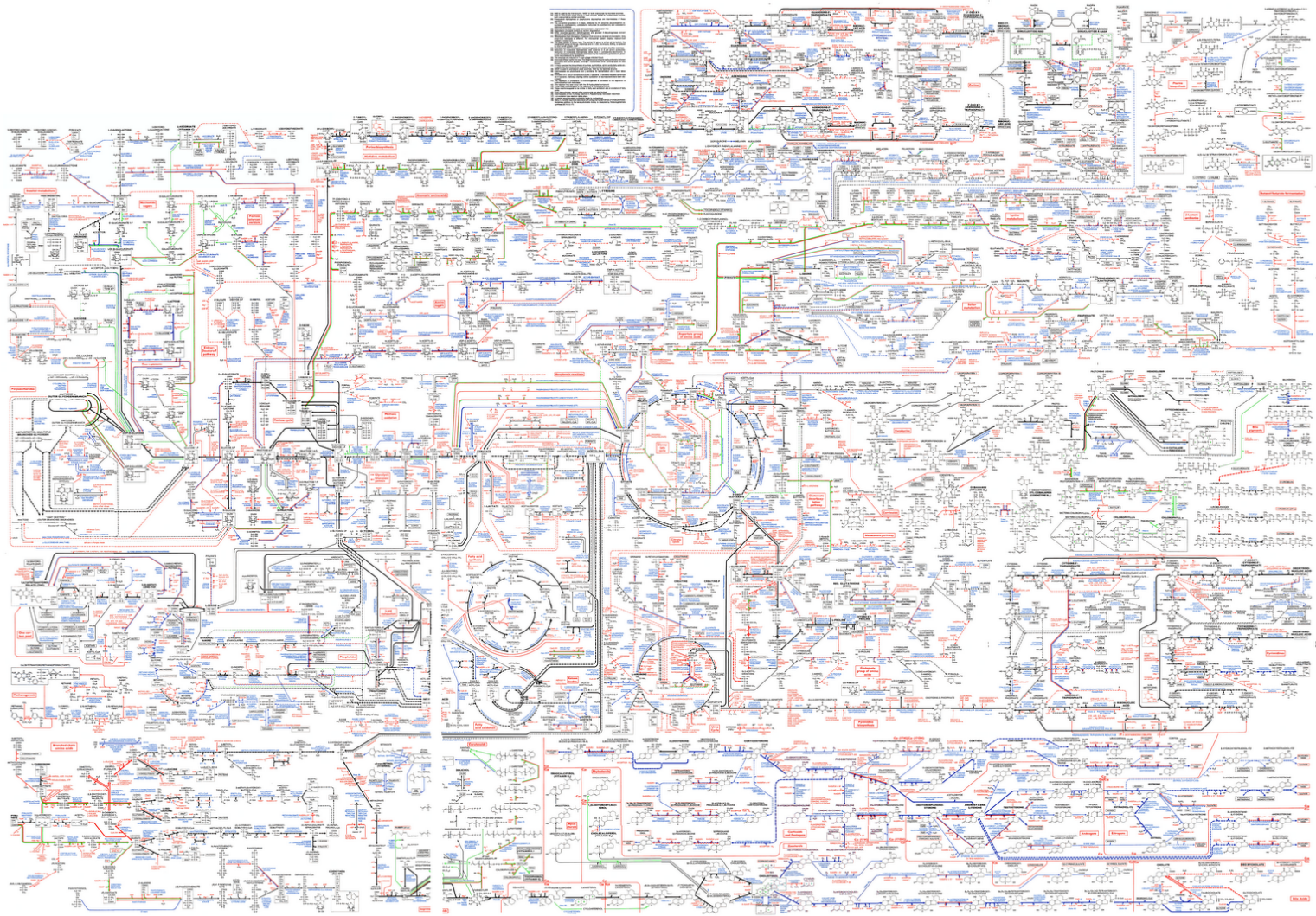
Handling complexity in large-scale (bio)-chemical reaction networks

February 17, 2017

Contents

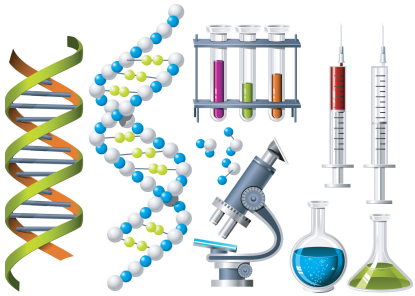
- Background and preliminaries on model-order reduction methods
- Kinetic modeling of Chemical Reaction Networks
- Handling the complexity via Kron reduction
- Robustness and multi-stability
- Conclusions and future works

Complexity in metabolic pathways



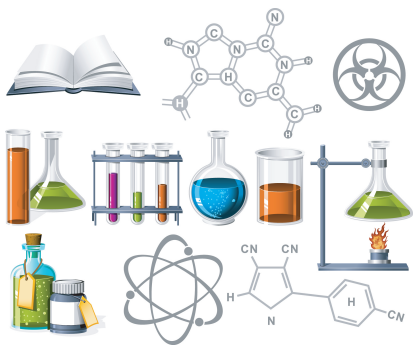
From the Biochemical Pathways chart (dr. Gerhard Michal, Roche)

Recent technological advances

- 

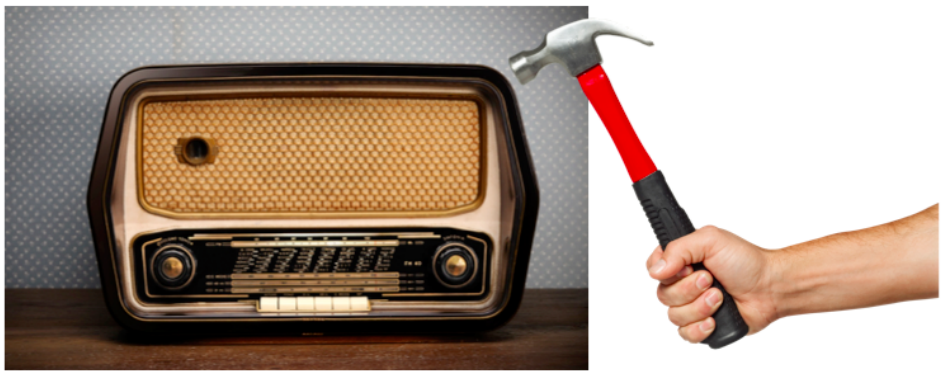
  High-throughput genomics, proteomics, metabolomics measurement systems

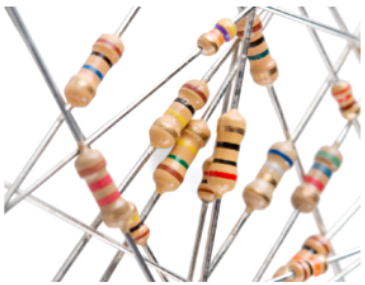
- Advances in genome-scale kinetic modeling

- 

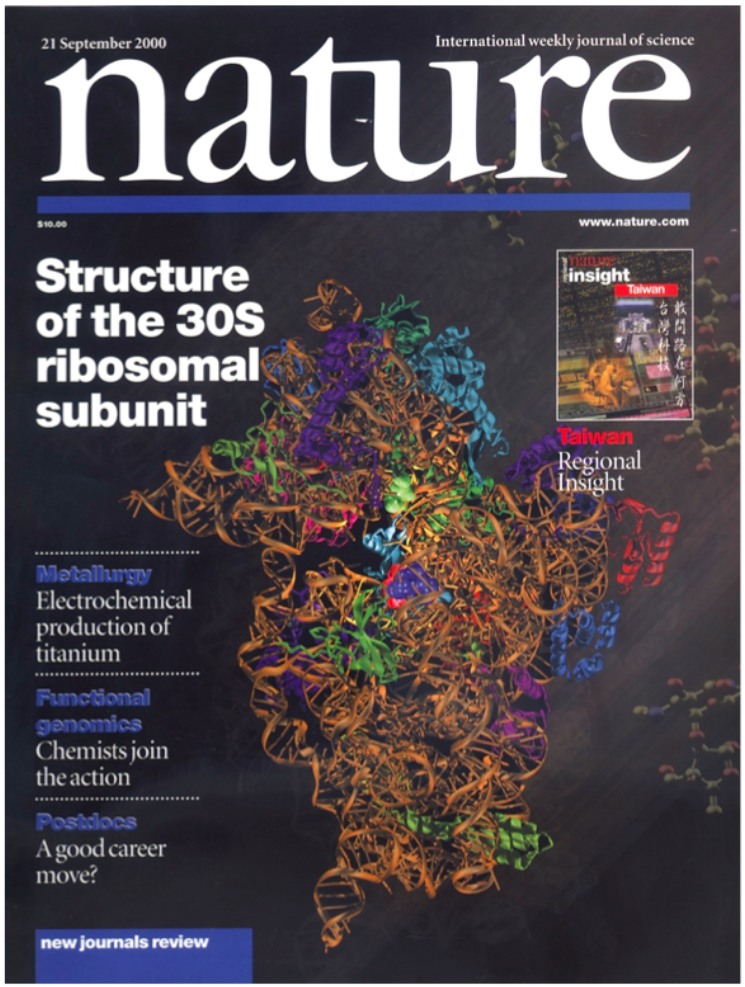
  Personalized medicine: Treatment of cancer, diabetes and other diseases

