

Chemical reaction networks: a system-theorist's point of view

Arjan van der Schaft

Dept. of Mathematics, University of Groningen

*Joint work with Bernhard Maschke, Université Claude Bernard,
Lyon*

Outline

1. Balance laws and the stoichiometric matrix
2. Basic analysis tools for the stoichiometric matrix
3. Steady-state analysis
4. Rate equations, thermodynamics, and port-Hamiltonian systems
5. Reaction-diffusion systems

The basic balance laws

Chemical reactions satisfy the balance laws

$$\dot{x} = Sv$$

where

$$x = (x_1, x_2, \dots, x_n)^T$$

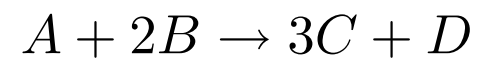
denotes the vector of **concentrations** of n chemical species, and

$$v = (v_1, v_2, \dots, v_m)^T$$

denotes the vector of **fluxes** corresponding to m chemical reactions within these species.

The $n \times m$ matrix S is called the **stoichiometric matrix**.

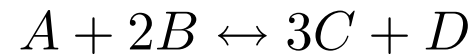
For example, the chemical reaction



will have the stoichiometric matrix

$$S = \begin{bmatrix} -1 \\ -2 \\ 3 \\ 1 \end{bmatrix}$$

In the first part of the talk the **reversible** reaction



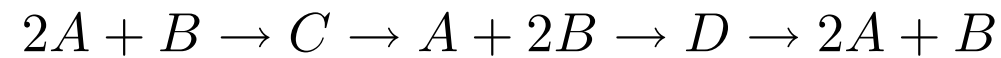
will be described by the stoichiometric matrix

$$S = \begin{bmatrix} -1 & 1 \\ -2 & 2 \\ 3 & -3 \\ 1 & -1 \end{bmatrix}$$

This convention implies that the **fluxes** are all non-negative:

$$v_i \geq 0, \quad i = 1, \dots, m$$

The sequence of chemical reactions



has the stoichiometric matrix

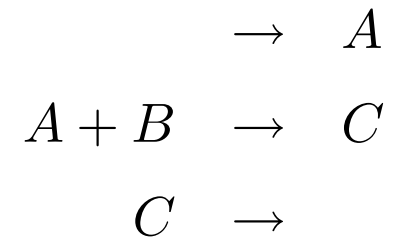
$$S = \begin{bmatrix} -2 & 1 & -1 & 2 \\ -1 & 2 & -2 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

In many cases of interest the total vector of fluxes can be split into a vector of **internal fluxes** v^i and a vector of **exchange fluxes** v^e , in which case the stoichiometric matrix S is correspondingly split as

$$S = \begin{bmatrix} S^i & S^e \end{bmatrix}$$

The vector v^e will be the vector of fluxes entering or leaving the reactor vessel, or cell.

Consider the reactions



having stoichiometric matrix

$$S = \left[\begin{array}{c|cc} -1 & 1 & 0 \\ -1 & 0 & 0 \\ 1 & 0 & -1 \end{array} \right]$$

Intermezzo

- The stoichiometric matrix S does **not** directly define a graph.
- A graph **can** be defined by equating the complete reactant, as well as the complete product, of any reaction with a vertex of the graph (see e.g. the work of Feinberg and co-workers).
- Chemical reaction networks can be also directly modelled as a **Petri-net** with the chemical species corresponding to the places, and the reactions corresponding to the transitions.

The balance laws

$$\dot{x} = Sv$$

do **not** yet determine the dynamics of the chemical reaction network.

Complete dynamics in terms of the concentration vector x is given once the *internal* fluxes v^i are specified as a function of x (the **reaction rates**):

$$v^i = v^i(x)$$

Then we obtain the set of ODEs

$$\dot{x} = S^i v^i(x) + S^e v^e$$

One of the problems in metabolic networks is that the rate functions are often unknown and difficult to identify.

Basic properties: conserved quantities

The **left-kernel** of the stoichiometric matrix determines the **conserved quantities**. Indeed, if k is a n -dimensional row-vector satisfying

$$kS = 0$$

then

$$\frac{d}{dt}(kx) = kSv = 0,$$

irrespective of the precise form of the fluxes. Thus kx is a conserved quantity of the chemical reaction network.

Note that the existence of such a k will imply that the system is **not completely controllable**.

Linear combinations of concentration variables are sometimes called metabolic **pools**.

