On the network thermodynamics of mass action chemical reaction networks

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Aim:

• To provide a, thermodynamically consistent, compact formulation of the dynamics of large-scale, isothermal, chemical reaction networks, emphasizing the network (graph) structure.
• The obtained formulation can bee seen as a full network version of the description by Oster & Perelson of mass action kinetics, and has a direct port-Hamiltonian interpretation.
• The formulation allows for a very easy and clear analysis of equilibria and stability.
• Main open problem: steady-state analysis of networks with inflows and outflows.
Outline

1 Chemical reaction networks

2 Reaction-diffusion networks

3 Conclusions and outlook
Consider a chemical reaction network with \( m \) chemical species, among which \( r \) chemical reactions take place.
The dynamics of the vector of concentrations \( \mathbf{x} \in \mathbb{R}^m_+ \) is has the form

\[ \dot{\mathbf{x}} = S \mathbf{v}(\mathbf{x}), \]

where the stoichiometric matrix \( S \) is an \( m \times r \) matrix consisting of (positive and negative) integer elements, and \( \mathbf{v}(\mathbf{x}) \in \mathbb{R}^r \) is the vector of reaction rates. E.g., for

\[ X_1 + 2X_2 \rightleftharpoons X_3 \rightleftharpoons 2X_1 + X_2 \]

\[
S = \begin{bmatrix}
-1 & 2 \\
-2 & 1 \\
1 & -1
\end{bmatrix}
\]
The complexes are the left- and right-hand sides of the reactions. The expression of the $c$ complexes in terms of the $m$ chemical species is defined by an $m \times c$ matrix $Z$: E.g., for $X_1 + 2X_2 \rightleftharpoons X_3 \rightleftharpoons 2X_1 + X_2$

$$Z = \begin{bmatrix}
1 & 0 & 2 \\
2 & 0 & 1 \\
0 & 1 & 0 
\end{bmatrix}$$

The complexes define the vertices of a directed graph, with edges corresponding to the reactions with incidence matrix $B$. In the example

$$B = \begin{bmatrix}
-1 & 0 \\
1 & -1 \\
0 & 1 
\end{bmatrix}$$

Basic relation

$$S = ZB$$
The basic model for specifying the reaction rates $v(x)$ is mass action kinetics. For the single reaction

$$X_1 + 2X_2 \rightleftharpoons X_3,$$

the mass action kinetics reaction rate is the combination of the forward reaction $X_1 + X_2 \rightarrow X_3$ with forward reaction rate $v^+(x_1, x_2) = k^+ x_1 x_2^2$ and the reverse reaction $X_1 + X_2 \leftarrow X_3$, with reaction rate $v^-(x_3) = k^- x_3$. The net reaction rate is

$$v(x_1, x_2, x_3) = k^+ x_1 x_2^2 - k^- x_3$$

Note that the powers of $x_1, x_2, x_3$ appear as coefficients of the matrix $Z$. 
In general, the mass action reaction rate of the \( j \)-th reaction, from a substrate complex \( S_j \) to a product complex \( P_j \), is given as

\[
v_j(x) = k_j^+ \prod_{i=1}^{m} x_i^{Z_{iS_j}} - k_j^- \prod_{i=1}^{m} x_i^{Z_{iP_j}}
\]

where \( Z_{i\rho} \) is the \((i, \rho)\)-th element of the complex stoichiometric matrix \( Z \).

**Crucial observation:** this can be also written as

\[
v_j(x) = k_j^+ \exp \left( Z_{S_j}^T \ln(x) \right) - k_j^- \exp \left( Z_{P_j}^T \ln(x) \right)
\]

where \( Z_{S_j} \) and \( Z_{P_j} \) are the columns of \( Z \) corresponding to the substrate and the product complex of the \( j \)-th reaction.

(The mapping \( \ln : \mathbb{R}^c_+ \to \mathbb{R}^c \) is the element-wise natural logarithm.)
Definition

A vector of concentrations $x^* \in \mathbb{R}_+^m$ is a **thermodynamic equilibrium** if

$$v(x^*) = 0$$

Basic paradigm from thermodynamics:

every well-defined chemical reaction network has a thermodynamic equilibrium

This corresponds to **microscopic reversibility**.