Bottom-up approach in biochemistry

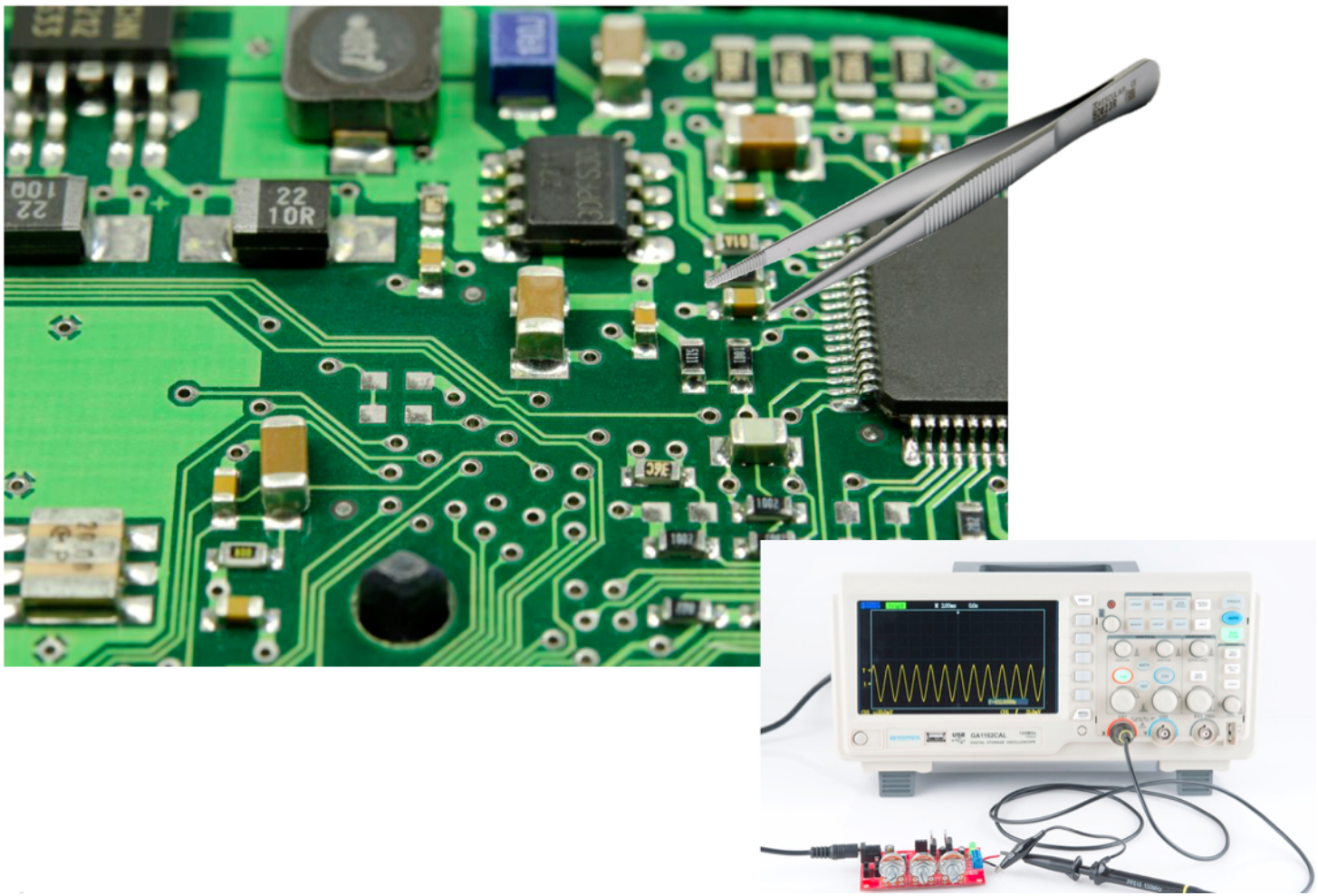




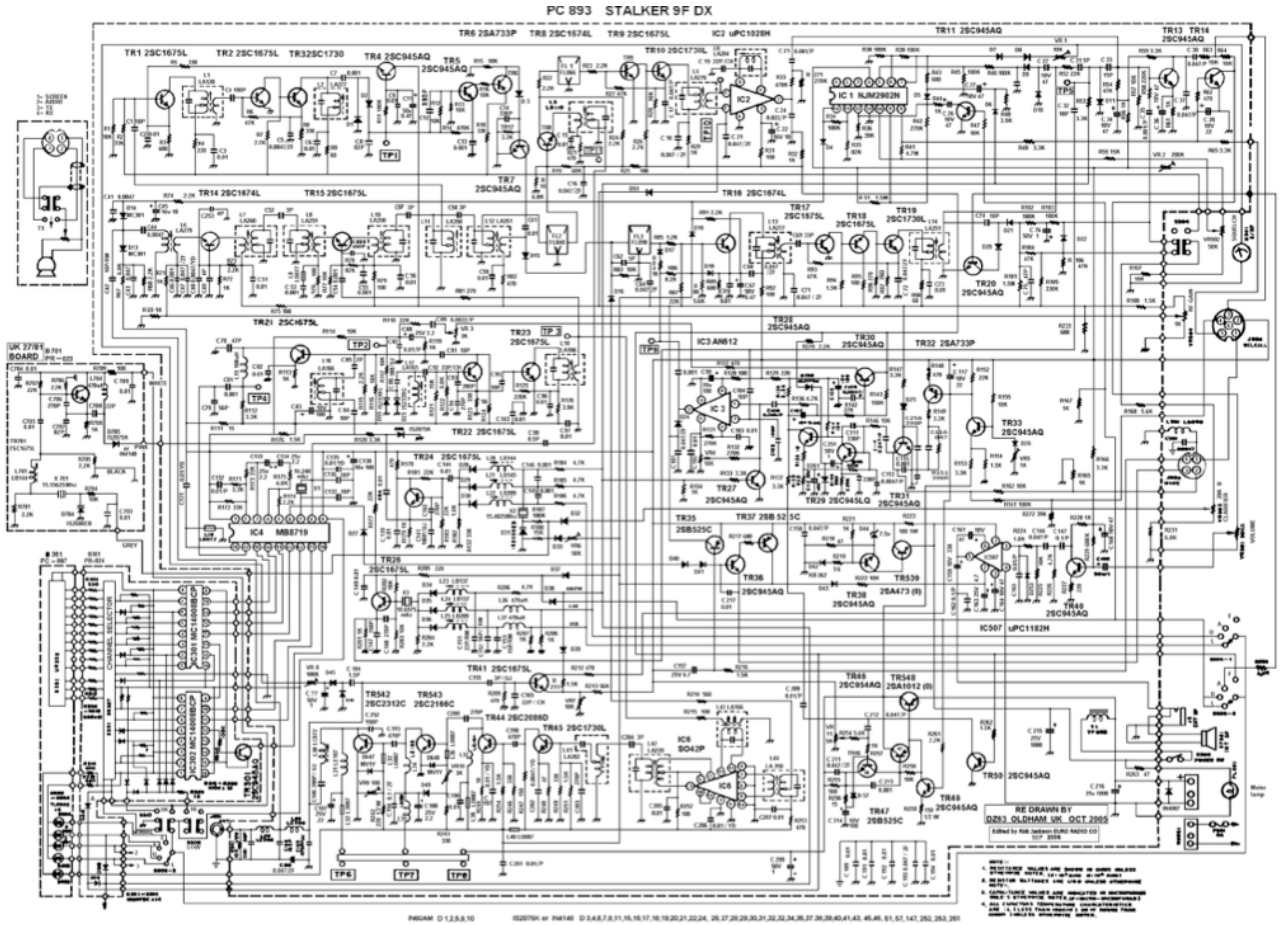
Bottom-up approach



Analogy of bottom-up in electrical systems



Analogy of bottom-up in electrical systems



Basic circuit systems theory

Resistor, R

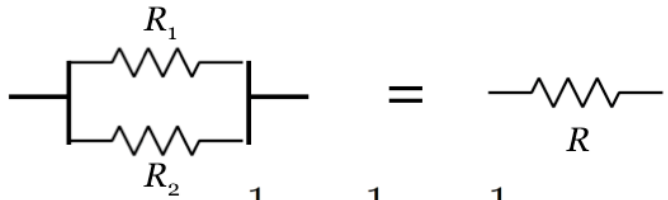
$$i = \frac{1}{R}e$$

Voltage, e
Capacitor, C

$$i = C\frac{de}{dt}$$

Current, i
Inductor, L

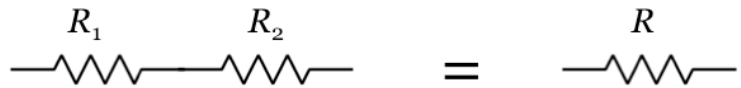
$$e = L\frac{di}{dt}$$



$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2}$$

Total conductance =
Conductance 1 + Conductance 2

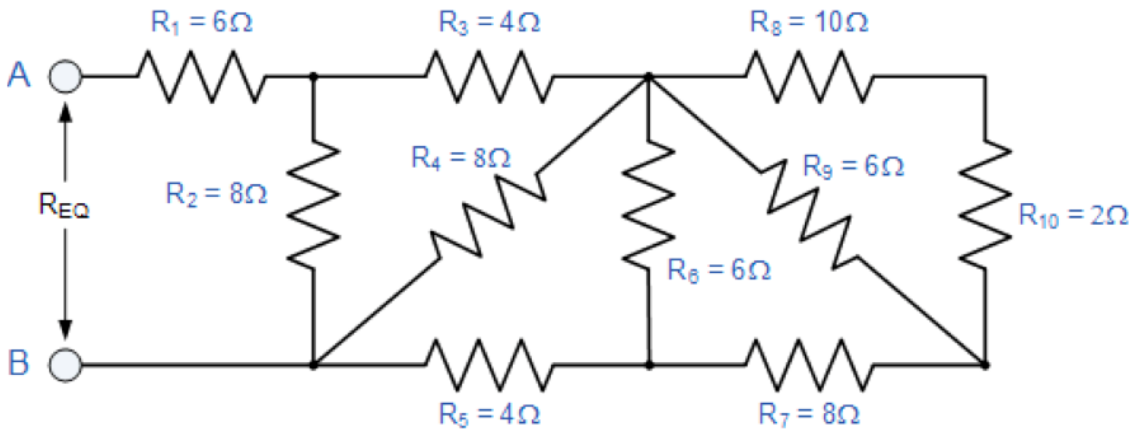
$$R = \frac{R_1 R_2}{R_1 + R_2}$$



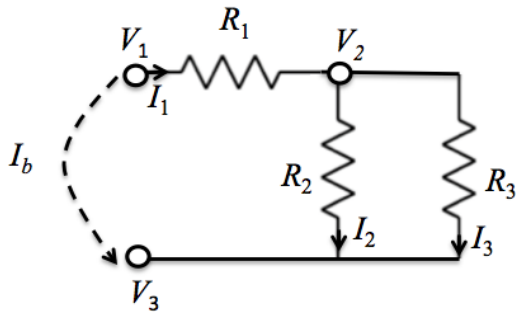
$$R = R_1 + R_2$$

Total resistance =
Resistance 1 + Resistance 2

Example in simple circuit systems



Graph theoretic approach for electrical circuit



Using Kirchoff voltage and current laws, we have

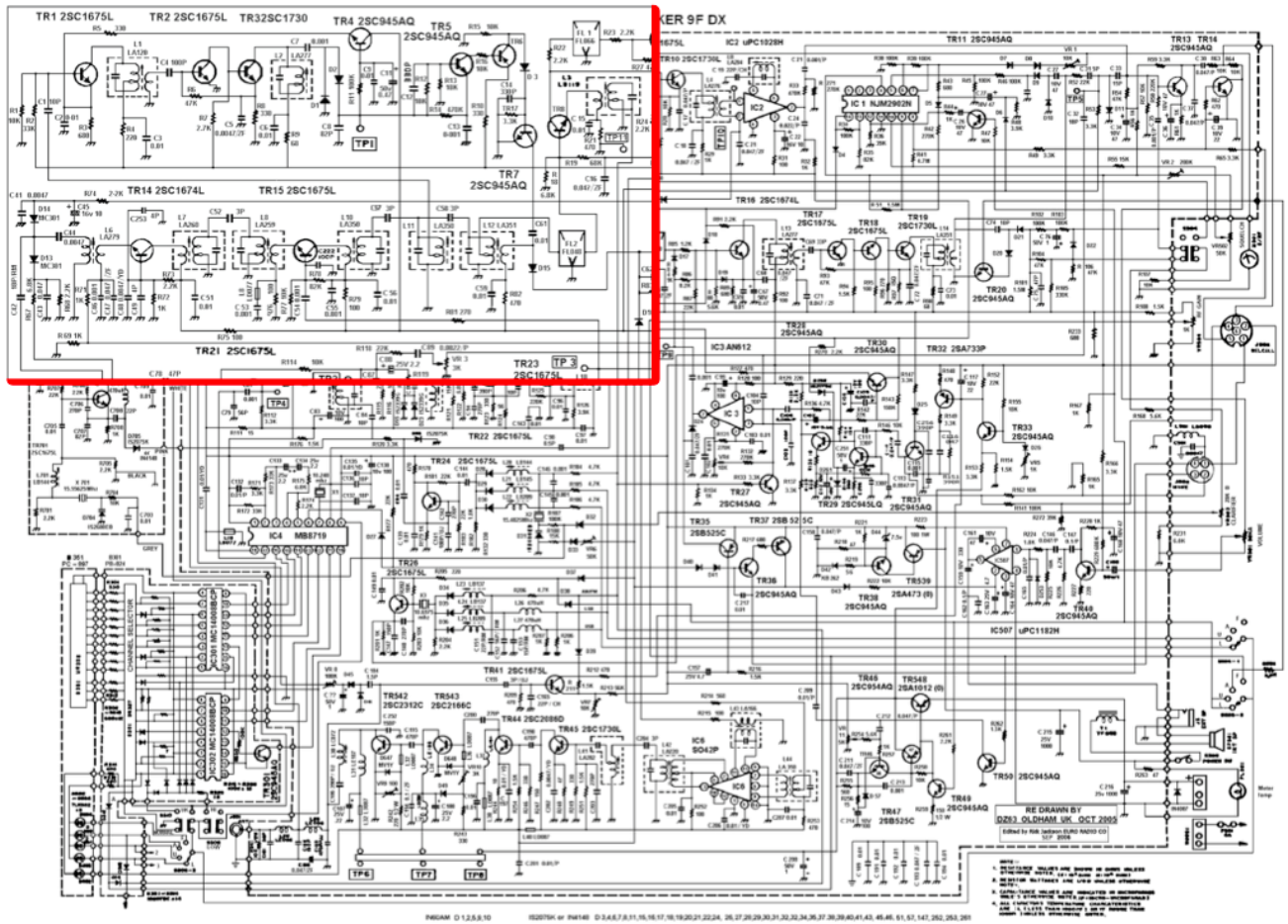
$$\begin{bmatrix} 0 \\ I_b \end{bmatrix} = \begin{bmatrix} B_i \\ B_b \end{bmatrix} \underbrace{\begin{bmatrix} 1/R_1 & 0 & 0 \\ 0 & 1/R_2 & 0 \\ 0 & 0 & 1/R_3 \end{bmatrix}}_{G} \begin{bmatrix} B_i^T & B_b^T \end{bmatrix} \begin{bmatrix} V_2 \\ V_1 \\ V_3 \end{bmatrix}$$

where $B_i = \begin{bmatrix} -1 & 1 & 1 \end{bmatrix}$ and $B_b = \begin{bmatrix} 1 & 0 & 0 \\ 0 & -1 & -1 \end{bmatrix}$. Eliminating the first row,

