

BioControl - Week 4, Lecture 1

Chemical Reaction Networks (CRNs)

April 20, 2010

Sources:

- Martin Feinberg, Notes available here:

[http://www.che.eng.ohio-state.edu/~FEINBERG/
LecturesOnReactionNetworks/](http://www.che.eng.ohio-state.edu/~FEINBERG/LecturesOnReactionNetworks/)

Review: Feinberg, M. Chemical Engineering Science, Vol. 42, No. 10, pp. 2229-2268, 1987.

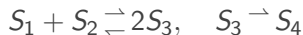
- Hans Othmer, Notes available here:

[http://www.math.leidenuniv.nl/~verduyn/Hans.Othmer_
course_notes.pdf](http://www.math.leidenuniv.nl/~verduyn/Hans.Othmer_course_notes.pdf)



What is a Chemical Reaction Network?

You might be familiar with writing down reactions schemes like this one below:



When we write this we mean that S_1 interacts with S_2 to form S_3 , and so on.

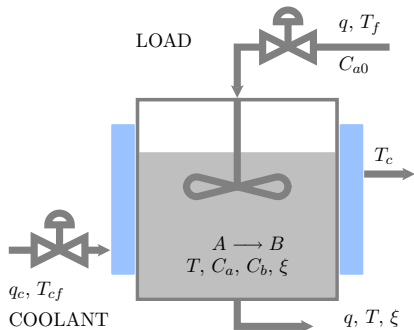
Let us throw some different initial amounts of S_1, \dots, S_4 in a pot, and assume that:

- The pot is perfectly stirred
- The temperature is constant
- The volume is constant

Then, can we find a general method to establish how do the molar concentrations x_i of each species vary over time? Do they have steady states? Where are such steady states?...

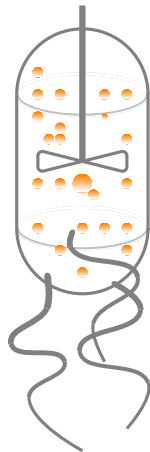


When is a CRN a good model?



Chemical reactors

High copy number bio-molecules

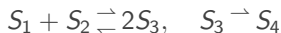


Definition of a CRN

A CRN is defined by three objects:

- A set of species $\mathcal{S} : \{S_i, i = 1, \dots, N\}$.
- A set of complexes $\mathcal{C} : \{C_j, j = 1, \dots, M\}$.
- A set of reactions $\mathcal{R} : \{R_k, k = 1, \dots, K\}$

Example:



- Species: S_1, S_2, S_3 and S_4
- Complexes: $C_1 = S_1 + S_2$, $C_2 = 2S_3$, $C_3 = S_3$ and $C_4 = S_4$
- Reactions: $R_1 : S_1 + S_2 \rightarrow 2S_3$, $R_2 : 2S_3 \rightarrow S_1 + S_2$, $R_3 : S_3 \rightarrow S_4$

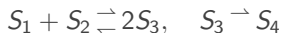


From a reaction network to ODEs

Let us go back to our pot or chemicals.

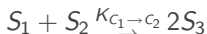
Each species S_i has an initial concentration $x_i(0)$. How will the composition vector $x(t) = [x_1(t), \dots, x_N(t)]$ vary over time?

Our old example:



Let us associate to each reaction in the network, a **reaction rate**, a non-negative real valued function that specifies how fast the reaction occurs.

E.g.



If species S_1 is a reactant in R_1 and a product of R_2 we can write its **dynamics** as follows:

$$\dot{x}_1(t) = -K_{C_1 \rightarrow C_2} + K_{C_2 \rightarrow C_1}$$

Similarly for the other species. Note that, in general, $K_{C_i \rightarrow C_j}$ is a functions of C_i and C_j .



From a reaction network to ODEs

- We will require that reaction rates are continuously differentiable functions.
- ODEs associated with a CRN must be **consistent**: the accumulation rate of an absent species must be non-negative.
- Trajectories of a CRN evolve in \mathbb{P}_0^N , the non-negative orthant of \mathbb{R}^N .

Most often, chemists and engineers assume that the reaction rates are of **mass action** type: the rate is proportional to the product of the instantaneous concentrations of species in a complex.

