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Chemical Reaction Networks as Compartmental Systems

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***Abstract*— Consider a chemical reaction network with general monotone rate functions. Conditions are given for the system to be reducible to a compartmental system. Consequently, every solution will approach an equilibrium point. Comparison is made with other approaches.**

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I. Chemical Reaction Networks

A chemical reaction network is described in terms of species, complexes and reactions.

Species: $A_1, \ldots, A_n$, $x_i =$ concentration of A_i.

Complexes: $C_1, \ldots, C_p$, $C_\ell = \sum_i \alpha_{\ell i} A_i$.

$\alpha_{\ell i} \in \mathbb{Z}_{\geq 0}$, $\alpha_\ell = (\alpha_{\ell 1}, \ldots, \alpha_{\ell n})^T$ [stoichiometric coefficient $\alpha_{\ell i}$].

Reactions: $C_\ell \xrightarrow{r_{\ell m}} C_m$, , [reaction rate $r_{\ell m}$].

The reaction rates are smooth functions from $\mathbb{R}^n_{\geq 0}$ to $\mathbb{R}_{\geq 0}$. The partial derivative of $r_{\ell m}$ with respect to x_q is denoted by $r_{\ell m,q}$. We use the following notation and terminology.

General Kinetics:

For $r_{\ell m} \not\equiv 0$, let $J_\ell = \{j : \alpha_{\ell j} > 0\}$.

$r_{\ell m} = 0$ if $x_j = 0$, $j \in J_\ell$

$r_{\ell m} > 0$ if $x_j > 0 \; \forall j \in J_\ell$

Monotone Kinetics: $r_{\ell m,q} \geq 0 \; \forall \; q \in J_\ell$.

Strictly Monotone Kinetics: For $r_{\ell m} \not\equiv 0$, $r_{\ell m,q} > 0$ for $x_j > 0 \; \forall j, q \in J_\ell$.

Mass–Action Kinetics: $r_{\ell m} = k_{\ell m} x_1^{\alpha_{\ell 1}} \cdots x_n^{\alpha_{\ell n}}$ [rate constant $k_{\ell m} > 0$].

The governing system (CRN) is then written:

$$\dot{x} = f(x) = \sum_{\ell,m;\ell \neq m} (\alpha_m - \alpha_\ell) r_{\ell m},$$

$$x = (x_1, \ldots, x_n)^T, \; x(0) \in \mathbb{R}^n_{\geq 0}$$

The non-negative orthant, $\mathbb{R}^n_{\geq 0}$, is positively invariant. In addition, the solution must lie in a particular plane, defined as follows.

Stoichiometric Subspace:

$S =$ span $\{\alpha_m - \alpha_\ell : m \neq \ell, \; r_{\ell m} \not\equiv 0\}$

Compatibility Class: $(x(0) + S) \cap \mathbb{R}^n_{\geq 0}$

$x(t) \in (x(0) + S) \cap \mathbb{R}^n_{\geq 0}$ for $t \geq 0$.

A positive compatibility class has a point in $\mathbb{R}^n_{>0}$.

By the positivity results of Vol'pert [7], either $x_i(t) \equiv 0$ or $x_i(t) > 0$ for $t > 0$. Restrict initial conditions to give $x(t) \in \mathbb{R}^n_{>0}$ for $t > 0$. Thus, $x(t)$ will lie in a positve compatibility class.

Question: When does a CRN have regular dynamics, that is every solution tends to an equilibrium?

Most theory concerns local and global asymptotic stability of a positive equilibrium relative to its compatibility class where the kinetics is mass–action.

II. Compartmental Systems

A closed compartmental systems with n compartments is described as follows.

State variable: $x = (x_1, \ldots, x_n)^T$

Flow rates: $r_{ij}(x)$, $i \neq j$

The governing system (CS) is written:

$$\dot{x}_i = f_i = -\sum_{j,j\neq i} r_{ij} + \sum_{j,j \neq i} r_{ji}.$$

Since $\sum \dot{x}_i = 0$, then $\sum x_i(t) = \sum x_i(0)$.

The system has a column diagonally dominant Jacobian when $f_{i,i} + \sum_{k,k\neq i} |f_{k,i}| \leq 0 \;\; \forall \; i$.

In the donor controlled case, $r_{ij} = r_{ij}(x_i)$ and $r'_{ij} \geq 0$, then $f_{i,i} \leq 0$, $f_{i,k} \geq 0$ for $i \neq k$ and the Jacobian is column diagonally dominant.

A generalization of a result of Maeda, Kodama and Ohta [5], [6] and Jacquez and Simon [4]: For a CS with column diagonally dominant Jacobian, any bounded solution converges to an equilibrium.

The proof uses the Lyapunov function $V = \sum |f_i| = |f|_1$. V decreases along solutions and for any two solutions $x^{(1)}(t)$ and $x^{(2)}(t)$, $|x^{(1)}(t) - x^{(2)}(t)|_1$ decreases. The latter comes from Coppel [2].

