Self-organization in abstract enzymatic networks

Petr Kůrka
Department of Philosophy of Mathematics and Physics,
Faculty of Mathematics and Physics, Charles University
Malostranské náměstí 25, 118 00 Praha 1, Czechoslovakia

1 Abstract chemical thermodynamics

A system with r chemical reactions and n chemical species is usually given by equations

$$\mu_{j1}^{+}X_1 + \ldots + \mu_{jn}^{+}X_n \underset{k_j^-}{\overset{k_j^+}{\rightleftharpoons}} \mu_{j1}^{-}X_1 + \ldots + \mu_{jn}^{-}X_n \tag{1}$$

where X_i is a symbol for i-th species, $\mu_{ji}^{+}, \mu_{ji}^{-}$ are nonnegative substrate and product stoichiometric coefficients and k_j^+, k_j^- are forward and backwards reaction rate constants. The thermostatics and thermodynamics of such system were treated from a mathematical point of view in [5] or [2]. The approach of Horn & Jackson [5] is based on the notion of complexes, which are left and right hand sides of equations 1. A dynamic system of chemical reactions is called complex balanced if the creation and annihilation rates of each complex are equal. Complex balanced systems are generalizations of detailed balanced systems, in which not only each complex but also each reaction is balanced in forward and backwards reaction rates. Complex balanced systems are considered as models of open systems, in which flows from environment are treated also as chemical reactions. Horn gives in [6] a necessary and sufficient condition for a system to be complex balanced and in [5] it is proved that for complex balanced systems there exist a pseudo-Helmholtz function, which is a Lyapunov function of their dynamics. This approach to open systems naturally fails for far from equilibrium systems which exhibit multiple steady states and oscillating behaviour. It seems therefore more suitable to treat these open systems as detailed balanced and consider the flows from environment explicitly. The condition for a mass action system to be detailed balanced has a particularly simple form and the approach has the additional advantage that the formulas for entropy balance can be derived explicitly as in [1].

In the present section we summarize abstract chemical thermodynamics of detailed balanced mass action systems, derive explicit formulas for (quasi)entropy balance and production and introduce as a new characteristics of such systems their information content, which is the amount of entropy produced, were the systems closed and allowed to attain the equilibrium state.

1.1 Closed systems

Definition. An abstract chemical system with n species and r reactions is given by n-vector α of nonnegative constants, $(r \times n)$-matrices μ^+, μ^- of forward and backwards stoichiometric coefficients, and r-vectors k^+, k^- of positive forward and backwards reaction rates, such that

$$\sum_{i=1}^{n} (\mu_{ji}^- - \mu_{ji}^+) \ln(\alpha_i) = \ln(k_j^+) - \ln(k_j^-) \tag{2}$$

Definition. A mass action system is a dynamical system acting in the space of positive concentration vectors

$$R_+^n = \{X = (X_i)_{i=1,\dots,n} | X_i > 0\}$$

given by differential equations

$$\frac{dX_i}{dt} = \sum_j (R_j^+(X) - R_j^-(X))(\mu_{ji}^- - \mu_{ji}^+) \tag{3}$$

where

$$R_j^+(X) = k_j^+ \prod_{i=1}^{n} X_i^{\mu_{ji}^+}, \; R_j^-(X) = k_j^- \prod_{i=1}^{n} X_i^{\mu_{ji}^-}$$

are the forward and backwards reaction rates.

Definition. We call the function

$$S(X) = \sum_i X_i(1 + \ln \alpha_i - \ln X_i)$$

defined on R_+^n the (pseudo)entropy of the mass action system.

The conditions $k_j^+ > 0, k_j^- > 0$, and 2 imply that the system is reversible and detailed balanced in the sense of Horn & Jackson [5]. In ideal mixtures the negative product of gas constant, temperature, volume and (pseudo)entropy S is the Helmholtz free enrergy. The constants α_i are related to chemical potentials m_j via

$$-\ln \alpha_j = \frac{m_j(T)}{RT} + \ln RT$$

Proposition. Entropy is a Lyapunov function, i.e. $\frac{dS}{dt} \geq 0$.