*Under which conditions on the reaction constants does there exist a thermodynamic equilibrium?*
The $j$-th reaction from substrate $S_j$ to product $P_j$

$$v_j(x) = k_j^+ \exp (Z_{S_j}^T \ln(x)) - k_j^- \exp (Z_{P_j}^T \ln(x))$$

satisfies $v_j(x^*) = 0$ if and only if (detailed balance equations)

$$k_j^+ \exp (Z_{S_j}^T \ln(x^*)) = k_j^- \exp (Z_{P_j}^T \ln(x^*)),$$  \quad  j = 1, \cdots, r

Defining the equilibrium constants $K_j^{eq}$ as $K_j^{eq} := \frac{k_j^+}{k_j^-}$ this is equivalent to

$$K_j^{eq} = \exp \left( Z_{P_j}^T \ln(x^*) - Z_{S_j}^T \ln(x^*) \right), \quad j = 1, \cdots, r$$

or equivalently

$$K^{eq} = \text{Exp} \left( B^T Z^T \ln(x^*) \right) = \text{Exp} \left( S^T \ln(x^*) \right),$$

where $\text{Exp} : \mathbb{R}^c \rightarrow \mathbb{R}^c_+$ is the element-wise exponential function.
**Proposition**

There exists a thermodynamic equilibrium $x^* \in \mathbb{R}_+^m$ if and only if $k_j^+ > 0, k_j^- > 0$, for all $j = 1, \ldots, r$, and furthermore

$$\ln(K_{eq}) \in \text{im } S^T$$

Non-trivial condition if $\ker S \neq \{0\}$ (e.g., if there are cycles in the graph). Furthermore the set of all thermodynamic equilibria $\mathcal{E}$ is equal to

$$\mathcal{E} = \{x^{**} \in \mathbb{R}_+^m \mid S^T\ln(x^{**}) = S^T\ln(x^*)\}$$

Assuming the existence of a thermodynamic equilibrium we obtain:
Define the conductance of reaction $j$ as

$$
\kappa_j(x^*) := k_j^+ \exp \left(Z_{S_j}^T \ln(x^*) \right) = k_j^- \exp \left(Z_{P_j}^T \ln(x^*) \right), \quad j = 1, \cdots, r
$$

Then

$$
v_j(x) = \kappa_j(x^*) \left[ \exp \left(Z_{S_j}^T \ln \left( \frac{x}{x^*} \right) \right) - \exp \left(Z_{P_j}^T \ln \left( \frac{x}{x^*} \right) \right) \right],
$$

where the quotient vector $\frac{x}{z} \in \mathbb{R}^m$ is defined element-wise. With

$$
\mathcal{K}(x^*) := \text{diag}(\kappa_1(x^*), \cdots, \kappa_r(x^*))
$$

it follows that

$$
v(x) = -\mathcal{K}(x^*) B^T \text{Exp} \left(Z^T \ln \left( \frac{x}{x^*} \right) \right),
$$

and thus the dynamics is

$$
\dot{x} = -ZB\mathcal{K}(x^*) B^T \text{Exp} \left(Z^T \ln \left( \frac{x}{x^*} \right) \right)
$$

Can be extended to Michaelis-Menten kinetics.
Although $\mathcal{K}(x^*)$ is dependent on the choice of the thermodynamic equilibrium $x^*$, this dependence is minor: $\mathcal{K}(x^*)$ is up to a positive multiplicative factor independent of the choice of $x^*$.

$B\mathcal{K}(x^*)B^T$ defines a Laplacian matrix for the graph of complexes, similar to ”consensus” (agreement) algorithms.

We expect convergence of $\exp\left(Z^T \ln \left( \frac{x(t)}{x^*} \right) \right)$ to a multiple of $1$, or equivalently, convergence of the vector of complex thermodynamical affinities

$$\gamma(t) := Z^T \ln \left( \frac{x(t)}{x^*} \right)$$

to a multiple of $1$. 

Chemical reaction networks

Thermodynamic interpretation

Up to the constant $RT$ (with $T$ temperature) we may interpret

$$\mu(x) := \ln \left( \frac{x}{x^*} \right)$$

as the vector of chemical potentials. Define the Gibbs’ free energy (corresponding to $x^*$) as

$$G(x) = x^T \ln \left( \frac{x}{x^*} \right) + (x^* - x)^T 1_m,$$

Then $\frac{\partial G}{\partial x}(x) = \ln \left( \frac{x}{x^*} \right) = \mu(x)$ and thus

$$\dot{x} = -ZBKC(x^*)B^T \exp \left( Z^T \frac{\partial G}{\partial x}(x) \right)$$
For an ideal dilute solution the standard definition of the chemical potential \( \mu_i \) of species \( X_i \) with mole number \( n_i \) is

\[
\mu_i(x_i) = \mu_i^o(T, p) + RT \ln\left(\frac{x_i}{x_\Sigma}\right),
\]

with \( \mu_i^o \) the standard potential (depending on temperature \( T \) and pressure \( p \)), and \( x_\Sigma \) the total molar density.