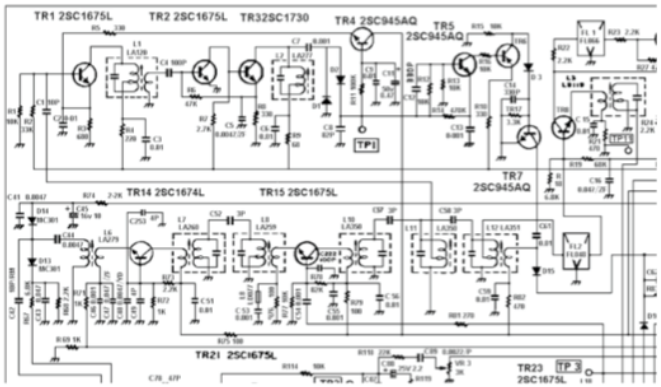
$$I_b = \underbrace{\left[B_b G B_b^T - B_b G B_i^T (B_i G B_i^T)^{-1} B_i G B_b^T\right]}_{\mathcal{L}_b} \begin{bmatrix} V_1 \\ V_3 \end{bmatrix}, \text{ or}$$

$$V_1 - V_3 = R_1 + \frac{1}{\frac{1}{R_2} + \frac{1}{R_3}} I_b$$

Back to the radio example



Thevenin circuit



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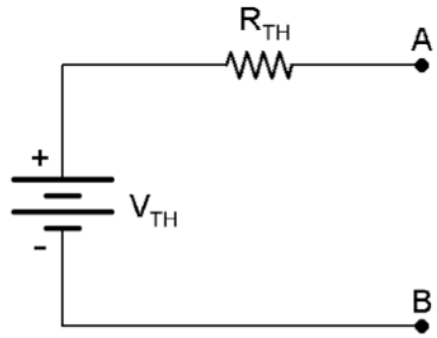


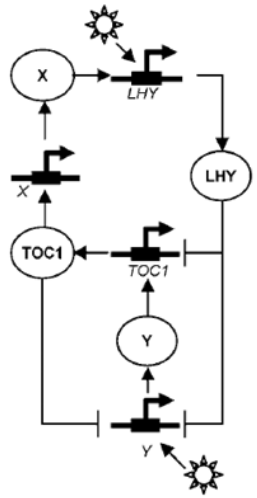
Different modeling approaches

THEVIRTUALBRAIN.

virtual liver network

The Virtual Physiological Rat Project

High-fidelity model



Simple model

Different modeling approaches

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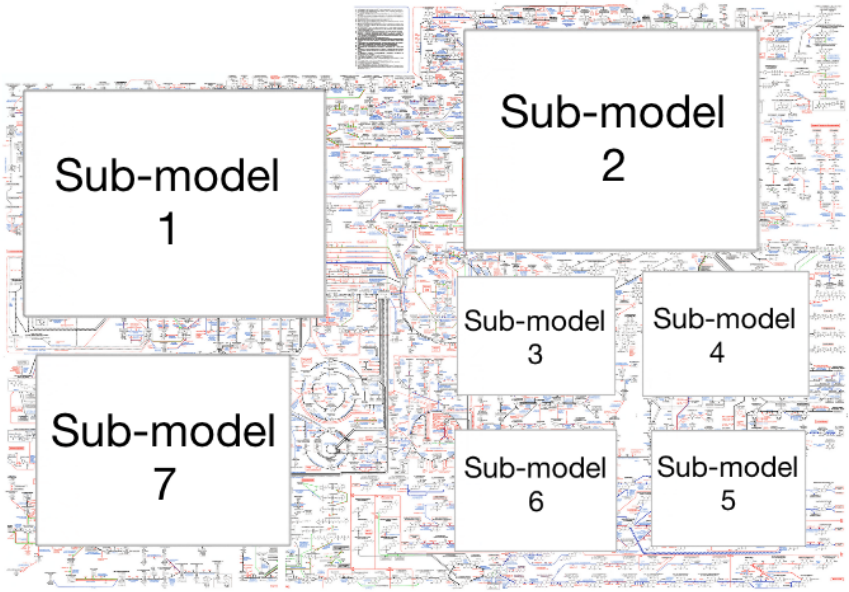
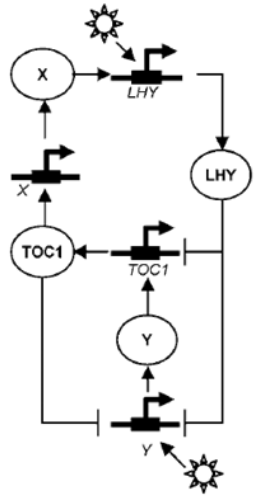


Coarse-grained model



Simple model

The graph representation of chemical networks (graph of complexes)

Example

$$X_1 + 2X_2 \longrightarrow X_3 \longrightarrow 2X_1 + X_2 \longrightarrow X_1 + 2X_2$$

- The *complexes* are the set of species that are on the left- and right-hand sides (substrates and products) of the reactions in the network.

The graph representation of chemical networks (graph of complexes)

Example

$$X_1 + 2X_2 \longrightarrow X_3 \longrightarrow 2X_1 + X_2 \longrightarrow X_1 + 2X_2$$

- The *complexes* are the set of species that are on the left- and right-hand sides (substrates and products) of the reactions in the network.
- For the above example, the complexes are $C_1 = X_1 + 2X_2, C_2 = X_3$ and $C_3 = 2X_1 + X_2$,

$$C_1 \xrightarrow{R_1} C_2 \xrightarrow{R_2} C_3 \xrightarrow{R_3} C_1$$

The graph representation of chemical networks (graph of complexes)

Example 1.

$$X_1 + 2X_2 \longrightarrow X_3 \longrightarrow 2X_1 + X_2 \longrightarrow X_1 + 2X_2$$

- The relation between the species concentrations and the complex concentrations can be given by a *complex composition matrix* Z.
- For the example above,

$$\underbrace{\begin{bmatrix} 1 & 2 & 0 \\ 0 & 0 & 1 \\ 2 & 1 & 0 \end{bmatrix}}_{Z^T} \begin{bmatrix} X_1 \\ X_2 \\ X_3 \end{bmatrix} = \begin{bmatrix} C_1 \\ C_2 \\ C_3 \end{bmatrix}.$$

The incidence matrix

Example 1.

$$X_1 + 2X_2 \longrightarrow X_3 \longrightarrow 2X_1 + X_2 \longrightarrow X_1 + 2X_2$$

- On the other hand, the relation between the set of fluxes and the rate changes of complexes can be given by an *incidence matrix* B.
- For the example above,

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} C_1 \\ C_2 \\ C_3 \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix}}_{B} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix},$$

where v_1, v_2, v_3 are the rate in the reactions R_1, R_2 and R_3, respectively

Stoichiometric matrix

Example 1.

$$X_1 + 2X_2 \longrightarrow X_3 \longrightarrow 2X_1 + X_2 \longrightarrow X_1 + 2X_2$$

- Using Z and B, the usual stoichiometric matrix S can be given by

$$S := ZB.$$

- For the aforementioned example,

$$S = \underbrace{\begin{bmatrix} 1 & 0 & 2 \\ 2 & 0 & 1 \\ 0 & 1 & 0 \end{bmatrix}}_{Z} \underbrace{\begin{bmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix}}_{B} = \begin{bmatrix} -1 & 2 & -1 \\ -2 & 1 & 1 \\ 1 & -1 & 0 \end{bmatrix}.$$

Mass-action kinetics

Example 1.

$$X_1 + 2X_2 \overset{k_{1,\text{forw}}}{\longrightarrow} X_3 \overset{k_{2,\text{forw}}}{\longrightarrow} 2X_1 + X_2 \overset{k_{3,\text{forw}}}{\longrightarrow} X_1 + 2X_2$$

For mass-action kinetics

$$v(x) = \begin{bmatrix} k_{1,\text{forw}} x_1 x_2^2 \\ k_{2,\text{forw}} x_3 \\ k_{3,\text{forw}} x_1^2 x_2 \end{bmatrix}.$$

Mass-action kinetics

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For mass-action kinetics

$$v(x) = \begin{bmatrix} k_{1,\mathsf{forw}} x_1 x_2^2 \\ k_{2,\mathsf{forw}} x_3 \\ k_{3,\mathsf{forw}} x_1^2 x_2 \end{bmatrix}.$$

For convenience,

$$v(x) = \mathrm{diag}\left(k_{1,\mathsf{forw}}, k_{2,\mathsf{forw}}, k_{3,\mathsf{forw}}\right) \mathsf{Exp}\left(Z^T \mathsf{Ln}\left(x\right)\right).$$

Mass-action kinetics

Example 1.

$$X_1 + 2X_2 \overset{k_{1,\text{forw}}}{\longrightarrow} X_3 \overset{k_{2,\text{forw}}}{\longrightarrow} 2X_1 + X_2 \overset{k_{3,\text{forw}}}{\longrightarrow} X_1 + 2X_2$$

For mass-action kinetics, the network dynamics is given by

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} &= ZBv(x) \\
&= Z\begin{bmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix} \operatorname{diag}\left(k_{1,\text{forw}}, k_{2,\text{forw}}, k_{3,\text{forw}}\right) \mathsf{Exp}\left(Z^T \mathsf{Ln}\left(x\right)\right) \\
&= Z\underbrace{\begin{bmatrix} -k_{1,\text{forw}} & 0 & k_{3,\text{forw}} \\ k_{1,\text{forw}} & -k_{2,\text{forw}} & 0 \\ 0 & k_{2,\text{forw}} & -k_{3,\text{forw}} \end{bmatrix}}_{-L} \mathsf{Exp}\left(Z^T \mathsf{Ln}\left(x\right)\right)
\end{aligned}$$

General kinetics

Example 1.

$$X_1 + 2X_2 \overset{k_{1,\text{forw}}}{\longrightarrow} X_3 \overset{k_{2,\text{forw}}}{\longrightarrow} 2X_1 + X_2 \overset{k_{3,\text{forw}}}{\longrightarrow} X_1 + 2X_2$$

If general kinetics is assumed

$$v(x) = \begin{bmatrix} d_1(x)x_1x_2^2 \\ d_2(x)x_3 \\ d_3(x)x_1^2x_2 \end{bmatrix}$$

where d_1, d_2 and d_3 are positive-definite rational functions.
As an example, $d_1(x) = \frac{k_{1,\text{forw}}}{1+\frac{x_1}{K_{m,1}}+\frac{x_2}{K_{m,2}}}$.

General kinetics

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where d_1, d_2 and d_3 are positive-definite rational functions.
As an example, $d_1(x) = \frac{k_{1,\text{forw}}}{1+\frac{x_1}{K_{m,1}}+\frac{x_2}{K_{m,2}}}$.

As before,

$$v(x) = \text{diag}\left(d_1(x), d_2(x), d_3(x)\right)\text{Exp}\left(Z^T\text{Ln}\left(x\right)\right).$$

General kinetics

Example 1.

$$X_1 + 2X_2 \overset{k_{1,\text{forw}}}{\longrightarrow} X_3 \overset{k_{2,\text{forw}}}{\longrightarrow} 2X_1 + X_2 \overset{k_{3,\text{forw}}}{\longrightarrow} X_1 + 2X_2$$

For general kinetics, the network dynamics is given by

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = Z \underbrace{\begin{bmatrix} -d_1(x) & 0 & d_3(x) \\ d_1(x) & -d_2(x) & 0 \\ 0 & d_2(x) & -d_3(x) \end{bmatrix}}_{-L(x)} \mathsf{Exp}\left(Z^T \mathsf{Ln}\,(x)\right)$$

Summary on the Network Dynamics

The network dynamics of chemical reactions with mass-action kinetics can be written as

$$\dot{x} = -ZL\mathrm{Exp}\left(Z^T \mathrm{Ln}\left(x\right)\right),$$

where L is a Laplacian matrix.
For general kinetics, they can be described by

$$\dot{x} = -ZL(x)\mathrm{Exp}\left(Z^T \mathrm{Ln}\left(x\right)\right),$$

with $L(x)$ be state-dependent Laplacian matrix.