Our old example:



So the dynamics of S_1 become:

$$\dot{x}_1(t) = -k_{12,3} x_1(t)x_2(t) + k_{3,12} x_3^2(t)$$

Similarly for the other species.



Open and closed systems

The example we have considered so far is a **closed** system. There is no input and no output.

To include an **exchange of mass** between the network and the outside world we can add a **zero node**.

- Influx of a reactant S_i :



For mass action kinetics:

$$\dot{x}_i = \xi x_i^{in}$$

Where in general ξ is the reciprocal of the residence time and x_i^{in} is a fixed reactant concentration in the feed stream. This is also called a *zero-th order* kinetic term. Note that the zero complex can be substituted to a complex whose concentration is assumed to be **constant** over time!

- Efflux or degradation of species S_j :



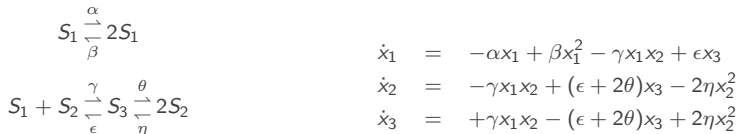
For mass action kinetics:

$$\dot{x}_j = -\xi x_j(t)$$



Questions that we want to ask

Consider the following example (mass action) reaction network



Regardless of the values of the reaction rates, we would like to answer the following questions:

- Does this system admit a positive steady state?
- Does it admit multiple steady states?
- Does it admit an unstable steady state?
- Does it admit a periodic orbit where all the states are positive?

We will use The Deficiency Zero and the Deficiency One Theorems...
after a general introduction to CRN theory!



Some definitions

- **Species vectors** - Associate to each species S_i a vector e_i of the canonical basis of \mathbb{P}^N .
- **Complexes vectors** - Each complex vector C_i is defined as a sum of species vectors: $y_i = \sum e_j$.
- **Reaction vectors** - $R_k = y_j - y_i$
 y_j is the product of R_k , y_i is the reactant complex.
- **Rank** - Size of the set of linearly independent reactions.

Our old example: $S_1 + S_2 \rightleftharpoons 2S_3$, $S_3 \rightarrow S_4$

$$\begin{array}{l} S_1 : e_1 \\ S_2 : e_2 \\ S_3 : e_3 \\ \dots \end{array} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ \dots & \dots & \dots & \dots \end{bmatrix} \quad \begin{array}{l} C_1 \\ C_2 \\ \dots \end{array} = \begin{array}{l} S_1 + S_2 : y_1 = e_1 + e_2 \\ 2S_3 : y_2 = 2e_3 \\ \dots \end{array} = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 2 & 0 \\ \dots & \dots & \dots & \dots \end{bmatrix}$$

$$\begin{array}{l} R_1 : \\ R_2 : \\ R_3 : \end{array} \begin{array}{l} -y_1 + y_2 \\ +y_1 - y_2 \\ -y_4 + y_5 \end{array} = \begin{bmatrix} -1 & -1 & +2 & 0 \\ +1 & +1 & -2 & 0 \\ 0 & 0 & -1 & +1 \end{bmatrix}$$

Rank of the reaction
matrix: $r = 2$.



Differential equations

A compact notation to write the ODEs modeling the time evolution of a CRN is:

$$\dot{x} = \sum K_{i \rightarrow j}(x)(y_j - y_i)$$

Where x is our vector of species concentrations, $K_{i \rightarrow j}(x)$ is the function defining the rate of the reaction generating complex C_j from complex C_i and y_i, y_j are the corresponding vectors in \mathbb{P}^N that define the complexes (on the species canonical basis).

- Recall that the equations must be consistent! The system evolves on the positive orthant.
- Solutions to this set of ODEs must be **stoichiometrically compatible**: a vector v is compatible with the equations iff $\exists \{\alpha_{i \rightarrow j} \in \mathbb{R}\} : v = \sum \alpha_{i \rightarrow j}(y_j - y_i)$. Equilibria must also satisfy this compatibility.
- For a mass action system, the equations can be written as:

$$\dot{x} = \sum k_{i \rightarrow j} \left(\prod_{H=1}^N x_H^{y_{iH}} \right) (y_j - y_i)$$

Where y_{iH} is the stoichiometric coefficient of species S_H in the reaction complex i .