Proof: $P(X) = \frac{dS(X)}{dt} = \sum_i \frac{\partial S}{\partial X_i} \frac{dX_i}{dt} = \sum_i \ln(\frac{\alpha_i}{X_i}) \sum_j R_j(X)(\mu_{ji}^- - \mu_{ji}^+) =$
$\sum_j R_j(X)(\ln(\frac{k_j^+}{k_j^-}) - \sum_i \ln(X_i)(\mu_{ji}^- - \mu_{ji}^+) = \sum_j R_j(X) F_j(X)$
where we denote

$$R_j(X) = R_j^+(X) - R_j^-(X) = k_j^+ \Pi_{i=1}^n X_i^{\mu_{ji}^+} - k_j^- \Pi_{i=1}^n X_i^{\mu_{ji}^-}$$

$$F_j(X) = F_j^+(X) - F_j^-(X) = \ln(k_j^+ \Pi_{i=1}^n X_i^{\mu_{ji}^+}) - \ln(k_j^- \Pi_{i=1}^n X_i^{\mu_{ji}^-})$$

Thus we obtain entropy production as a sum of products of thermodynamic flows $R_j(X)$ and thermodynamic forces $F_j(X)$ and it is easy to see that $R_j(X) \geq 0$ iff $F_j(X) \geq 0$ so that $P(X) \geq 0$ and $P(X) = 0$ only if all $R_j(X)$ and $F_j(X)$ vanish.

Let us now fix some $n \times p$ matrix β such that $rank(\beta) = p$, $p = n - rank(\mu^- - \mu^+)$ and $(\mu^- - \mu^+) \cdot \beta = 0$. We call β an invariant matrix since

$$\frac{dX}{dt} \cdot \beta = 0$$

and therefore $X \cdot \beta$ is a constant vector. Given a p-vector $C = (C_k)_{k=1,\ldots,p}$, we denote

$$P_C = \{X \in R_+^n | X \cdot \beta = C\}$$

its concentration polyhedron. When $p = 0$, then β and C are null and the concentration polyhedron is the whole R_+^n. On the other hand, P_C may be empty. P_C is an invariant space of dynamic system.

Proposition. If P_C is nonempty, then there exists in P_C unique stationary state $X^{eq} \in P_C$ of the mass action system, which is called equilibrium. All trajectories in P_C converge to X^{eq} and in X^{eq} all rates vanish: $R_j(X^{eq}) = 0$.

Proof: Extend $S(X)$ on the closure $\overline{P_C}$ by $S(X) = 0$ for $X \in \overline{P_C} - P_C$. If $Y \in P_C$ is any point, then it is easy to see that the set

$$\{X \in P_C | S(X) \geq S(Y)\}$$

is bounded. Therefore there exists $X^{eq} \in P_C$ where S attains its maximum value, and since $S(X)$ is increasing in neighbourhood of hyperplanes $X_i = 0$, we have $X^{eq} \in P_C$. Thus X^{eq} is a local maximum of $S(X)$ on P_C and it is the only local maximum. Indeed suppose that $Y \in P_C$ is another local maximum and $S(Y) \leq S(X^{eq})$. Since S is a concave function (the Hessian $\partial^2 S / \partial X_i \partial X_j = -\delta_{ij}/X_i^2$ is negative definite) all points on the line connecting X^{eq} and Y have greater entropy than $S(Y)$, which is a contradiction. Therefore all trajectories in P_C converge to X^{eq}. Since $S(X)$ has a local maximum at X^{eq} , we have for any j

$$0 = \sum_i (\mu_{ji}^- - \mu_{ji}^+) \frac{\partial S}{\partial X_i}(X^{eq}) = \sum_i (\mu_{ji}^- - \mu_{ji}^+) \ln \frac{\alpha_i}{X_i^{eq}} = R_j(X^{eq})$$

i.e. in equilibrium all reaction rates vanish.

Another thermodynamic quantity of interest is information content of a state $X \in R_+^n$ measured as the amount of entropy produced on the path from X to the equilibrium. Given $X \in R_+^n$, we define its constant by $C = X \cdot \beta$ and denote $e \in P_C$ the unique equilibrium state. Then we define

$$I(X) = S(e) - S(X) \geq 0$$

1.2 Open systems

Definition. An open mass action system is a dynamical system given by differential equations

$$\frac{dX_i}{dt} = \sum_i (R_j^+(X) - R_j^-(X))(\mu_{ji}^- - \mu_{ji}^+) + T_i(X)$$

where $T_i(X)$ is the flow from environment. Usually we suppose that some species are kept constant so that

$$T_i(X) = -\sum_i (R_j^+(X) - R_j^-(X))(\mu_{ji}^- - \mu_{ji}^+)$$

for them.