Quasi Steady State Approximation

$$X_1 \underset{k_{1,\text{rev}}}{\overset{k_{1,\text{forw}}}{\rightleftharpoons}} X_2 \underset{k_{2,\text{rev}}}{\overset{k_{2,\text{forw}}}{\rightleftharpoons}} X_3$$

Consider the above example which has the following dynamics

$$\begin{aligned}
\dot{x}_1 &= -\frac{k_{1,\text{forw}} x_1}{p_1(x_1,x_2)} + \frac{k_{1,\text{rev}} x_2}{p_1(x_1,x_2)} \\
\dot{x}_2 &= \frac{k_{1,\text{forw}} x_1}{p_1(x_1,x_2)} - \frac{k_{1,\text{rev}} x_2}{p_1(x_1,x_2)} - \frac{k_{2,\text{forw}} x_2}{p_2(x_2,x_3)} + \frac{k_{2,\text{rev}} x_3}{p_2(x_2,x_3)} \\
\dot{x}_3 &= \frac{k_{2,\text{forw}} x_2}{p_2(x_2,x_3)} - \frac{k_{2,\text{rev}} x_3}{p_2(x_2,x_3)},
\end{aligned}$$

where $p_1(x_1,x_2) = \left(1 + \frac{x_1}{K_m^{I,1}} + \frac{x_2}{K_m^{I,2}}\right)$ and $p_2(x_2,x_3) = \left(1 + \frac{x_2}{K_m^{II,2}} + \frac{x_3}{K_m^{II,3}}\right)$.

Quasi Steady State Approximation

$$X_1 \underset{k_{1,\text{rev}}}{\overset{k_{1,\text{forw}}}{\rightleftharpoons}} X_2 \underset{k_{2,\text{rev}}}{\overset{k_{2,\text{forw}}}{\rightleftharpoons}} X_3$$

When X_2 reaches steady state, we have

$$x_2 = \frac{k_{1,\text{forw}} x_1 p_2(x_2, x_3) + k_{2,\text{rev}} x_3 p_1(x_1, x_2)}{k_{1,\text{rev}} p_2(x_2, x_3) + k_{2,\text{forw}} p_1(x_1, x_2)}$$

If we use QSSA (and using p_1, p_2 as before), we need to solve for x_2 from

$$\begin{aligned} & x_2^2 \left(\frac{k_{2,\text{forw}}}{K_m^{I,2}} + \frac{k_{1,\text{rev}}}{K_m^{II,2}} \right) \\ & + x_2 \left(k_{2,\text{forw}} + k_{1,\text{forw}} + \frac{k_{2,\text{forw}} x_1}{K_m^{I,1}} - \frac{k_{1,\text{forw}} x_1}{K_m^{II,2}} + \frac{k_{1,\text{rev}} x_3}{K_m^{II,3}} - \frac{k_{2,\text{rev}} x_3}{K_m^{I,2}} \right) \\ & - k_{1,\text{forw}} x_1 \left(1 + \frac{x_3}{K_m^{II,3}} \right) - k_{2,\text{rev}} x_3 \left(1 + \frac{x_1}{K_m^{I,1}} \right) = 0. \end{aligned}$$

Let $x_2 = f(x_1, x_3)$ denote the solution of the above quadratic equation.

QSSA-based reduced model

$$X_1 \rightleftharpoons X_3$$

The reduced dynamics is given by

$$\dot{x}_1 = -\frac{k_{1,\text{forw}}k_{2,\text{forw}}x_1 - k_{1,\text{rev}}k_{2,\text{rev}}x_3}{k_{2,\text{forw}}p_1(x_1, f(x_1, x_3)) + k_{1,\text{rev}}p_2(f(x_1, x_3), x_3)}$$

$$\dot{x}_3 = \frac{k_{1,\text{forw}}k_{2,\text{forw}}x_1 - k_{1,\text{rev}}k_{2,\text{rev}}x_3}{k_{2,\text{forw}}p_1(x_1, f(x_1, x_3)) + k_{1,\text{rev}}p_2(f(x_1, x_3), x_3)}.$$

QSSA

$$X_1 + X_2 \rightleftharpoons 2X_3 \rightleftharpoons X_4 + X_5$$

For this example, the computation of QSSA for removing X_3 leads to a more complicated expression.

Our approach is based on the application of Kron reduction/Schur complement applied to the Laplacian-based description as before.

Recall on the Network Dynamics of CRN

The network dynamics of chemical reactions with general kinetics and with external fluxes can be written as

$$\dot{x} = -ZL(x)\mathrm{Exp}\left(Z^T \mathrm{Ln}\,(x)\right) + Zv_b(x),$$

where $v_b(x)$ is the vector of external flux.

Consider a partition of $Z, v_b(x)$ and $L(x)$ according to the complexes that will be retained or removed:

$$L(x) = \begin{bmatrix} L_{11}(x) & L_{12}(x) \\ L_{21}(x) & L_{22}(x) \end{bmatrix} \qquad Z = \begin{bmatrix} Z_1 & Z_2 \end{bmatrix} \qquad v_b(x) = \begin{bmatrix} v_{b1}(x) \\ v_{b2}(x) \end{bmatrix}.$$

Partitioning the dynamics

$$\dot{x} = -\begin{bmatrix} Z_1 & Z_2 \end{bmatrix} \left(\begin{bmatrix} L_{11}(x) & L_{12}(x) \\ L_{21}(x) & L_{22}(x) \end{bmatrix} \begin{bmatrix} \mathrm{Exp}\left(Z_1^T \mathrm{Ln}\,(x)\right) \\ \mathrm{Exp}\left(Z_2^T \mathrm{Ln}\,(x)\right) \end{bmatrix} + \begin{bmatrix} v_{b1}(x) \\ v_{b2}(x) \end{bmatrix} \right),$$

Consider now the auxiliary system

$$\begin{bmatrix} \dot{y}_1 \\ \dot{y}_2 \end{bmatrix} = -\begin{bmatrix} L_{11}(x) & L_{12}(x) \\ L_{21}(x) & L_{22}(x) \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \end{bmatrix} + \begin{bmatrix} v_{b1}(x) \\ v_{b2}(x) \end{bmatrix}.$$

Imposing complex-balanced condition on the complexes Y_2 (i.e., $\dot{y}_2 = 0$) leads to

$$w_2 = -L_{22}(x)^{-1}(v_{b2}(x) - L_{21}(x)w_1).$$

Substituting it to the first equation gives

$$\dot{y}_1 = -\hat{L}(x)w_1 + \begin{bmatrix} I & -L_{12}(x)L_{22}^{-1} \end{bmatrix} v_b(x)$$

where $\hat{L}(x) = L_{11}(x) - L_{12}(x)L_{22}(x)^{-1}L_{21}(x)$ is the Schur complement of $L(x)$ with respect to the removed complexes.

Our reduced model

$$\dot{x} = -Z_1\hat{L}(x)\mathrm{Exp}\left(Z_1^T\mathrm{Ln}(x)\right) + Z_1 \underbrace{\begin{bmatrix} I & -L_{12}(x)L_{22}^{-1} \end{bmatrix} v_b(x)}_{\hat{v}_b(x)}$$

Here $\hat{v}_b(x)$ becomes a modified external flux and $\hat{L}(x)$ is the new Laplacian. The above equation describes again a proper chemical reaction network.

Proposition 1 (SR, vdS & BJ, 2014)

Consider a weighted Laplacian $L(x)$ as before. The Schur complement of $L(x)$ with respect to any cluster of complexes satisfies the following properties

1. *All diagonal elements of $\hat{L}(x)$ are positive and off-diagonal elements are non-negative for all x in positive orthant*
2. $\mathbb{1}^T \hat{L}(x) = 0$

This proposition shows that the resulting reduced model is again a CRN with general kinetics described by

$$\dot{x} = -Z_1 \hat{L}(x) \mathrm{Exp}\left(Z_1^T \mathrm{Ln}(x)\right) + Z_1 \hat{v}_b(x)$$

Stability property is preserved (since it is again a chemical reaction network as before). The original set of equilibrium points $\mathcal{E}$ is a subset of the set of equilibrium points of reduced model $\hat{\mathcal{E}}$ (SR, vdS & BJ, 2013).

Recall an Example

$$X_1 \underset{k_{1,\text{rev}}}{\overset{k_{1,\text{forw}}}{\rightleftharpoons}} X_2 \underset{k_{2,\text{rev}}}{\overset{k_{2,\text{forw}}}{\rightleftharpoons}} X_3$$

The reduced CRN

$$X_1 \rightleftharpoons X_3$$

$$\dot{x}_1 = -\frac{k_{1,\text{forw}}k_{2,\text{forw}}x_1 - k_{1,\text{rev}}k_{2,\text{rev}}x_3}{1 + \frac{x_1}{K_m^{\text{red},1}} + \frac{x_3}{K_m^{\text{red},3}}}$$

$$\dot{x}_3 = \frac{k_{1,\text{forw}}k_{2,\text{forw}}x_1 - k_{1,\text{rev}}k_{2,\text{rev}}x_3}{1 + \frac{x_1}{K_m^{\text{red},1}} + \frac{x_3}{K_m^{\text{red},3}}}$$

where $K_m^{\text{red},1}, K_m^{\text{red},3}$ are linearly dependent on all K_ms and $k_{\text{forw}}, k_{\text{rev}}$ from the original network.

Again Another Example

$$X_1 + X_2 \rightleftharpoons 2X_3 \rightleftharpoons X_4 + X_5$$

The reduced CRN

$$X_1 + X_2 \rightleftharpoons X_4 + X_5$$

$$v(x) = \begin{bmatrix} \frac{k_{1,\text{forw}} k_{2,\text{forw}} x_1 x_2}{p(x)} \\ \frac{k_{1,\text{rev}} k_{2,\text{rev}} x_4 x_5}{p(x)} \end{bmatrix},$$

where

$$p(x) = 1 + \frac{x_1}{K_m^{\text{red},1}} + \frac{x_2}{K_m^{\text{red},2}} + \frac{x_4}{K_m^{\text{red},4}} + \frac{x_5}{K_m^{\text{red},5}} + \frac{x_1 x_2}{K_m^{\text{red},12}} + \frac{x_4 x_5}{K_m^{\text{red},45}}$$

with K_m^{red}s are again linearly dependent on all K_ms and $k_{\text{forw}}, k_{\text{rev}}$ from the original network.

Systematic Model Reduction

Model reduction of high-order model can be done systematically.

$$\text{Full Network:} \qquad \mathcal{C}_1 \rightleftharpoons \mathcal{C}_2 \rightleftharpoons \mathcal{C}_3 \rightleftharpoons \cdots\cdots \rightleftharpoons \mathcal{C}_n$$

$$\text{Reduced Network:} \qquad \mathcal{C}_1 \rightleftharpoons \mathcal{C}_3 \rightleftharpoons \cdots\cdots \rightleftharpoons \mathcal{C}_n$$

Systematic Model Reduction

Model reduction of high-order model can be done systematically.

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$$\text{Reduced Network:} \qquad \mathcal{C}_1 \rightleftharpoons \mathcal{C}_3 \rightleftharpoons \cdots\cdots \rightleftharpoons \mathcal{C}_n$$

$$\text{Full Network 1:} \qquad \cdots \quad \mathcal{C}_1 \rightleftharpoons \mathcal{C}_2 \rightarrow \mathcal{C}_3 \quad \cdots$$

$$\text{Reduced Network 1:} \qquad \cdots \quad \mathcal{C}_1 \rightarrow \mathcal{C}_3 \quad \cdots$$

Systematic Model Reduction

Model reduction of high-order model can be done systematically.