A more general version is obtained for k satisfying

$$kS^i = 0$$

in which case

$$\frac{d}{dt}(kx) = k \begin{bmatrix} S^i & S^e \end{bmatrix} v = kS^e v^e,$$

expressing that the evolution of kx only depends on the exchange fluxes v^e .

Alternatively, if k is satisfying

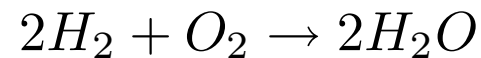
$$kS^e = 0$$

then

$$\frac{d}{dt}(kx) = k \begin{bmatrix} S^i & S^e \end{bmatrix} v = kS^i v^i,$$

expressing that the evolution of kx is independent of the exchange fluxes v^e .

One special type of conserved quantities is specified by the expression of the chemical species involved in the reactions in chemical elements. For example, in the chemical reaction



the number of oxygen and hydrogen elements is preserved. This is reflected by the fact that

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

Steady-state analysis

Steady-state solutions are solution for which $\dot{x} = 0$, or equivalently the **flux balance** equation

$$Sv = 0$$

The steady-state solutions v_{ss} are thus determined by the **right-kernel** of S . This is primarily of interest whenever there are exchange fluxes v^e .

Steady-state analysis is quite similar to steady-state analysis of a linear system

$$\dot{x} = Ax + Bu$$

which leads to the consideration of

$$Ax_{ss} + Bu_{ss} = 0$$

which usually can be solved as

$$x_{ss} = -A^{-1}Bu_{ss}$$

together with an input-output relation (the **static gain**)

$$y_{ss} = Cx_{ss} = -CA^{-1}Bu_{ss}$$

Somewhat similarly, the equation

$$\begin{bmatrix} S^i & S^e \end{bmatrix} v_{ss} = 0$$

can be solved for part of the vector of steady-state fluxes v_{ss} as function of the complementary part.

Singular value decomposition

One way of trying to get a grip on the most important reactions in a chemical reaction network is by applying a **singular value decomposition** to the stoichiometric matrix S :

$$S = U\Sigma V^T$$

where U is an $n \times n$ orthonormal matrix, and V is an $m \times m$ orthonormal matrix, while Σ consists of a diagonal matrix and a zero block, whose diagonal elements are ordered in a decreasing sequence, and are called the singular values $\sigma_1, \sigma_2, \dots, \sigma_r$.

Then the balance laws are written as

$$\dot{x} = U\Sigma V^T v$$

and defining $x = Uz$ and $v = Vw$ this can be rewritten as

$$\dot{z} = \Sigma w$$

Drawback is that in general the transformed concentration vector z and the transformed flux vector w does not have any physical interpretation. Furthermore, the positivity conditions on the flux vector v are lost in general.

Convex analysis

Consider the flux balance equation

$$Sv = 0$$

together with the positivity conditions (componentwise)

$$v \geq 0$$

Together they describe a polyhedron (the **flux cone**) in \mathbb{R}^m .

This may be sharpened by imposing maximality conditions on the flux components:

$$0 \leq v_i \leq v_{i,\max}, \quad i = 1, \dots, m$$

This flux cone has **extremal rays** $p_j, j = 1, \dots, l$, and thus any steady-state flux vector can be represented as

$$v_{ss} = \alpha_1 p_1 + \dots + \alpha_l p_l, \quad 0 \leq \alpha_i \leq \alpha_{i,\max}, i = 1, \dots, m$$

The vectors p_1, \dots, p_l are called the **extreme pathways**.
(Sometimes also equivalently, -as long as the exchange fluxes are non-negative-, called **elementary modes**.)

The pathway matrix

$$P = \begin{bmatrix} p_1 & p_2 & \cdots & p_l \end{bmatrix}$$

provides much structural information about the chemical reaction network.

One can also look for **optimal** flux vectors in the flux cone (where *optimal* is defined with respect to some, say, linear function of the fluxes).

Metabolic control analysis

Suppose the internal fluxes v are expressed as functions of the concentration vector x and parameters p :

$$v^i = v^i(x, p)$$

then the steady-state solutions are determined as

$$S^i v_{ss}^i(x, p) + S^e v_{ss}^e = 0$$

Metabolic flux analysis is concerned with a sensitivity analysis of v_{ss}^i with respect to p (and possibly v_{ss}^e).

Thus it is comparable to shaping the static gain of an input-state-output system.

How to express the rate equations ?