In open systems the entropy change is

$$\frac{dS(X)}{dt} = P(X) + Q(X)$$

where

$$P(X) = \sum_j R_j(X) F_j(X)\ ,\ Q(X) = \sum_i \ln \frac{\alpha_i}{X_i} T_i(X)$$

The entropy change consists of entropy production $P(X)$, which is nonnegative, and entropy flow $Q(X)$ from environment. In (nonequilibrium) stationary states the entropy change is zero, so the entropy production is exactly balanced by entropy flow. The entropy of a stationary state may be lower or higher than that of equilibrium.

1.3 Fast reactions

The analysis of a mass action systems simplifies significantly when some of the reactions proceed much faster than others, so that they attain equilibrium before any slow reactions intervene. The dynamic systems with such a time hiererchy have been treated for example in [3] and [7]. Consider therefore an open system with slow reactions with stoichiometric matrices μ^+, μ^-, slow reactions σ^+, σ^- and slow flows $T_i(X)$. Then we obtain a mass action system

$$\frac{dX_i}{dt} = \sum_j (R_j^+(X) - R_j^-(X))(\mu_{ji}^- - \mu_{ji}^+) + \epsilon \sum_j (R_j^+(X) - R_j^-(X))(\sigma_{ji}^- - \sigma_{ji}^+) + \epsilon T_i(X)$$

with $\epsilon \ll 1$. Let β be an invariant matrix of the fast reactions, so $(\mu^+ - \mu^-)\beta = 0$ and denote

$$Y_r = \sum_i X_i \beta_{ir}$$

the constants of the fast reactions. Then

$$\frac{dY_i}{dt} = \epsilon \sum_j \sum_i (R_j^+(X) - R_j^-(X))(\sigma_{ji}^- - \sigma_{ji}^+)\beta_{ir} + \epsilon \sum_i T_i(X)\beta_{ir}$$

For given vector Y there is by Proposition 1 the unique equilibrium vector X with $X\beta = Y$, therefore we may express in the above equations X as functions of Y and obtain a differential system in Y_i.

2 Abstract biochemical networks

Biochemistry or chemistry of carbon is based on the possibility of forming high energy bonds in chains of molecules. We therefore suppose that the chemical species are chains of smaller elementary units (monomers). The longer molecules act as catalysts and their catalytical activity is determined by their structure. We then obtain an infinite number of chemical species, for which the dynamical system 3 does not straightforwradly apply. We consider therefore finite fragments of this system consisting of species of restricted length. We say that the system is autoorganizing when the its entropy decreases to $-\infty$ with increasing length.

Example: synthesis Consider chemical species $A, B, X_0, X_1, X_2, ...$ with chemical activities

$$\alpha(A) = c^2,\ \alpha(B) = c^{-1},\ \alpha(X_0) = c,\ i \geq 0 \Rightarrow \alpha(X_i) = c^{i-1}\ ,\ \ 0 < c \ll 1$$

Here A is the substrate, B is the waste product, X_0, X_1 are energy rich and energy poor monomers and X_i is a polymer consisting of i monomers X_1. Let us consider chemical reactions

$$A \underset{c}{\overset{1}{\rightleftharpoons}} X_0 \underset{c}{\overset{1}{\rightleftharpoons}} X_1 \underset{c}{\overset{1}{\rightleftharpoons}} B \qquad X_n + X_0 \underset{d}{\overset{d}{\rightleftharpoons}} X_{n+1}$$

Thus substrate A decays to B via X_0 and X_1, but the free energy of X_0 may be also used to form a bond between X_n and X_1. Consider the initial segment of this scheme cosisting of first n polymers $A, B, X_0, X_1, ..., X_n$ and all reactions between them. The only constant of this reaction scheme is

$$W = A + B + X_0 + X_1 + 2X_2 + ... + nX_n$$

We suppose that A, B are kept constant and $A \geq c^3 B$. Suppose further that the bond forming reactions are fast $d \gg 1$, so they attain equilibrium before any slower reactins intervene. Then in fast equilibrium

$$X_n = X_1 X_0^{n-1}$$

and we have two constants

$$Y = X_0 + X_1 + 2X_2 + ... + nX_n \ , \ Z = X_1 + X_2 + ... + X_n$$

The slow dynamics is then

$$\begin{aligned} \dot{Y} &= A - cX_0 + cB - X_1 \\ \dot{Z} &= X_0 - cX_1 + cB - X_1 \end{aligned}$$