The following special form (S) will be useful: $r_{ij} = r_{ij}(x_i, x_j)$, $r_{ij} \geq 0$ $r_{ij} = 0$ for $x_i = 0$, $r_{ij,i} \geq 0$, $r_{ij,j} \leq 0$. Let $x(0) \in \mathbb{R}^n_{\geq 0}$, then $x(t) \in \mathbb{R}^n_{\geq 0}$ for $t > 0$. Every solution is bounded and the Jacobian is column dominant. Thus every solution converges to an equilibrium point.

III. Reduction Based on Conservation Laws

Consider a CRN with monotone kinetics and no auto–catalytic reactions (where a species is both a reactant and a product). The CRN may be written $\dot{x} = \Gamma R(x)$ where $R(x) = (R_1(x), \ldots, R_p(x))^T$, the non–zero reaction rates, listed in some order. Let N_0 be a positive integer

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less than n and suppose that one $A_i,\ 1 \le i \le N_0$, with the same stoichiometric coefficient α_i, occurs in each complex and also that for any $i > N_0,\ 1 \le N(i) \le N_0$ and $(e_i - c_i e_{N(i)})^T\Gamma = 0$ for some $c_i \neq 0$.Then for all $i > N_0,\ x_i(t) = \gamma_i + c_i x_{N(i)}(t) \quad \forall t$. Let $x_i = \alpha_i y_i$ for $1 \le i \le N_0$. Using these gives a reduced system $\dot{y} = \tilde{f}(y),\ y = (y_1, \ldots, y_{N_0})^T$ which is a compartmental system of type S. Hence the system has regular dynamics.

CRN's with each species appearing in one complex can be reduced to compartmental sytem of type S with $\tilde{r}_{ij} = \tilde{r}_{ij}(y_i)$.

Example 1 $\quad 2A_1 \rightleftarrows A_2 + A_3$

Complexes: $C_1 = 2A_1,\ C_2 = A_2 + A_3$

$$\begin{aligned}\dot{x}_1 &= -2r_{12} + 2r_{21}\\ \dot{x}_2 &= r_{12} - r_{21}\\ \dot{x}_3 &= r_{12} - r_{21}\end{aligned}$$

Using $x_3 = \gamma + x_2,\ x_1 = 2y_1,\ x_2 = y_2$, gives the reduced system

$$\begin{aligned}\dot{y}_1 &= -r_{12}(\tfrac{y_1}{2}) + r_{21}(y_2, \gamma + y_2)\\ \dot{y}_2 &= r_{12}(\tfrac{y_1}{2}) - r_{21}(y_2, \gamma + y_2)\end{aligned}$$

This is a compartmental system of type S with flow rates $\tilde{r}_{12}(y_1) = r_{12}(\frac{y_1}{2})$ and $\tilde{r}_{21}(y_2) = r_{21}(y_2, \gamma + y_2)$.

Here is a different type of example.

Example 2 (Donell and Banaji [3])

$B + D \rightleftarrows A \rightleftarrows C + D,\ B \rightleftarrows C$

Species: $A,\ B,\ C,\ D$

Complexes: $C_1 = A,\ C_2 = B + D,\ C_3 = C + D,\ C_4 = B,\ C_5 = C$

Using $x_4 = \gamma - x_1,\ x_i = y_i$ for $1 \le i \le 3$, we obtain a reduced system which is compartmental of type S with flow rates $\tilde{r}_{12} = r_{12}(y_1),\ \tilde{r}_{21} = r_{21}(y_2, \gamma - y_1),\ \tilde{r}_{13} = r_{13}(y_1),\ \tilde{r}_{31} = r_{31}(y_3, \gamma - y_1),\ \tilde{r}_{23} = r_{45}(y_2),\ \tilde{r}_{32} = r_{54}(y_3)$.

We next give two notable biochemical examples. In these examples each species and its concentration are denoted by the same letter. The forward reactions are numbered in order and backward reactions are indicated by a minus sign.

Example 3 [Michaelis–Menten enzyme model]

$S + E \rightleftarrows C \longrightarrow P + E$

Conservation relations: $S + C + P = \alpha,\ E + C = \beta$, with $\alpha,\ \beta > 0$. Use $E = \beta - C$ to obatain a reduced system:

$$\begin{aligned}\dot{S} &= -r_1(S, \beta - C) + r_{-1}(C)\\ \dot{C} &= r_1(S, \beta - C) - r_{-1}(C) - r_2(C)\end{aligned}$$

$$D\tilde{f} = \begin{pmatrix} -r_{1,1} & r_{1,2} + r'_{-1}\\ r_{1,1} & -r_{1,2} - r'_{-1} - r'_2 \end{pmatrix}$$

Equilibria: $r_2(C) = 0 \;\Rightarrow\; C = 0 \;\Rightarrow\; r_1(S, \beta) = 0 \;\Rightarrow\; S = 0$.

It follows that $(S, C, P, E) \to (0, 0, \alpha, \beta)$.