Differential equations

When we write:

$$\dot{x} = \sum K_{i \rightarrow j}(x)(y_j - y_i)$$

We are linking the dynamics of a vector of species to a set of reactions. We can rewrite it as an explicit mapping:

$$\dot{x} = \nu \mathcal{E} R(x)$$

- The **matrix** $[\nu_{ij}]$ identifies the **molarity of species** S_i in complex C_j , and is an $N \times M$ matrix.
- The **vector** $R(x)$ is composed by all the **reaction rates** $K_{i \rightarrow j}(x)$ in the network. For mass action kinetics, each reaction rate is simply $k_{i \rightarrow j} \prod_{H=1}^N x_H^{y_{iH}}$, where y_{iH} is the stoichiometric coefficient of species S_H in the reaction complex i
- The **matrix** \mathcal{E} represents the **incidence graph** that maps complexes to reactions. Each element $[\mathcal{E}_{h,k}]$ maps complex C_h to reaction $R_k(x)$: $[\mathcal{E}_{h,k}] = 1$ if C_h is a product, $[\mathcal{E}_{h,k}] = -1$ if C_h is a reactant, $[\mathcal{E}_{h,k}] = 0$ if C_h does not participate in the reaction. \mathcal{E} can also be viewed as the matrix corresponding to the incidence graph that links complexes to reactions.



Our old example

$$S_1 + S_2 \rightleftharpoons 2S_3, \quad S_3 \rightleftharpoons S_4$$

$$C_1 = S_1 + S_2, \quad C_2 = 2S_3, \quad C_3 = S_3, \quad C_4 = S_4$$

$$\nu = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 2 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \quad \mathcal{E} = \begin{bmatrix} -1 & +1 & 0 \\ +1 & -1 & 0 \\ 0 & 0 & +1 \\ 0 & 0 & -1 \end{bmatrix} \quad R(x) = \begin{bmatrix} K_{C_1 \rightarrow C_2} \\ K_{C_2 \rightarrow C_1} \\ K_{C_3 \rightarrow C_4} \end{bmatrix}$$



CRN invariants

Let us continue with this structure: $\dot{x} = \nu \mathcal{E} R(x)$.

The evolution of trajectories of a CRN is heavily constrained. We can find **reaction invariant subspaces**. An invariant subspace Ω is any vector that satisfies:

$$\langle \Omega, \nu \mathcal{E} R(x) \rangle = 0 \Leftrightarrow \langle \Omega, \dot{x} \rangle = 0 \Rightarrow \langle \Omega, x(t) \rangle = \langle \Omega, x(0) \rangle$$

The above inner product can be rewritten as:

$$R(x)^\top \mathcal{E}^\top \nu^\top \Omega = 0.$$

- Invariant l_1 : $\text{span} \Omega$ such that $\Omega \in \ker(\nu^\top)$, depends only on the stoichiometry of complexes.
- Invariant l_2 : $\text{span} \Omega$ such that $\nu^\top \Omega \in \ker(\mathcal{E}^\top)$, $\Omega \notin (\ker \nu^\top)$, depends on the graph structure.
- Invariant l_3 : $\text{span} \Omega$: $\langle \Omega, \nu \mathcal{E} R(x) \rangle = 0$, $\Omega \notin \ker(\mathcal{E} \nu)^\top$, for $x \in \mathbb{P}_0^N$

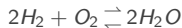
Note 1: $\ker(\nu \mathcal{E})^\top = l_1 \oplus l_2$.

Note 2: The image of $(\nu \mathcal{E})^\top$ is the reaction subspace.



CRN invariants: example

Note that the invariants I_1 and I_2 we just defined do not depend on the kinetic rates! An example will clarify the importance of this fact.