In this equation we may express X_0, X_1 as function of Y, Z and obtain a dynamic system in Y, Z. In fact

$$Y = X_0 + X_1(1 + 2X_0 + ... + nX_0^{n-1}) \ , \ Z = X_1(1 + X_0 + ... + X_0^{n-1})$$

This is a one-to-one mapping from

$$\{(X_0, X_1) | X_0, X_1 \geq 0\} \mapsto \{(Y, Z) | Y \geq Z \geq 0\}$$

with Jacobian

$$det \frac{\partial Y, Z}{\partial X_0, X_1} = \begin{vmatrix} 1 + X_1(1 + ... + n(n-1)X_0^{n-2} & , 1 + X_0 + ... + nX_0^{n-1} \\ X_1(1 + ... + (n-1)X_0^{n-2}) & , 1 + X_0 + ... + X_0^{n-1} \end{vmatrix} > 0$$

The only slow stationary state is

$$X_0 = \frac{A + cA + c^2 B}{1 + c + c^2} \ , \ X_1 = \frac{A + cB + c^2 B}{1 + c + c^2}$$

and using the inverse of the above Jacobian, the stability of this state can be proved. When $X_0 > 1$ then the concentration of X_i grows geometrically and the entropy of the stationary state decreases to minus infinity with increasing n. Indeed

$$S_n = A(1 + 2\ln c - \ln A) + B(1 - \ln c - \ln B) + X_0(1 + \ln c - \ln X_0)$$

$$+X_1 \sum_{i=1}^{n} X_0^{i-1}(1 - \ln X_1 + (i-1)\ln \frac{c}{X_0}) \to -\infty \text{ as } n \to \infty$$

However, the entropy flow is bounded

$$P(X_0, X_1) = (A - cX_0)\ln \frac{c^2}{A} + -(X_1 - cB)\ln(cB)$$

Example: destruction

Consider again species $A, B, X_\#, X_1, X_2, ...$ with the same chemical activities and chemical reactions

$$A \underset{c}{\overset{1}{\rightleftharpoons}} X_0 \underset{c}{\overset{1}{\rightleftharpoons}} X_1 \underset{c}{\overset{1}{\rightleftharpoons}} B \qquad X_{n+1} \underset{cd}{\overset{d}{\rightleftharpoons}} X_n + X_1$$

Again $d \gg 1$ so the bond breaking reactions are fast and the only constant is

$$W = A + B + X_0 + X_1 + 2X_2 + ... + nX_n$$

In fast equilibrium

$$X_n = X_1^n c^{n-1}$$

and we have constants

$$X_0 \ , \ Y = X_1 + 2X_2 + ... + nX_n$$

The fast dynamics is

$$\dot{X}_0 = A - cX_0 + cX_1 - X_0$$
$$\dot{Y} = X_0 - cX_1 + cB - X_1$$

with the same stationary state

$$X_0 = \frac{A + cA + c^2B}{1 + c + c^2} \ , \ X_1 = \frac{A + cB + c^2B}{1 + c + c^2}$$

The network is selforganizing if $cX_1 > 1$

Let us combine these two examples. As we suppose $A > c^3B$, we have $X_0 > cX_1$. Therefore the real autoorganizing behaviour is possible for those values of A, B for which

$$cX_1 < 1 < X_0$$

This might be seen from the next example, where we consider several monomers which may combine to form strings.