Define the vector \( C \) of capacities with \( i \)-th component

\[
C_i := x_\Sigma \exp\left(\frac{-\mu_i^o}{RT}\right), \quad i = 1, \ldots, m
\]

Using the inverse relation \( \mu_i^o = -\ln\left(\frac{C_i}{x_\Sigma}\right) \) it follows that

\[
\mu_i = -\ln\left(\frac{C_i}{x_\Sigma}\right) + \ln\left(\frac{x_i}{x_\Sigma}\right) = RT \ln\left(\frac{x_i}{C_i}\right)
\]

and thus \( C \) defines a 'canonical' thermodynamical equilibrium.
Port-Hamiltonian formulation

Fundamental property: Let $\gamma(x) := Z^T \mu(x)$ be the vector of complex thermodynamical affinities. Then

$$\gamma^T B K(x^*) B^T \text{Exp}(\gamma) \geq 0, \quad \forall \gamma$$

with equality if and only if

$$B^T \gamma = 0$$

This implies that mass action kinetics chemical reaction networks are port-Hamiltonian. They arise from

$$\dot{x} = Z f_r$$

$$e_r = Z^T \frac{\partial G}{\partial x}(x)$$

together with the nonlinear resistive relation

$$f_r = -B K(x^*) B^T \text{Exp}(e_r), \quad e_r^T f_r \leq 0$$
Chemical reaction networks

Equilibria and stability

The Gibbs’ free energy $G$ satisfies

$$G(x^*) = 0, \quad G(x) > 0, \quad \forall x \neq x^*,$$

$$\dot{G}(x) = -\frac{\partial^T G}{\partial x}(x)ZB\kappa(x^*)B^T\text{Exp}\left(Z^T\frac{\partial G}{\partial x}(x)\right) \leq 0$$

while $\dot{G}(x) = 0$ if and only if $x \in \mathcal{E}$.

Theorem

Consider a balanced mass action kinetics chemical reaction network with thermodynamic equilibrium $x^*$. Then all positive equilibria are thermodynamic equilibria, and for every initial condition $x_0 \in \mathbb{R}_+^m$ there exists a unique thermodynamic equilibrium $x_\infty$ such that

$$\lim_{t \to \infty} x(t) = x_\infty$$

\(^a\)If the network does not have accumulation points at the boundary of $\mathbb{R}_+^m$. 

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Generalized gradient system formulation

By the mean value theorem there exists $\sigma_k \in (\gamma_i, \gamma_j)$ such that
\[
\exp(\gamma_j) - \exp(\gamma_i) = \exp(\sigma_k)(\gamma_j - \gamma_i)
\]
Doing this for every edge one thus rewrites $B^T\text{Exp}(\gamma)$ as
\[
B^T\text{Exp}(\gamma(x)) = \Delta B^T \gamma(x),
\]
with $\Delta$ the diagonal matrix with positive diagonal elements $\exp(\sigma_k)$, $k = 1, \ldots, r$. Thus we obtain the generalized gradient system
\[
\dot{x} = -ZB\mathcal{K}\Delta B^T Z^T \frac{\partial G}{\partial x}(x)
\]
with (pseudo-) Riemannian metric given by the inverse (if it exists) of the positive semi-definite matrix
\[
\mathcal{M} := ZB\mathcal{K}\Delta B^T Z^T
\]
Inflows and outflows

Open balanced chemical reaction networks are given by

\[
\dot{x} = -ZBK(x^*)B^T \exp \left( Z^T \ln \left( \frac{x}{x^*} \right) \right) + S_b v_b,
\]
\[
\mu_b = S_b^T \ln \left( \frac{x}{x^*} \right),
\]

which define a port-Hamiltonian input-state-output system with inputs \( v_b \) (boundary fluxes) and outputs \( \mu_b \) (boundary potentials). It follows that

\[
\frac{d}{dt} G(x) = -\gamma^T(x) BK(x^*) B^T \exp(\gamma(x)) + \mu_b^T v_b
\]

thus showing the passivity property

\[
\frac{d}{dt} G \leq \mu_b^T v_b
\]

Existence and stability of steady states for non-zero \( v_b \) is much less clear!
Outline

1. Chemical reaction networks
2. Reaction-diffusion networks
3. Conclusions and outlook
Consider a spatial domain $\mathcal{Z} \subset \mathbb{R}^3$ with boundary $\partial \mathcal{Z}$. Define

$$\mathcal{F}_x = \mathcal{E}_x = C^\infty(\mathcal{Z}, \mathbb{R})$$
$$\mathcal{F}_d = \mathcal{E}_d = C^\infty(\mathcal{Z}, \mathbb{R}^3)$$
$$\mathcal{F}_b = \mathcal{E}_b = C^\infty(\partial \mathcal{Z}, \mathbb{R})$$