One possibility is **mass action kinetics**.

The reversible reaction



is a combination of the **forward reaction**



with rate equation $r_f = k_f ab$, and the **reverse reaction**

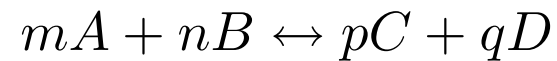


with rate equation $r_r = k_r c$.

The net rate is thus the mass-action kinetics

$$v = r_f - r_r = k_f ab - k_r c$$

More generally, the reversible reaction



has net reaction rate

$$v = k_f a^m b^n - k_r c^p d^q$$

At equilibrium (assuming no exchange fluxes)

$$k_f a_{\text{eq}} b_{\text{eq}} = k_r c_{\text{eq}}$$

The constant

$$K_{\text{eq}} = \frac{c_{\text{eq}}}{a_{\text{eq}} b_{\text{eq}}} = \frac{k_f}{k_r}$$

is called the equilibrium constant.

On the thermodynamical perspective

Gibbs law is expressed as

$$dU = TdS - PdV + \sum \mu_i(n) dn_i$$

with U the total energy, and

$$n = (n_1, n_2, \dots, n_k)$$

the (mole) numbers of chemical species involved in the reactions,
and

$$\mu = (\mu_1, \mu_2, \dots, \mu_k)$$

the chemical potentials of these species.

Typical example of a chemical potential

$$\mu_i = c_i(T, P) + RT \ln \frac{n_i}{V}$$

This also constitutes one of the starting points of port-Hamiltonian systems theory, which starts off with

$$\frac{dH}{dt} = e_R^T f_R + e_P^T f_P$$

where f_R, e_R are the flow and effort variables corresponding to the power-dissipating port, and f_P, e_P are the flow and effort variables corresponding to the external port.

Furthermore, with x being the state variables, and $\nabla H(x)$ the vector of partial derivatives of the Hamiltonian H

$$\frac{dH}{dt} = \nabla H(x) \dot{x}$$

The vectors $e_S = \nabla H(x)$, $f_S = -\dot{x}$ are the flow and effort variables of the port connected to the energy-storing elements.

In fact, in the port-Hamiltonian description all vectors of flow and effort variables

$$f_S, e_S, f_R, e_R, f_P, e_P$$

are related through a **Dirac structure**, which is power-conserving:

$$e_S^T f_S + e_R^T f_R + e_P^T f_P = 0$$

Furthermore, the resistive port is terminated by a resistive relation

$$R(f_R, e_R) = 0, \quad e_R^T f_R \leq 0$$

and the energy-storing port is terminated by

$$f_S = -\dot{x}, \quad e_S = \nabla H(x)$$

Let us for chemical reactions now concentrate on the 'chemical reaction part' of Gibbs law

$$dG = \sum \mu_i(n) dn_i$$

with G the Gibbs free energy.

We would like to express the change in mole numbers \dot{n} (the flow variables) as a function of $\mu(n)$ (the effort variables).

Or better, we want to express the flux variables v as functions of the vector of so-called **chemical affinities**

$$A = S^T \mu$$

(Note that $\mu(n)^T \dot{n} = A^T v$.) This will define the dynamics on \mathbb{R}^m , the space of reaction extents.

In general (far from thermodynamical equilibrium) this is **not** possible, e.g., it is not possible for mass action kinetics.

In case of e.g. mass action kinetics (and some other cases) we can however do the following (see the work of Oster, Perelson and Katchalsky).

Consider the stoichiometric matrix S corresponding to **reversible** reactions.

Write $S = S_P - S_R$, where

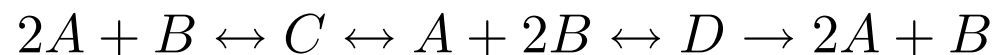
S_R stoichiometric matrix corresponding to reactants

S_P stoichiometric matrix corresponding to products

Example: The stoichiometric matrix

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

corresponding to the reactions



is split into

$$S_R = \begin{bmatrix} 2 & 0 & 1 & 0 \\ 1 & 0 & 2 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \quad S_P = \begin{bmatrix} 0 & 1 & 0 & 2 \\ 0 & 2 & 0 & 1 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}$$