Full Network: $\mathcal{C}_1 \rightleftharpoons \mathcal{C}_2 \rightleftharpoons \mathcal{C}_3 \rightleftharpoons \cdots\cdots \rightleftharpoons \mathcal{C}_n$

Reduced Network: $\mathcal{C}_1 \rightleftharpoons \mathcal{C}_3 \rightleftharpoons \cdots\cdots \rightleftharpoons \mathcal{C}_n$

Full Network 1: $\cdots \quad \mathcal{C}_1 \rightleftharpoons \mathcal{C}_2 \to \mathcal{C}_3 \quad \cdots$

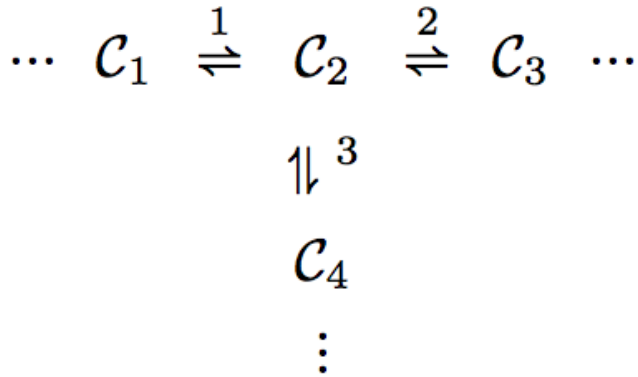
Reduced Network 1: $\cdots \quad \mathcal{C}_1 \to \mathcal{C}_3 \quad \cdots$

Full Network 2: $\cdots \quad \mathcal{C}_1 \to \mathcal{C}_2 \rightleftharpoons \mathcal{C}_3 \quad \cdots$

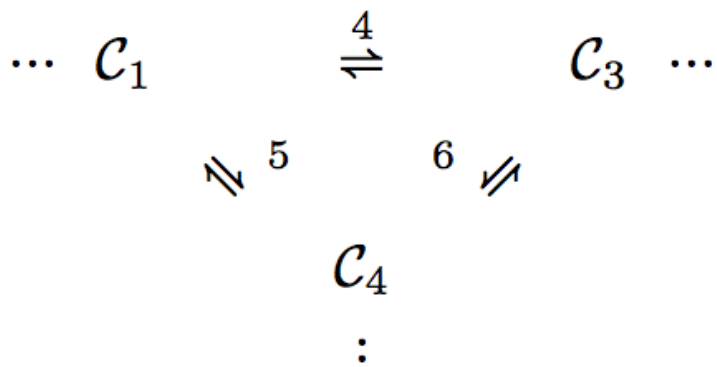
Reduced Network 2: $\cdots \quad \mathcal{C}_1 \to \mathcal{C}_3 \quad \cdots$

Systematic Model Reduction

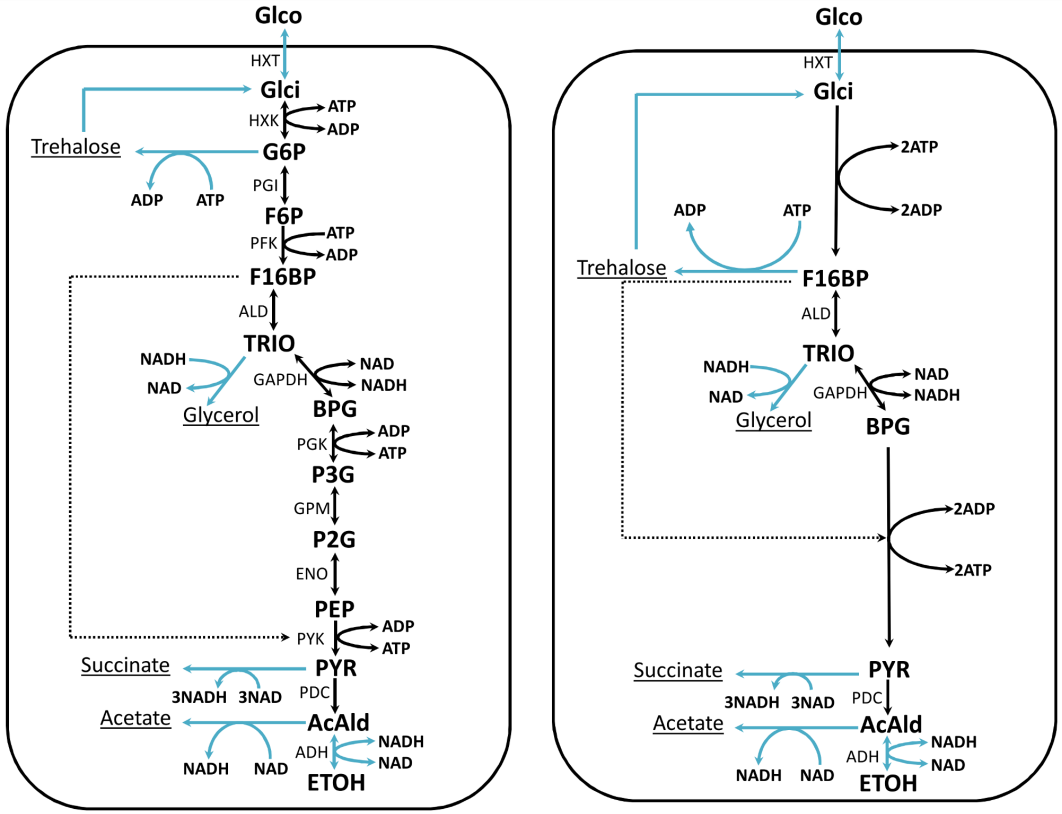
Full Network



Reduced Network



Simplifying Glycolysis Model

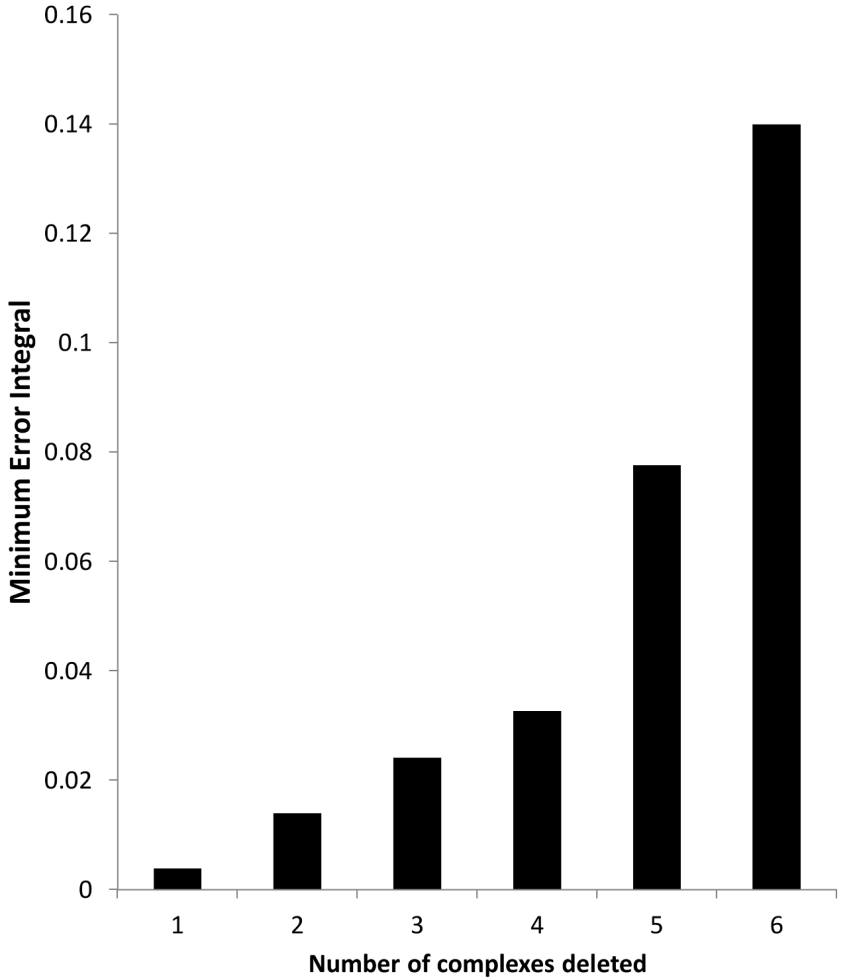


The following normalized error integral is used to evaluate the quality

$$I = \sum_{i \in \mathcal{M}} \frac{1}{T \dim(\mathcal{M})} \left\| 1 - \frac{x_{i,\text{red}}}{x_{i,\text{full}}} \right\|_{L^1} \quad \text{or} \quad I = \sum_{i \in \mathcal{M}} \frac{1}{T \dim(\mathcal{M})} \frac{\| x_{i,\text{full}} - x_{i,\text{red}} \|_{L^1}}{\| x_{i,\text{full}} \|_{L^1}}$$

with T be the time interval of interest and L^1-norm is taken over $[0, T]$.