We have three chemical species, two complexes and two reactions.

$$\nu = \begin{bmatrix} 2 & 0 \\ 1 & 0 \\ 0 & 2 \end{bmatrix} \quad \mathcal{E} = \begin{bmatrix} -1 & +1 \\ +1 & -1 \end{bmatrix}$$

$I_1 = \ker(\nu^T) = \text{span} [1 \quad -2 \quad 0]^T$. This means that the concentrations must evolve as $x_1(t) - 2x_2(t) = 0$.

I_2 is non empty only if the image of ν^T is non empty, which happens when the complexes are linearly independent. In this case they are and we can find I_2 as the subspace spanned by the vector u solving $u \in \ker(\nu^T)^\perp$ and $\mathcal{E}u = 0$.



CRN invariants: examples

Another example (with mass action kinetics) will clarify how these results help us to visualize the evolution of trajectories, regardless of their reaction rates.



$$\nu = \begin{bmatrix} 1 & 0 \\ 0 & 2 \end{bmatrix}, \mathcal{E} = \begin{bmatrix} -1 & +1 \\ +1 & -1 \end{bmatrix}$$

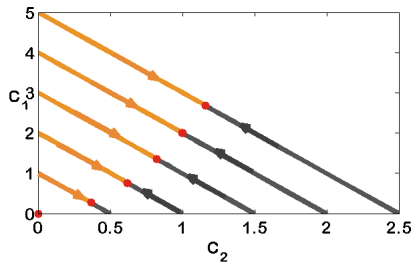
Reaction matrix:

$$R = \begin{bmatrix} -1 & 2 \\ 1 & -2 \end{bmatrix} = (\nu\mathcal{E})^\top$$

$$\ker(\nu^\top) = \emptyset$$

Stoichiometric subspace: $\text{range}(\nu\mathcal{E})^\top \cap \mathbb{P}_0^N$,
in our case all vectors parallel to $\begin{bmatrix} 1 & -2 \end{bmatrix}$

Space of equilibria: $x_1 = \frac{2\beta}{\alpha}x_2^2$.

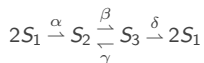


- Equilibria
 - Trajectories starting at $C_2 = 0$
 - Trajectories starting at $C_1 = 0$
- $\alpha = 0.08, \beta = 0.04$



CRN invariants: examples

Another example in 3D.



$$\nu = \begin{bmatrix} 2 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \mathcal{E} = \begin{bmatrix} -1 & 0 & 0 & +1 \\ +1 & -1 & 1 & 0 \\ 0 & +1 & -1 & -1 \end{bmatrix}$$

Reaction matrix:

$$R = \begin{bmatrix} -2 & 0 & 0 & 2 \\ 1 & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix} = (\nu\mathcal{E})^\top$$

$$\ker(\nu^\top) = \emptyset$$

Stoichiometric subspace:

$\text{range}(\nu\mathcal{E})^\top \cap \mathbb{P}_0^N$, in our case it's a plane passing through the points $(-2, 1, 0)$, $(0, -1, 1)$, $(0, 1, -2)$ and $(2, 0, -1)$.

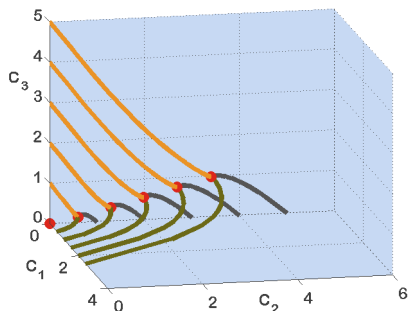
$$\alpha = 0.08, \beta = 0.05, \delta = .1, \gamma = 0.05$$

• Equilibria

— Trajectories starting at $C_3 = C_1 = 0$

— Trajectories starting at $C_3 = C_2 = 0$

— Trajectories starting at $C_1 = C_2 = 0$



CRN invariants: examples

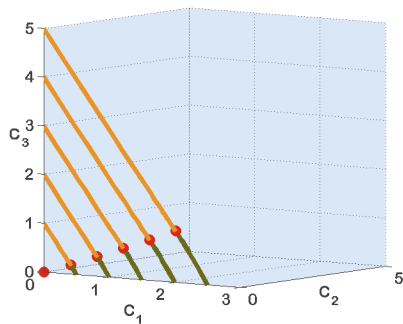
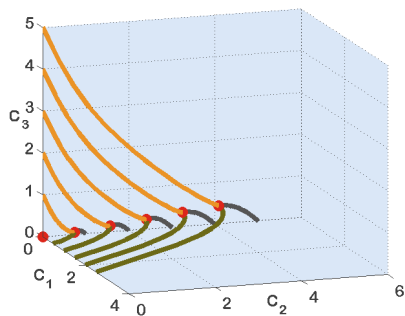
$$\alpha = 0.1, \beta = 0.02, \delta = .05, \gamma = 0.1$$