Example. Consider now polymers consisting of several kind of monomers. We have again a substrate A, waste product B and a finite set of monomeres M. Our further species are strings of elements of M, which form the set M^*. We denote $|u|$ the length of a string $u \in M^*$. The string $0 \in M^*$ of zero length is the common high energy form of the monomeres, the strings $i \in M$ of length 1 are the low energy form of the monomers. The chemical constants are

$$\alpha(A) = c^2,\ \alpha(B) = c^{-1},\ \alpha(X_0) = c,\ u \in M^+ \Rightarrow \alpha(X_u) = c^{|u|-1}\ ,\ \ \text{for}\ \ |u| > 0$$

where $0 < c \ll 1$. We consider following reactions

$$A \underset{cm}{\overset{m}{\rightleftharpoons}} X_0 \qquad X_0 \underset{c}{\overset{1}{\rightleftharpoons}} X_y \underset{c}{\overset{1}{\rightleftharpoons}} B \qquad y \in M$$

$$X_u + X_v + X_0 \underset{d}{\overset{d}{\rightleftharpoons}} X_u + X_{vy} \qquad \text{for}\ \ (u, vy) \in G$$

$$X_u + X_v + X_y \underset{d}{\overset{cd}{\rightleftharpoons}} X_u + X_{vy} \qquad \text{for}\ \ (u, vy) \in D$$

Here $G, D \subseteq M^+ \times MM^+$ are given growth and decay relations. Thus some strings act as enzymes in catalyzing the growth or disolution of other strings. Denote

$$G_0 = \{vy \in MM^+ | \exists u(u, vy) \in G\}\ ,\ D_0 = \{vy \in MM^+ | \exists u(u, vy) \in D\}$$

and suppose that G_0, D_0 are finite, disjoint and that their union is closed with respect to initial segments. Then we have in fast equilibrium

$$\begin{aligned} X_{vy} &= X_0 X_v \quad &, vy \in G_0 \\ X_{vy} &= c X_y X_v \quad &, vy \in D_0 \end{aligned}$$

and we have constants of fast reactions

$$Y = X_0 \cup \sum_{u \in G_0 \cup D_O} |u| X_u\ ,\ Z_y = \sum_{u \in G_0 \cup D_O} X_u y \in M$$

We have then slow reactions

$$\frac{dY}{dt} = m(A - cX_0 + cB) - \sum_{y \in M} X_y$$

$$\frac{dZ_y}{dt} = X_0 - cX_y + cB - X_y\ ,\ y \in M$$

The system has again unique stationary state

$$X_0 = \frac{A + cA + c^2 B}{1 + c + c^2} \ , \ X_1 = \frac{A + cB + c^2 B}{1 + c + c^2}$$

Under the assumption $A > c^3 B$ we have $X_0 > cX_1$. The opportunity for enzymatic activity arises when $cX_1 < 1 < X_0$

Example. As a more realistic example modify the preceding example by adding reactions

$$X_{uv} \underset{c}{\overset{1}{\rightleftharpoons}} X_u + X_v \qquad \text{for } \ u, v \in M^+$$

Thus beside catalyzed bond formation and destruction the bonds between monomers also break spontaneously. The scheme has the same slow invariants and unique stationary state. The condition for catalytic action is again $cX_1 < 1 < X_0$.

3 Enzymes as recognizing devices

Definition A set $Q \subseteq M^*$ is self-reproducing if it is close with respect to the initial segments and if for any $v \in Q$ of length at least 2 there is some $u \in Q$ with $(u, v) \in G$.

References

[1] H.Atlan, M.Koppel: The cellular computer DNA: program or data. Bull.Math.Biol. vol.52, No.3,335-348(1990)

[2] B.L.Clarke: Stability of complex reactions networks. Advances in chemical physics (I.Prigogine and S.A.Rice,Eds.), 43:1-215 (1980)

[3] I.Dvořák, J.Šiška: Analysis of metabolic systems with complex slow and fast dynamics. Bull.Math.Biol. Vol.51,No.2,255-274(1989)

[4] F.Dyson: Origins of Life. Cambridge Univ. Press, Cambridge, 1985

[5] F.Horn, R.Jackson: General mass action kinetics. Archive for Rational Mechanics and Analysis, 47:81-116 (1972)

[6] F.Horn: Necessary and sufficient conditions for complex balancing in chemical kinetics. Archive for Rational Mechanics and Analysis, 49:172-194 (1972)

[7] P.Kůrka:Markov chains with infinite transition rates. Mathematical Biosciences 62.1:137,1982

[8] G.Nicolis, I.Prigogine: Self-Organization in Nonequilibrium Systems. Wiley-Interscience, New York, 1977