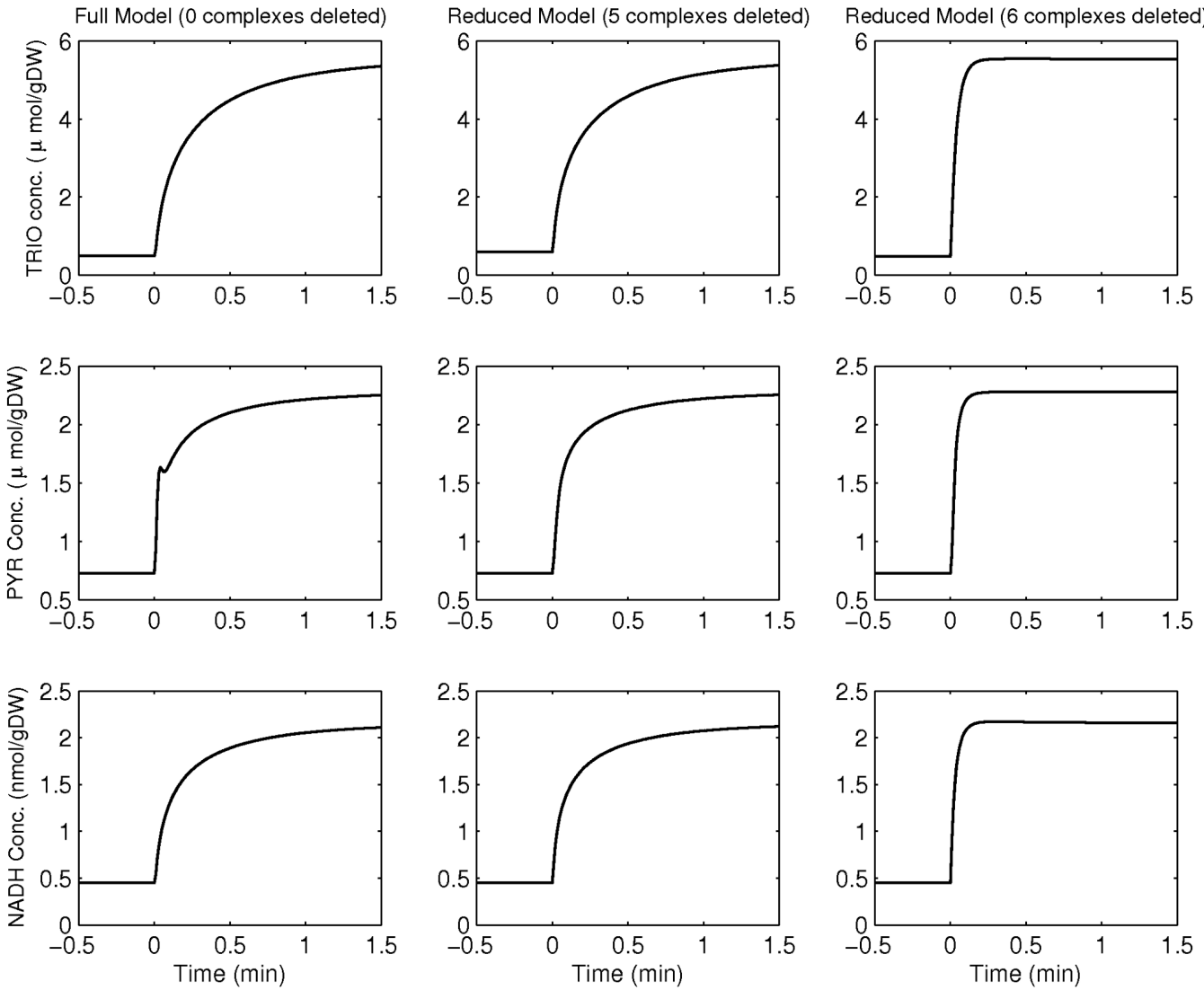
Simplifying Glycolysis Model



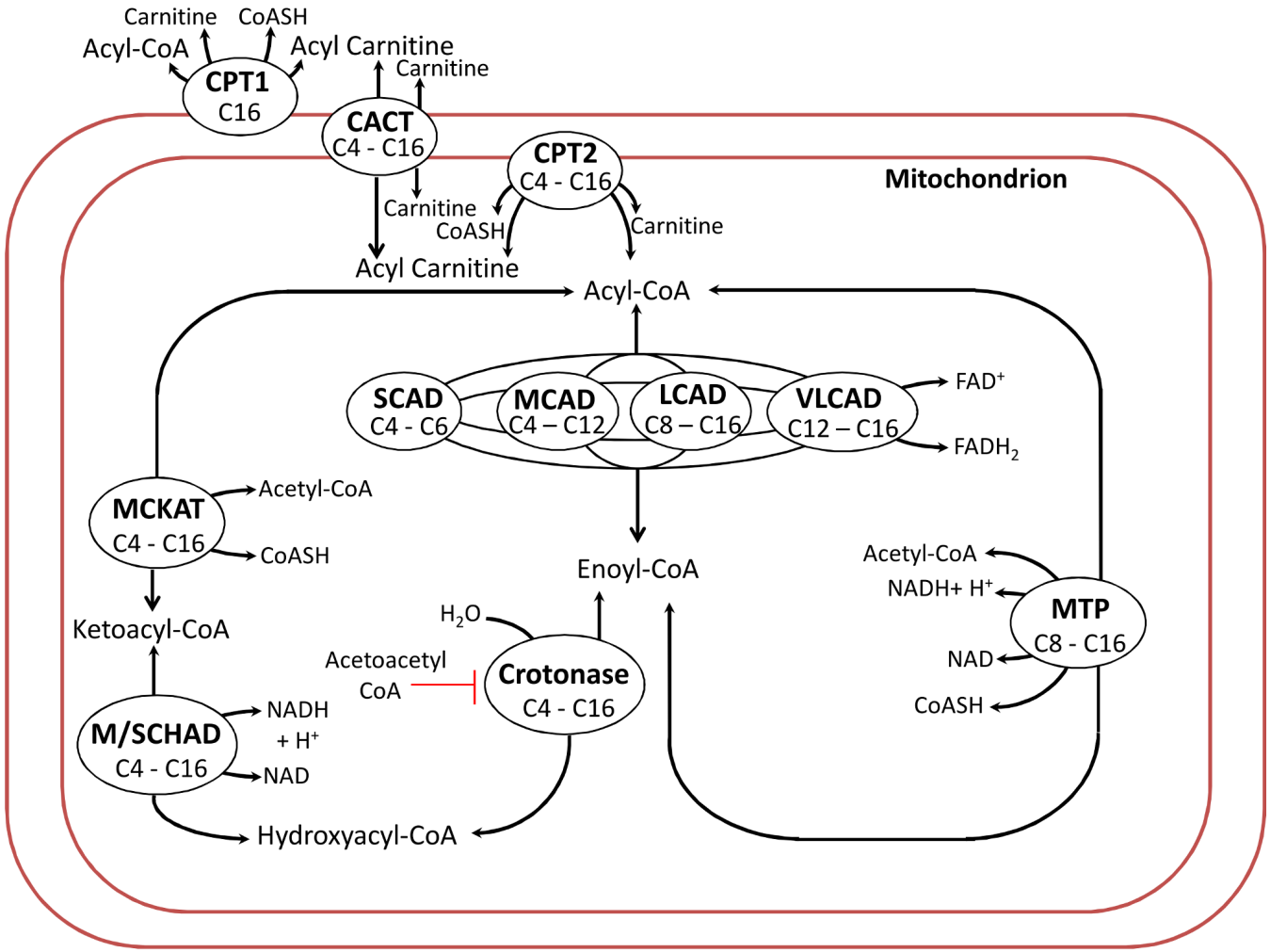
Order of deletion	Complex deleted	Time to converge (min)
1	F6P	0.70
2	G6P	0.65
3	P2G	0.69
4	P3G	1.72
5	PEP	0.07
6	F16BP	1.71

Error integral vs number of complexes deleted from the glycolysis model.

Simplifying Glycolysis Model

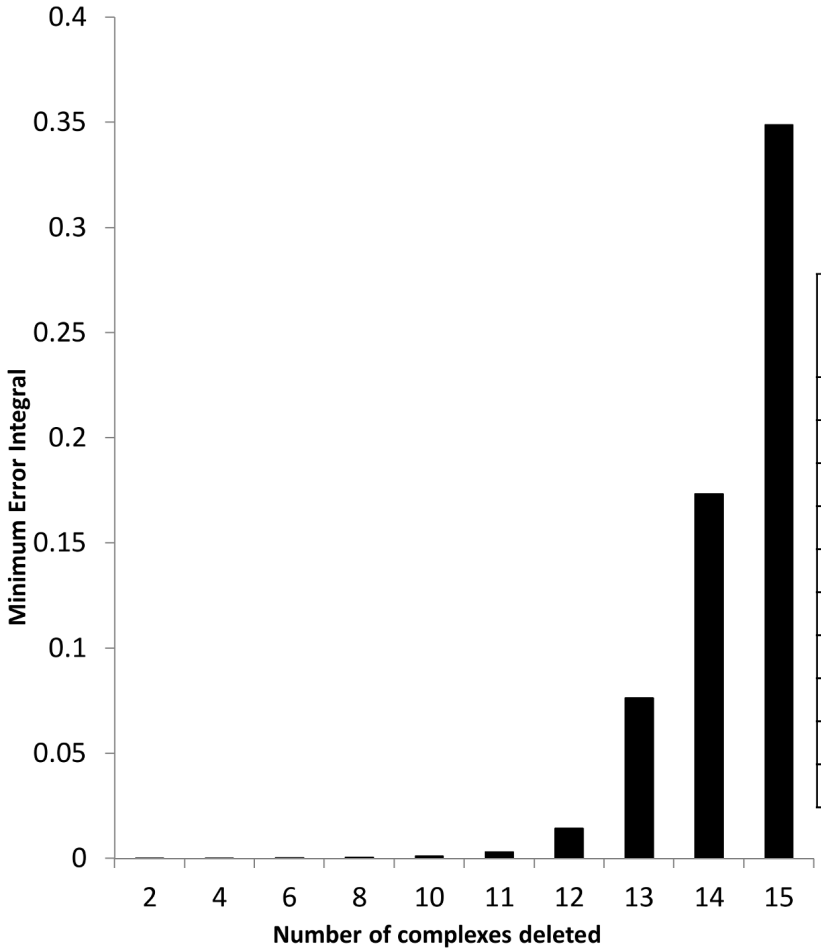


Simplifying Fatty-acid Oxidation Model



The full model

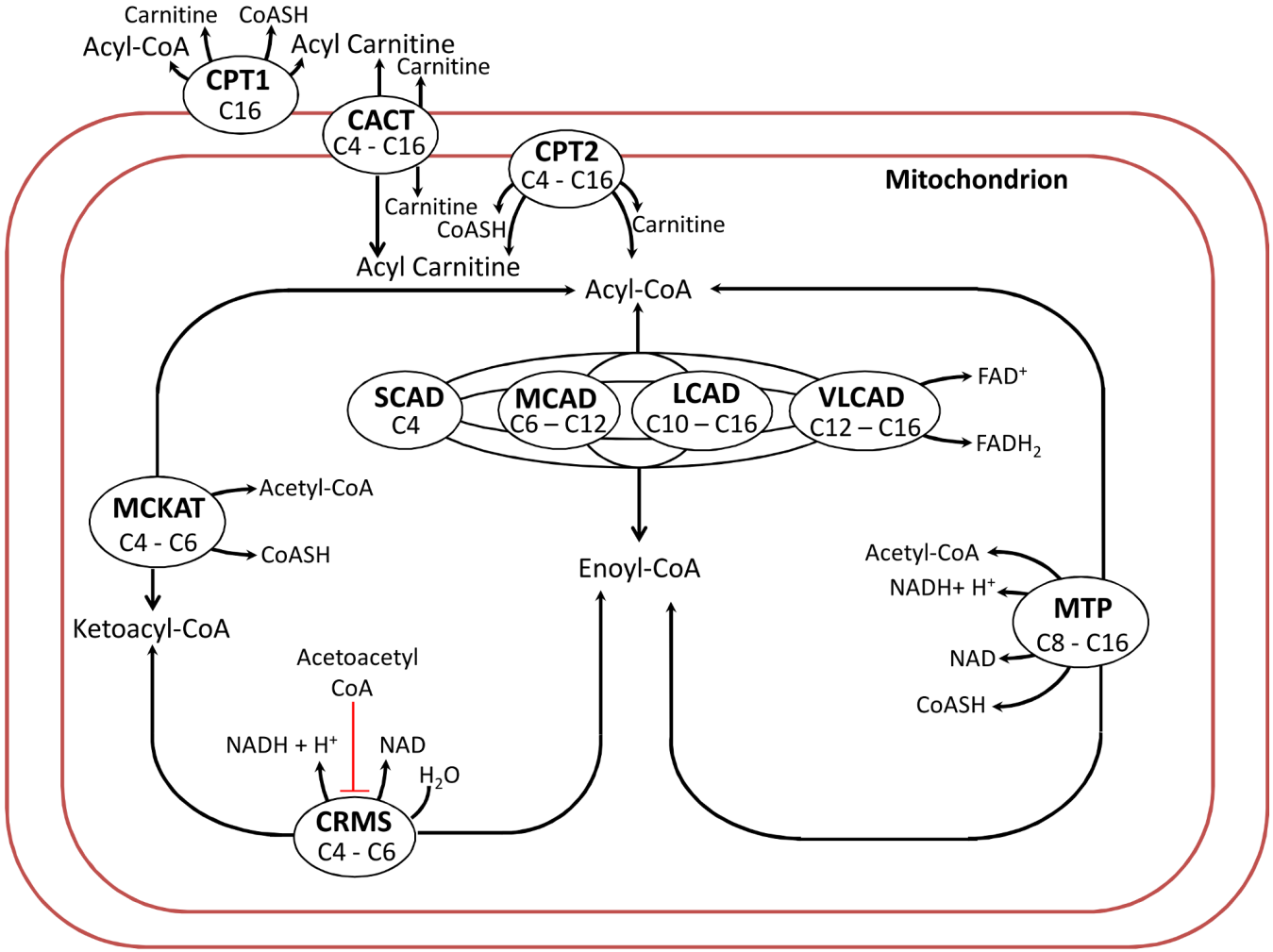
Simplifying Fatty-acid Oxidation Model



Order of deletion	Deleted complexes
2	C16HydroxyacylCoA, C16KetoacylCoA
4	C14HydroxyacylCoA, C14KetoacylCoA
6	C12HydroxyacylCoA, C12KetoacylCoA
8	C10HydroxyacylCoA , C10KetoacylCoA
10	C8HydroxyacylCoA, C8KetoacylCoA
11	C6HydroxyacylCoA
12	C4HydroxyacylCoA
13	C8AcylCoA
14	C6AcylCoA
15	C10AcylCoA

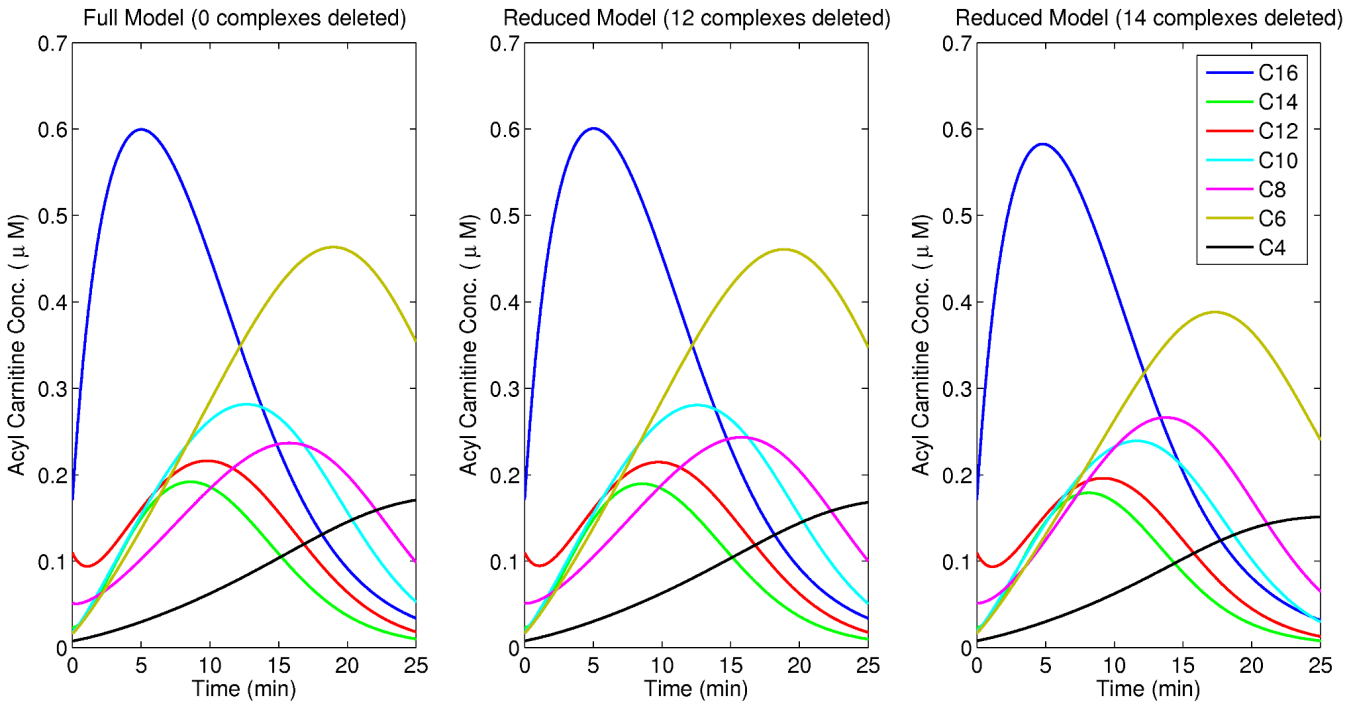
Error integral vs number of complexes deleted from the fatty-acid model.