Define the **forward** and **backward** chemical affinities

$$\begin{bmatrix} A_f \\ A_r \end{bmatrix} = \begin{bmatrix} S_R^T \\ S_P^T \end{bmatrix} \mu = \begin{bmatrix} S_R & S_P \end{bmatrix}^T \mu$$

while we rewrite the mass balance equations as

$$\dot{x} = \begin{bmatrix} S_R & S_P \end{bmatrix} \begin{bmatrix} v_f \\ v_r \end{bmatrix}$$

where

$$\begin{bmatrix} v_f \\ v_r \end{bmatrix} = \begin{bmatrix} -I \\ I \end{bmatrix} v$$

The dual relation is

$$A = \begin{bmatrix} -I & I \end{bmatrix} \begin{bmatrix} A_f \\ A_r \end{bmatrix} = -A_f + A_r = S^T \mu$$

Now the net rate equation is

$$v = r_f - r_r$$

where r_f can be expressed as a function of A_f (and involving the coefficients in S_R) and r_r can be expressed as function of A_r (and the coefficients in S_P).

It can then be shown that mass-action kinetics is **passive**, and thus corresponds to a kind of **resistive relation**.

Reaction-diffusion systems

In some cases it is not appropriate to model the chemical reactions with a uniform concentration vector x ; instead one has to take diffusion phenomena into account.

Historical intermezzo at the Centre Interfacultaire Bernoulli:

Daniel Bernoulli, founding father of (among others) fluid dynamics and diffusion models.



Figure 1: Daniel Bernoulli, born in Groningen in 1700

Daniel Bernoulli was born in 1700 in Groningen as son of Johann Bernoulli, professor of mathematics at the University of Groningen. Johann formulated in 1696 the **Brachistochrone problem**, published its solution in 1697 (with competing solutions provided by his elder brother Jakob, l' Hôpital, Newton, Leibniz, ..), and thus became one of the founding fathers of the Calculus of Variations (and of Optimal Control !)

Johann returned with his family in 1705 to Basel, succeeding his brother Jakob.



Figure 2: Johann Bernoulli, professor in Groningen from 1695-1705



Figure 3: Artist's impression of the brachistochrone, erected in 1997 at the Zernike campus of the university of Groningen; celebrating the 300 year anniversary of the brachistochrone problem



Figure 4: The Bernoulli's in carton board; at the entrance of the building housing the mathematics department: the Bernoulli-borg

Consider a diffusion system on a spatial domain $Z \subset \mathbb{R}^3$, with spatially distributed concentration

$$x : Z \rightarrow \mathbb{R}$$

Consider the infinite-dimensional Dirac structure (in vector calculus notation)

$$f_S = \operatorname{div} e - u$$

$$f = \operatorname{grad} e_x$$

$$y = e_S$$

with boundary variables (defined on ∂Z)

$$f_b = e \times n, \quad e_b = e_x$$

It follows that

$$e_S^T f_S + e^T f + y^T u + e_b^T f_b = 0$$

Consider now the constitutive relations for the energy-storage:

$$\dot{x} = -f_S, \quad e_S = \nabla H(x), \quad \mathcal{H} = \int_Z H(x(z)) dz$$

together with the following constitutive relations for power-dissipation

$$e = -R(z)f, \quad R(z) = R^T(z) \geq 0$$

Then we obtain the diffusion system

$$\begin{aligned}\dot{x} &= \operatorname{div} (R(z)\operatorname{grad} \nabla H(x)) + u \\ y &= \nabla H(x)\end{aligned}$$

This describes a diffusion system (in the spatially distributed concentration vector $x(z)$, where u and y are the distributed inputs and outputs).

It defines a distributed-parameter port-Hamiltonian system, satisfying the energy-balance

$$\frac{d}{dt}\mathcal{H} = - \int_Z f^T R(z) f dz + \int_Z y^T u dz + \int_{\partial Z} e_b^T f_b$$

Chemical reactions may now be added through the vector of distributed inputs u , that is, by substituting $u(z) = F(x(z))$, where F represents the chemical reaction rate equations.

Alternative Spatially discretize the reaction-diffusion system in a structure-preserving manner to a finite-dimensional **compartmental** model.

Concluding Remarks

- Going back to the basics of chemical reaction networks for the analysis and control of large-scale networks.
- Relations to port-Hamiltonian systems theory.
- Use of these models for stability and robustness analysis (see e.g. work of Arcak and Sontag).

See www.math.rug.nl/~arjan for further info.

See also the forthcoming book

Modeling and Control of Complex Physical Systems; the Port-Hamiltonian Approach, Geoplex consortium, Springer, 2009.