Then $\mathcal{D} \subset \mathcal{F}_x \times \mathcal{F}_d \times \mathcal{F}_b \times \mathcal{E}_x \times \mathcal{E}_d \times \mathcal{E}_b$ defined as

$$\mathcal{D} := \{(f_x, f_d, f_b, e_x, e_d, e_b) \in \mathcal{F} \times \mathcal{E} \mid f_x = \text{div} e_d, \ f_d = \text{grad} e_x \text{ on } \mathcal{Z}, \ e_b = \text{tr} e_x, \ f_b = \nu \cdot \text{tr} e_d \text{ on } \partial \mathcal{Z}\}$$

is a **Stokes-Dirac structure**. In particular we have power-conservation

$$\int_{\mathcal{Z}} f_x(z)e_x(z)dz + \int_{\mathcal{Z}} f_d^T(z)e_d(z)dz + \int_{\partial\mathcal{Z}} f_b(z)e_b(z)dz = 0$$
Constitutive relations

Let $x(z, t) \in \mathcal{R}$ be a distributed variable. Consider an energy density $H$, and total energy $\mathcal{H}$

$$H(x(z, t)) \in \mathbb{R}, \quad \mathcal{H}(x(\cdot, t)) = \int_{\mathcal{Z}} H(x(z, t)) dz \in \mathbb{R},$$

and terminate the $f_x, e_x$ port of $\mathcal{D}$ by

$$f_x(z, t) = -\frac{\partial}{\partial t} x(z, t), \quad e_x(z, t) = \frac{d}{dx} H(x(z, t))$$

Terminate the $f_d, e_d$ port of $\mathcal{D}$ by the resistive relation

$$e_d = -\mathcal{R}_d(x) f_d$$

with the $3 \times 3$-matrix $\mathcal{R}_d(x) = \mathcal{R}_d^T(x) \geq 0$, ensuring that

$$e_d^T f_d \leq 0$$
Substitution yields

\[ \frac{\partial}{\partial t} x(z, t) = -f_x = -\text{div } e_d = \text{div } \left[ R_d(x) f_d \right] = \text{div } \left[ R_d(x) \text{ grad } e_x \right] = \text{div } \left[ R_d(x) \text{ grad } \frac{d}{dx} H(x(z, t)) \right] \]

and, since \( \text{grad } \frac{d}{dx} H(x(z, t)) = \frac{d^2 H}{dx^2}(x(z, t)) \text{ grad } x(z, t), \)

\[ \frac{\partial}{\partial t} x(z, t) = \text{div } \left[ R_d(x(z, t)) \frac{d^2 H}{dx^2}(x(z, t)) \text{ grad } x(z, t) \right] \]

which is in the general form of a scalar diffusion system

\[ \frac{\partial}{\partial t} x(z, t) = \text{div } \left[ D(x(z, t)) \text{ grad } x(z, t) \right] \]
Port-Hamiltonian reaction-diffusion networks

We will merge the two port-Hamiltonian descriptions. Let

\[ x_1(z, t), \cdots, x_m(z, t) \]

denote the concentrations of the chemical species, which now are spatially distributed.

Define the combined Dirac structure

\[ D := \{(f_x, f_d, f_b, f_r, \nu, e_d, e_b, e_r, \mu_b) \in F \times E | \]

\[ f_x = \text{Div } e_d - Z f_r - S_b \nu_b, \quad f_d = \text{Grad } e_x \text{ on } Z, \quad e_r = Z^T e_x \]

\[ e_b = \text{tr } e_x, \quad f_b = \nu \cdot \text{tr } e_d \text{ on } \partial Z, \quad \mu_b = S_b^T e_x \}

and consider as Hamiltonian the Gibbs’ free energy

\[ G(x) = x^T \ln \left( \frac{x}{x^*} \right) + (x^* - x)^T 1_m \]

and retain the same resistive relations:

\[ e_d = -R_d(x)f_d, \quad f_r = -BK(x^*)B^T \text{Exp}(e_r) \]
Figure: The port-Hamiltonian formulation of a mass-action kinetics reaction-diffusion system on a spatial domain $M$ with chemical in/outflows $u = v_b$ and outputs $y = \mu_b$. 
Outline

1 Chemical reaction networks

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Conclusions and outlook

Chemical reaction networks:
- Structured description of chemical reaction networks: dynamics is similar to mass-damper systems with nonlinear dampers.
- Framework can be extended from mass action kinetics to Michaelis-Menten kinetics (enzymatic reactions).
- Although stability picture for closed ($v_b = 0$) chemical reaction networks is clear, the steady-state analysis for open reaction networks is not well understood (due to the nonlinear resistive relation).

Reaction-diffusion systems:
- Port-Hamiltonian formulation provides a good starting point for analysis: to be worked out.
- Structure-preserving discretization leads to port-Hamiltonian compartmental models: see the thesis of Marko Seslija.

To be done: analysis and control of reaction-diffusion systems.

Papers can be found on my homepage: [www.math.rug.nl/~arjan](http://www.math.rug.nl/~arjan)
The 21st International Symposium on Mathematical Theory of Networks and Systems will be hosted by the University of Groningen, the Netherlands. [WWW.RUG.NL/MTNS2014]