Simplifying Fatty-acid Oxidation Model



The reduced model

Simplifying Fatty-acid Oxidation Model



The dynamic behaviour of the full model in comparison to the reduced ones.

Preserving multi-stability in sporulation initiation in Bacillus Subtilis

B. Subtilis can undergo sporulation to survive harsh condition where the resulting spore can last for years.
This process should be initiated under right (environmental) conditions.
In (Jabbari, 2010), a model with four external signals is proposed, they are:

- Population size
- DNA condition
- Competency
- Nutrient level

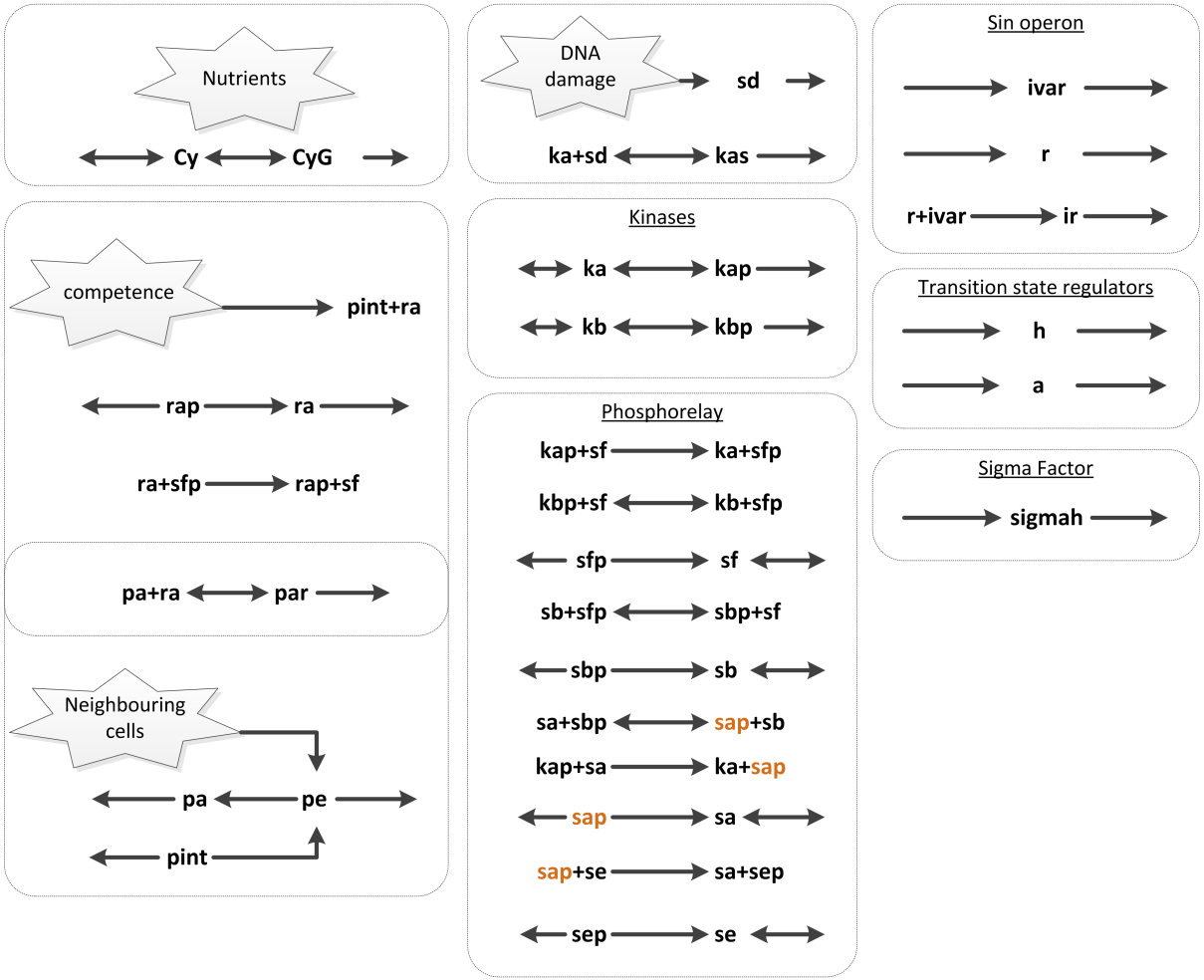
Depending on the initial conditions of these signals, sporulation phosphorelay will respond to them.

Preserving multi-stability in sporulation initiation in Bacillus Subtilis

State	Population size	DNA	Competent	Nutrients	Sporulation desirable?
1	Small	Healthy	No	High	No
2	Small	Healthy	No	Low	Yes
3	Small	Healthy	Yes	High	No
4	Small	Healthy	Yes	Low	No
5	Small	Damaged	No	High	No
6	Small	Damaged	No	Low	No
7	Small	Damaged	Yes	High	No
8	Small	Damaged	Yes	Low	No
9	Large	Healthy	No	High	No
10	Large	Healthy	No	Low	Yes
11	Large	Healthy	Yes	High	No
12	Large	Healthy	Yes	Low	Yes
13	Large	Damaged	No	High	No
14	Large	Damaged	No	Low	No
15	Large	Damaged	Yes	High	No
16	Large	Damaged	Yes	Low	No

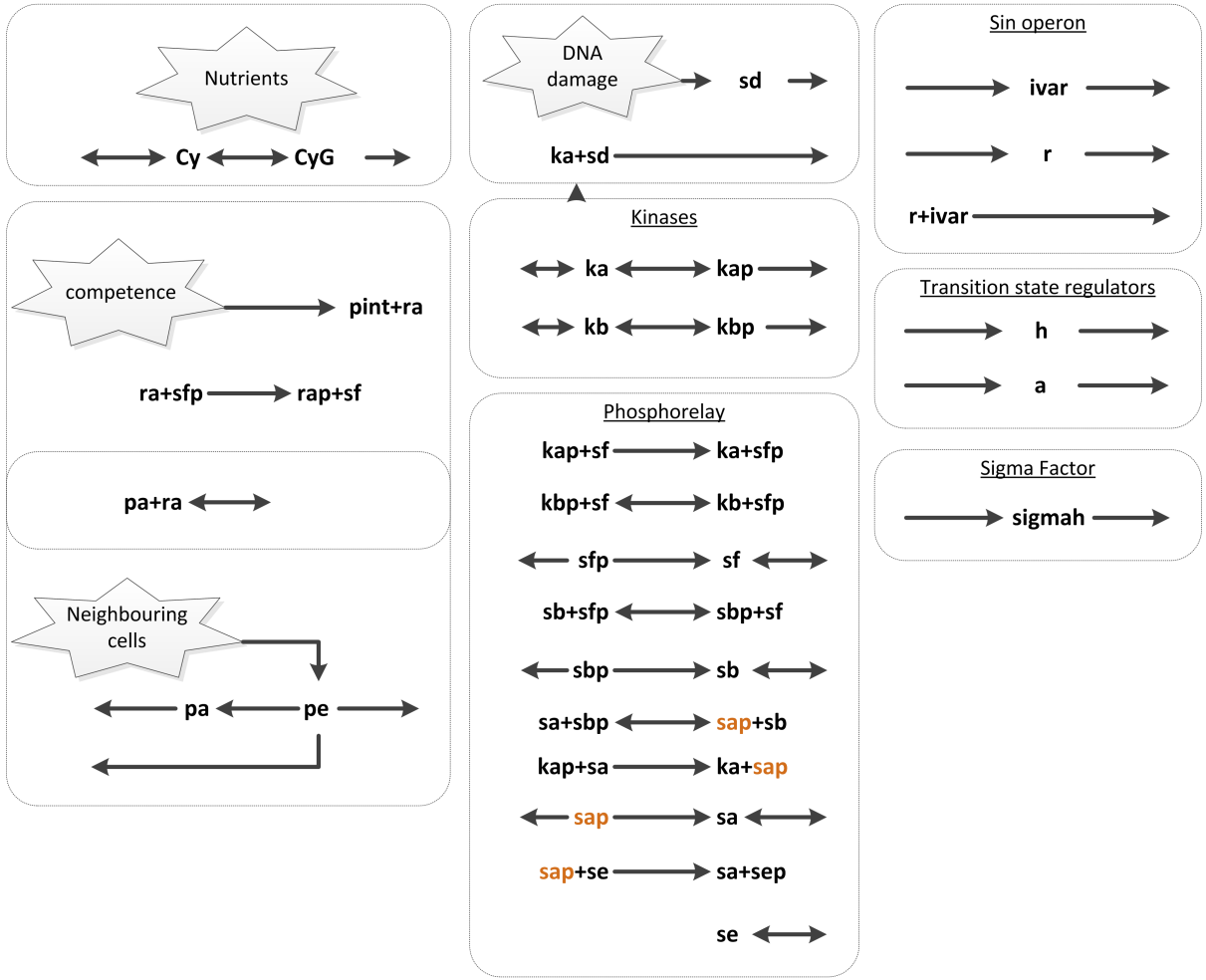
Possible combinations of the 4 different signals on the initiation of sporulation.

Preserving multi-stability in sporulation initiation in Bacillus Subtilis



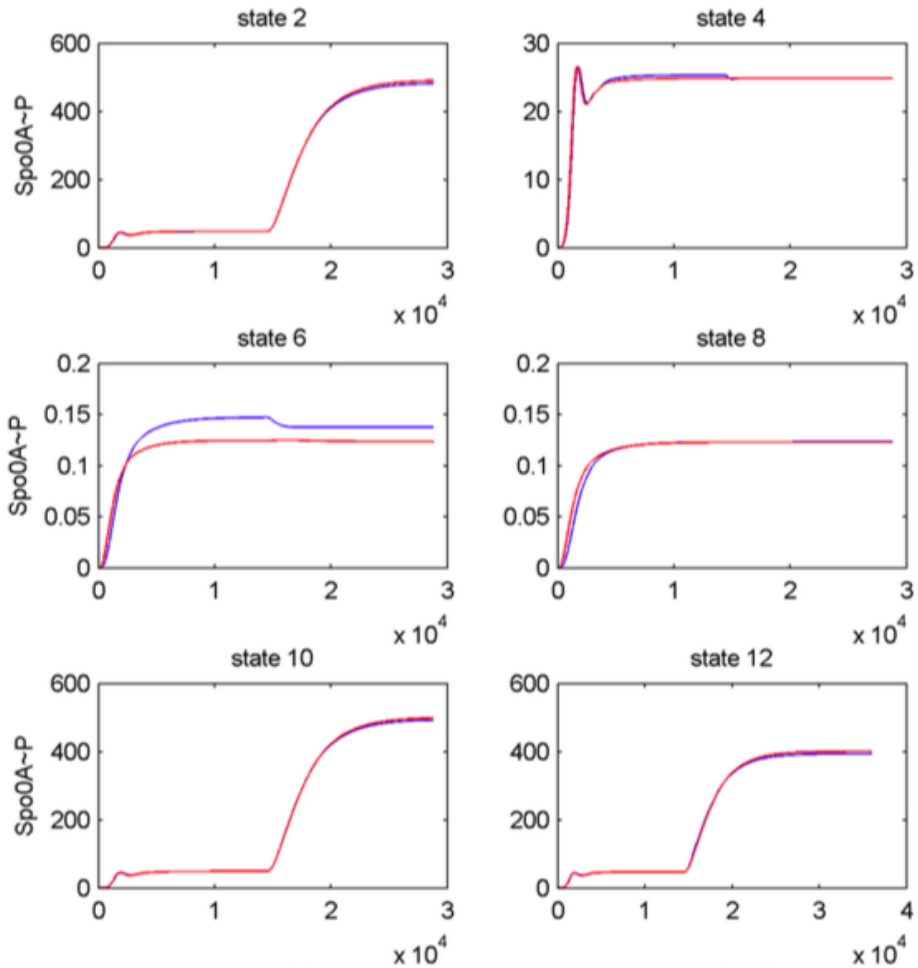
Full model

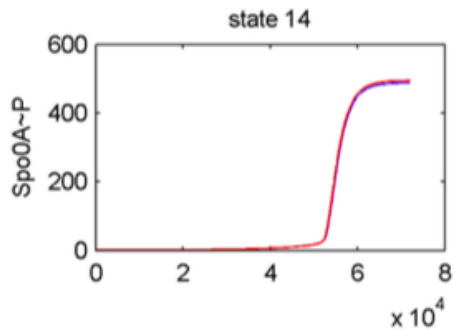
Preserving multi-stability in sporulation initiation in Bacillus Subtilis