● Equilibria

— Trajectories starting at $C_3 = C_1 = 0$

— Trajectories starting at $C_3 = C_2 = 0$

— Trajectories starting at $C_1 = C_2 = 0$

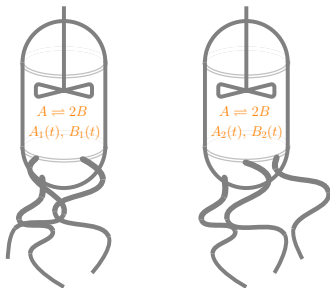


Studying general CRNs is helpful in practical cases

Consider two cells where the same reaction is occurring:



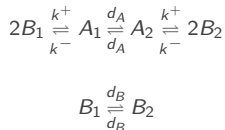
Also assume there is an exchange of reactants proportional to a diffusion constant multiplied by the concentration difference between the two cells.



The corresponding ODE model would be:

$$\begin{aligned}\dot{A}_1 &= -k^+ A_1 + k^- B_1^2 + d_A(A_2 - A_1) \\ \dot{B}_1 &= 2k^+ A_1 - 2k^- B_1^2 + d_B(B_2 - B_1) \\ \dot{A}_2 &= -k^+ A_2 + k^- B_2^2 + d_A(A_1 - A_2) \\ \dot{B}_2 &= 2k^+ A_2 - 2k^- B_2^2 + d_B(B_1 - B_2)\end{aligned}$$

We could map the system above to an underlying "model" CRN:



This CRN is fictitious, but we can study some features of its dynamics based on network structure only.



Structural properties of CRNs

- **Reversibility** - Each reaction in the network is accompanied by its reverse.
E.g. $S_i \rightleftharpoons S_j$
- **Weak Reversibility** - If there is a directed pathway in the network (composed of one or more arrows) from complex C_i to C_j , there exist a pathway pointing back from C_j to C_i .
- **Linkage classes** - The complexes in a CRN can be divided into disjoint sets if they are not linked by any reaction arrow. E.g. $S_1 \rightleftharpoons S_2, S_3 \rightarrow S_4$ has two linkage classes: $\{S_1, S_2\}$ and $\{S_3, S_4\}$.
 - **Note 1:** Any two CRNs with the same complexes and the same linkage classes also have the same rank (**proof: your homework**). Thus, to determine the rank of a CRN it is sufficient to study the properties of another CRN with same complexes and linkage classes but a minimal number of reactions.
 - **Note 2:** Adding or removing reaction arrows influences the rank of a CRN only if the linkage classes are modified.
 - **Note 3:** The rank of a CRN having L linkage classes cannot exceed $M - L$, where M is the number of complexes present.
 - **Note 4:** The rank of a CRN is not equal to the sum of the ranks of each linkage class...

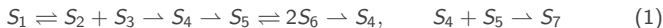


Structural properties of CRNs: Linkage classes

We have seen that **linkage class** are not affected by the directions in which the reaction arrows point. To include this information in the characterization of complexes we need a few more definitions.

- Two complexes are **strongly linked** if there exists a directed arrow pathway from one complex to the other *and* a directed arrow pathway pointing from the second complex back to the first.
- Every complex is strongly linked to itself by convention.
- A **strong linkage class** is a set of complexes where: every pair of complexes in the set is strongly linked, and no complex in the set is strongly linked to a complex not in the set. Each complex is a member of only one strong linkage class.