Example 4 [futile cycle enzyme model]

$$\begin{cases} S + E \rightleftarrows C \longrightarrow P + E\\ P + F \rightleftarrows D \longrightarrow S + F \end{cases}$$

Conservation relations: $S + C + D + P = \alpha,\ E + C = \beta,\ F + D = \gamma$ with $\alpha,\ \beta,\ \gamma > 0$. Use $E = \beta - C$ and $F = \gamma - C$ to obtain a reduced system:

$$\begin{aligned}\dot{S} &= -r_1(S, \beta - C) + r_{-1}(C) + r_4(D)\\ \dot{C} &= r_1(S, \beta - C) - r_{-1}(C) - r_2(C)\\ \dot{D} &= r_3(P, \gamma - D) - r_{-3}(D) - r_4(D)\\ \dot{P} &= r_2(C) + r_{-3}(D) - r_3(P, \gamma - D)\end{aligned}$$

The Jacobian matrix is column diagonally dominant and there are no boundary equilibria. It follows that every solution approaches a positive equilibrium point.

IV. Other Approaches

There are three other approaches to establishing the regular dynamics of chemical reaction networks with general monotone or strictly monotone kinetics.

Factoring Γ (Donnel and Banaji [3])

Suppose that $\Gamma = \Gamma_1\Gamma_2$.

Each row of Γ_1 has one nonzero entry and there is no zero column. Each column of Γ_2 has one positive and one negative entry and Γ_2^T has one-dimensional kernel with a strictly positive element.

Let $K(\Gamma_1) = \{\Gamma_1 y : y \in \mathbb{R}^p_{\ge 0}\}$; $K(\Gamma_1) \cap \mathbb{R}^n_{\le 0} = \{0\}$.

Assume no auto–catalytic reactions, strictly monotone kinetics and the system is persistent. Then in each positive compatibility class there is a unique positve equilibrium which is globally asymptotically stable.

Reaction Coordinates (Angeli, DeLeenheer and Sontag [1])

Let $x = x_0 + \Gamma y$. Then $\dot{y} = R(x_0 + \Gamma y),\ y(0) = 0$.

Suppose that the reaction graph (R–graph) has no negative cycle. Let K be the orthant determined by the R–graph so that the system for y is monotone with respect to K. Assume no auto–catalytic reactions, strictly monotone kinetics, compatibility classes are compact and the system is persistent. Then

(1) $\ker(\Gamma) \cap \operatorname{int}(K) \neq \emptyset \quad \Rightarrow$ every positive solution converges to a positive equilibrium

(2) $\ker(\Gamma) \cap K = \{0\} \quad \Rightarrow$ almost all postive solutions converge to the set of equilibria

There is substantial overlap between the methods of factoring Γ, case (1) of reaction coordinates and the method of reduction to a compartmental system as presented in section III.

Balance Inequality (Vol'pert [7])

Suppose there exist postive vectors α and β so that BI: $\alpha^T\Gamma = -\beta^T$. Assume general kinetics. Then the CRN has regular dynamics. Also, if the directed species–reaction (DSR) graph is acyclic then BI holds. However, this graphical condition is not necessary.

Example 5 $2B \longrightarrow C + D,\ D \longrightarrow B$

Here $\Gamma = \begin{pmatrix} -2 & 1 \\ 1 & 0 \\ 1 & -1 \end{pmatrix}$, $\alpha^T = (3, 1, 4)$ and $\beta^T = (1, 1)$ satisfy BI. The DSR–graph contains a cycle: $B \to R_1 \to D \to R_2 \to B$.

Example 6 ([7]) $\begin{cases} A + B \xrightarrow{r_{12}} C \\ A + D \xrightarrow{r_{34}} E \end{cases}$

DSR–graph:

$$\begin{array}{ccccc} B & \longrightarrow & R_{12} & \longrightarrow & C \\ & \nearrow & & & \\ A & \longrightarrow & R_{34} & \longrightarrow & E \\ & \nearrow & & & \\ D & & & & \end{array}$$

As the DSR–graph is acyclic, there are regular dynamics. For some compatibility classes there is a line segment of equilibria on the boundary of $\mathbb{R}^5_{\geq 0}$.

This type of result should be generalized, as it allows dynamics in which some components tend to zero.

A final example shows that a chemical reaction network may behave differently with mass–action kinetics than with strictly monotone kinetics.

Example 7 $A \overset{\longrightarrow}{\longleftarrow} B \overset{\longrightarrow}{\longleftarrow} 2A$

Species: $A,\ B$

Complexes: $C_1 = A,\ C_2 = B,\ C_3 = 2A$

This cannot be put into the form of a compartmental system of type S. In reaction coordinates the system is monotone with respect to the nonnegative quadrant in $\mathbb{R}^2$. The compatibility class is the nonnegative quadrant and $\ker(\Gamma) = \{0\}$. Both Angeli, DeLeenheer, Sontag [1] and Donnell, Banaji [3] do not apply. There are strictly monotone kinetics with no positive equilibrium point. However, under mass–action kinetics there is a unique globally stable positive equilibrium.

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