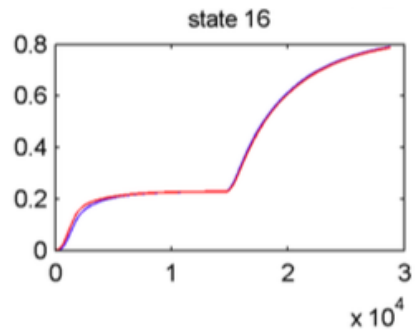


Reduced model

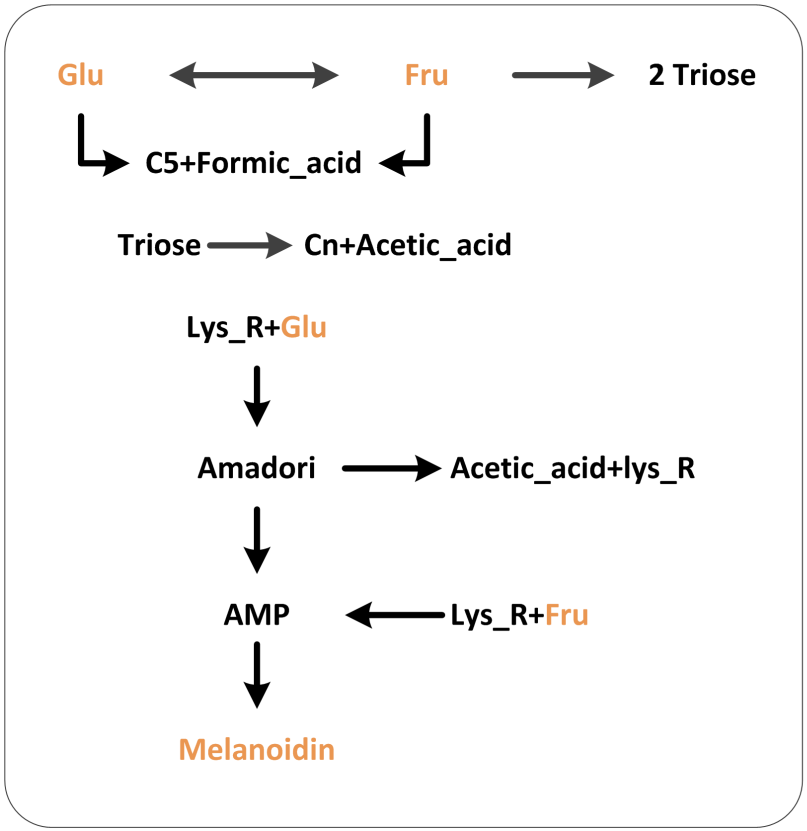
Preserving multi-stability in sporulation initiation in Bacillus Subtilis

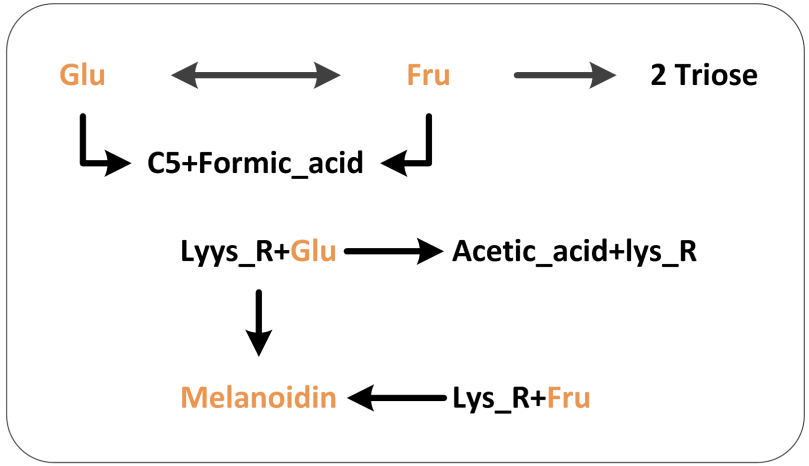






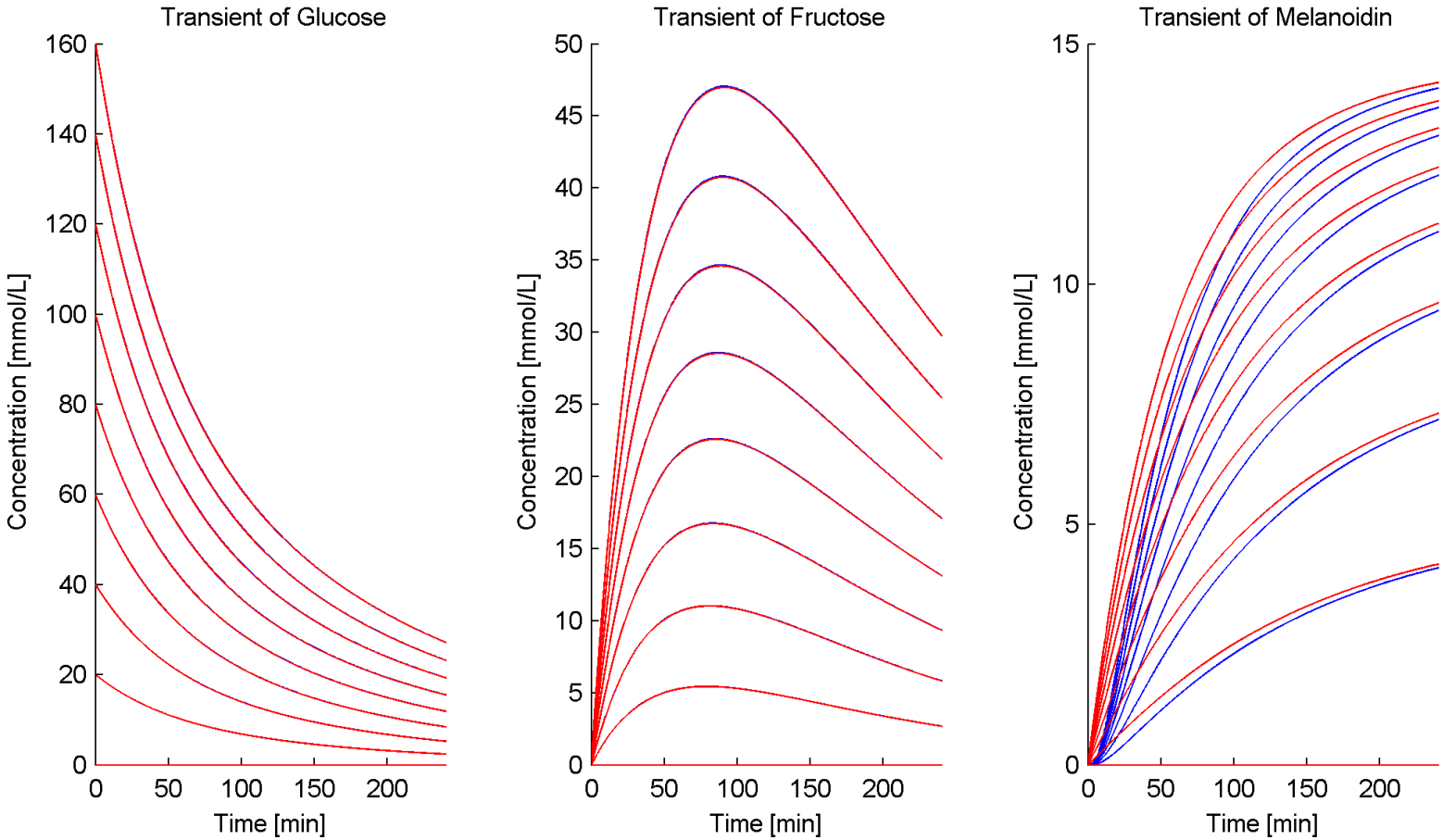
Maillard reaction





Full and reduced model of Maillard model

Robustness to different initial condition



Transient behaviour of the full and reduced model under different initial condition of glucose and fructose

Conclusions and Future Works

- We have presented a model reduction approach for CRN which preserve the structure and stability properties.
- The efficacy of the approach has been shown in several examples (i.e., curated models from BioModels).

Acknowledgments

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- Shodhan Rao (Ghent University Global Campus)
- Ward Sikkema

Model-order reduction (literature overview (1980s - onwards))

For a high-order linear system

$$\dot{x}(t) = Ax(t) + Bu(t)$$
$$y(t) = Cx(t) + Du(t)$$

where $x(t) \in \mathbb{R}^n, u(t) \in \mathbb{R}^m, y(t) \in \mathbb{R}^p$ are state, input and output variables.

Model-order reduction problem

Find a low-order system

$$\dot{\hat{x}}(t) = A_r\hat{x}(t) + B_r u(t)$$
$$\hat{y}(t) = C_r\hat{x}(t) + Du(t)$$

with $\hat{x}(t) \in \mathbb{R}^N$, $N \ll n$, such that the input-output behaviour $u \mapsto \hat{y}$ is close to $u \mapsto y$ and the approximation error $x - \hat{x}$ is small.

How close is close?

The closeness of input-output behaviour and nicety of systems' matrices can be in terms of

- Systems' properties: controllability & observability (balanced truncation), passivity-preserving method, moment-matching method.
- Trajectories for a given class of input signals: POD-based

Commonality: Find $V, W \in \mathbb{R}^{n \times N}$ with $W^*V = I_N$ so that VW^* is a projection matrix.
Define $\hat{x} = W^*x$ (in which case, $x \approx V\hat{x}$) and we have

$$\dot{\hat{x}}(t) = W^*AV\hat{x}(t) + W^*Bu(t)$$
$$\hat{y}(t) = CV\hat{x}(t) + Du(t).$$

Projection approach for nonlinear systems

For a non-linear system

$$\dot{x}(t) = f(x(t), u(t))$$
$$y(t) = h(x(t), u(t))$$

As before, we can find $V, W \in \mathbb{R}^{n \times N}$ with $W^*V = I_N$ and the reduced-order model through projection is given by

$$\dot{\hat{x}}(t) = W^* f(V\hat{x}(t), u(t))$$
$$\hat{y}(t) = h(V\hat{x}(t), u(t)).$$

Nonlinear mapping has also been explored in literature. In (Scherpen, 1993), generalization of balanced trunction for nonlinear systems is given. The moment-matching approach for linear systems has been generalized to nonlinear ones in (Astolfi, 2010).

Applicability for general chemical reaction networks

- These systems are nonlinear systems with a "nice" certain structure.
- The linear projection approach can lead to state variables that do not have chemical interpretation.
- Linearization combined with linear projection provides good approximation only locally (Hardin, 2012).
- The generalization as in (Scherpen, 1993) & (Astolfi, 2010) requires the solvability of nonlinear PDEs.
- Quasi Steady State Approximation (QSSA) is one of popular techniques. It is effective for small network (e.g., less than three reactions). We will review this again later.
- There are many other heuristic approaches: (Bhattacharjee etal, 2003), (Dano etal, 2006), (Schmidt etal, 2008), (Apri etal, 2012). These results focuses mainly on model reduction for simulation purposes, i.e., preservation of systems properties is NOT considered.