Example:



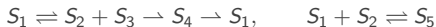
Strong linkage classes: $\{S_1, S_2 + S_3\}$, $\{S_4, S_5, 2S_6\}$, $\{S_4 + S_5\}$ and $\{S_7\}$ (the last two by convention). $\{S_5, 2S_6\}$ is not a strong linkage class, because both S_5 and $2S_6$ are strongly linked to S_4 , which lies outside of $\{S_5, 2S_6\}$. $\{S_4 + S_5\}$ is strongly linked to itself but to no other complex, and so is $\{S_7\}$.



Structural properties of CRNs: Linkage classes

- Every strong linkage class lies within a linkage class.
- Can a linkage class in a network be also a strong linkage class? Sure! It is easy to prove that **weakly reversible networks** are precisely those for which **each linkage class is also a strong linkage class**.

Example:



- A strong linkage class that contains no complex that reacts to a complex in a different strong linkage class is called a **terminal linkage class**. The example in reactions (1) has two terminal strong linkage classes: $\{S_4, S_5, 2S_6\}$ and S_7 .
- Each linkage class must contain *at least* one terminal strong linkage class. So the number T of such classes satisfies: $T \geq L$, where L is the number of linkage classes of a network.
- Finally: **weakly reversible networks** are those for which linkage classes, strong linkage classes and terminal strong linkage classes **coincide!** This implies that $T = L$.



Structural properties of CRNs: Deficiency

- We have seen that the rank of a CRN cannot exceed $M - L$, where M is the number of complexes present, and L is the number of linkage classes. Therefore, if r is the rank of the CRN:

$$M - L - r \geq 0$$

- The **deficiency** of a network is defined as:

$$\delta = M - L - r$$

Note 1: Any two networks with the same complexes and linkage classes also have the same deficiency.

Note 2: Reaction arrows influence the deficiency only insofar as they determine linkage classes (the direction of the arrow does not matter).

Our old example: $S_1 + S_2 \rightleftharpoons 2S_3$, $S_3 \rightarrow S_4$

Number of complexes: 4, Rank: 2, Linkage classes: 2, Deficiency: 0

Another example: $S_1 \rightleftharpoons S_2 \rightleftharpoons S_3$, $S_1 + S_2 \rightleftharpoons 2S_3$

Number of complexes: 5, Rank: 2, Linkage classes: 2, Deficiency: 1



Deficiency: geometric interpretation

The network deficiency was defined as:

$$\delta = M - L - r$$

Where M is the number of complexes, L is the number of linkage classes, and r is the rank of the network. Any linkage class defines a **connected component** in the graph \mathcal{E} , so L is the number of connected components of \mathcal{E} . It can be easily proved that $\text{rank}(\mathcal{E}) = M - L$. So we can conclude that:

$$\delta = \text{rank}(\mathcal{E}) - \text{rank}(\nu\mathcal{E})$$

Which means that the deficiency is the difference between the maximal number of independent reactions based on the graph structure, and the actual number of independent reactions. **It can also be proved (homework) that:**

$$\delta = \dim\{\ker(\nu) \cap \text{range}(\mathcal{E})\}$$

When ν does not annihilate any element in $\text{range}(\mathcal{E})$, it is a one-to-one application and is left-invertible. The reaction subspace defined by the range of $\nu\mathcal{E}$ is therefore isomorphic to the range of \mathcal{E} .



The Deficiency Zero Theorem

For any reaction network of deficiency zero the following statements hold true:

- (i) If the network is **not weakly reversible** then, for arbitrary kinetics (not necessarily mass action), the differential equations for the corresponding reaction system **cannot admit a positive steady state** (i.e. a steady state in \mathbb{P}^n).
- (ii) If the network is **not weakly reversible** then, for arbitrary kinetics (not necessarily mass action), the differential equations for the corresponding reaction system **cannot admit a cyclic composition trajectory** along which all species concentrations are positive.
- (iii) **If the network is weakly reversible** then, for mass action kinetics (but regardless of the positive values the rate constants take), the differential equations for the corresponding reaction system have the following properties: **There exists within each positive stoichiometric compatibility class precisely one steady state; that steady state is asymptotically stable**; and there is no nontrivial cyclic composition trajectory along which all species concentrations are positive

Proof - next lecture!

