(stochastic) Chemical Reaction networks

Examples

chemistry

$$H_2O \rightleftharpoons H^+ + OH^-$$

or

$$N_2 + 3H_2 \rightleftharpoons 2NH_3$$

} chemical reactions (CR)

(In equilibrium, at constant T & P) $\mu_{H_2O} = \mu_{H^+} + \mu_{OH^-}$ or $\mu_{N_2} + 3\mu_{H_2} = 2\mu_{NH_3}$

Biology

Enzyme kinetics

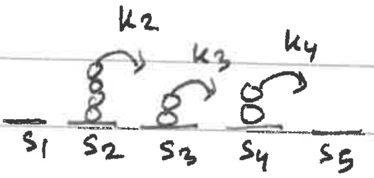
$$E+S \underset{\bar{k}_1}{\overset{k_1}{\rightleftharpoons}} ES \underset{\bar{k}_2}{\overset{k_2}{\rightleftharpoons}} E+P$$

$$E \underset{\bar{k}_3}{\overset{k_3}{\rightleftharpoons}} \phi \underset{k_4}{\overset{\bar{k}_4}{\rightleftharpoons}} P$$

} chemical reaction networks (CRN)

- Species $\{E, S, ES, P\}$ → these are what change in time
- Complexes $\{E+S, ES, E+P, E, \phi, P\}$ → these are how the species interact
- rate constants $\{k_1, \bar{k}_1, k_2, \bar{k}_2, k_3, \bar{k}_3, k_4, \bar{k}_4\}$
- linkage classes $\equiv \ell = 2$ for this CRN
- this CRN is "reversible" since all reactions go both ways.

Physics : zero-range process (with periodic bcs)



$$S_1 \xrightarrow{k_1} S_2 \xrightarrow{k_2} S_3 \xrightarrow{k_3} S_4 \xrightarrow{k_4} S_5, \quad S_5 \xrightarrow{k_5} S_1$$

This is "weakly reversible"

Ecology : Lotka-Volterra eqn. ~~Epo~~
(or population biology)

$$\left.\begin{array}{l} X \to 2X \\ X+Y \to 2Y \\ Y \to 0 \end{array}\right\}$$ not reversible & not ~~[illegible]~~ weakly reversible ! !

SIRS models in epidemiology

~~[illegible]~~

what is the goal ?

If we specify how this system evolves in time & it reaches a fixed point (steady state), we could ask

For deterministic modeling (rate equations)
↳ are there positive fixed pts
↳ do these depend on initial conditions
↳ only exist for certain values of rate constants

For stochastic modeling (master equations)
↳ what sort of steady state ?
↳ for any value of rate constants ?

In general, for non-equilibrium systems we don't know any general results. But for these CRN's (or systems that can be modelled by CRN's) we do have some general results. The goal is to understand these results.

NO time dependence → we are not studying approach to fixed pts. Also rate constants are time-independent

see next page ← **ACK defns 2.1 & 2.2**

Definitions

- Let $\mathcal{S} = \{S_i\}$, $\mathcal{C} = \{\nu_k\}$, and $\mathcal{R} = \{\nu_k \to \nu_k'\}$ denote the set of species, complexes and reactions respectively. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is called a chemical reaction network.

- The chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is called *weakly reversible* if for any reaction $\{\nu_k \to \nu_k'\}$, there is a sequence of directed reactions beginning with ν_k' as a source complex and ending with ν_k as a product complex. That is, there exist complexes $\nu_1, ..., \nu_r$ such that $\nu_k' \to \nu_1, \nu_1 \to \nu_2, ..., \nu_r \to \nu_k \in \mathcal{R}$. A network is called *reversible* if $\nu_k' \to \nu_k \in \mathcal{R}$ whenever $\nu_k \to \nu_k' \in \mathcal{R}$.

David F. Anderson, Gheorghe Craciun and Thomas G. Kurtz, Bull. Math. Biol. 72 ,1947 (2010)

Deterministic modeling + Mass-action rates

$$E+S \underset{\bar{k}_1}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_2}{\overset{\bar{k}_2}{\rightleftharpoons}} E+P \;; \qquad E \underset{\bar{k}_3}{\overset{k_3}{\rightleftharpoons}} \phi \underset{k_4}{\overset{\bar{k}_4}{\rightleftharpoons}} S$$

$E+S \xrightarrow{k_1} ES$ with rate $k_1 x_E x_S$

let $\{x_E, x_S, x_{ES}, x_P\} \rightarrow$ conc/fractions of species

The rate equations for this system are

$$\frac{d}{dt} x_E = -k_1 x_E x_S - k_2 x_E x_P + (\bar{k}_1 + \bar{k}_2) x_{ES} \; k_3 x_E x_p + \bar{k}_3$$

$$\frac{d}{dt} x_S = -k_1 x_E x_S + \bar{k}_1 x_{ES} + \bar{k}_4 - k_4 x_S$$

$$\frac{d}{dt} x_{ES} = k_1 x_E x_S + \bar{k}_2 x_E x_P - (\bar{k}_1 + \bar{k}_2) x_{ES}$$

$$\frac{d}{dt} x_P = -k_2 x_E x_P + \bar{k}_2 x_{ES}$$

Systems of such coupled ODEs can exhibit myriads of behaviours such as multiple fixed points, absorbing states etc. But we will see that there is an easy to check condition, which if present, guarantees a unique fixed point independent of the value of the rate constants. To see this, lets define two matrices

$$Y = \begin{array}{c} \\ E \\ S \\ ES \\ P \end{array} \begin{array}{c} \begin{array}{cccccc} \phi & E & S & E{+}S & ES & E{+}P \end{array} \\ \begin{bmatrix} 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

$\Rightarrow$ carries information about stoichiometry

4 Species as "vectors"

$$E \to \begin{bmatrix}1\\0\\0\\0\end{bmatrix};\quad S \to \begin{bmatrix}0\\1\\0\\0\end{bmatrix};\quad ES \to \begin{bmatrix}0\\0\\1\\0\end{bmatrix};\quad P \to \begin{bmatrix}0\\0\\0\\1\end{bmatrix}$$

6 complexes as "vectors"

$$\phi \to \begin{bmatrix}0\\0\\0\\0\end{bmatrix},\quad E \to \begin{bmatrix}1\\0\\0\\0\end{bmatrix},\quad E+S \to \begin{bmatrix}1\\0\\1\\0\end{bmatrix},\quad E+P \to \begin{bmatrix}1\\0\\0\\1\end{bmatrix}$$

$$S \to \begin{bmatrix}0\\1\\0\\0\end{bmatrix} \quad \& \quad ES \to \begin{bmatrix}0\\0\\1\\0\end{bmatrix}$$

Matrix depicting "adjacency" on the network

$$A \equiv \begin{array}{c} \\ \phi \\ E \\ S \\ E+S \\ ES \\ E+P \end{array} \begin{array}{c} \begin{array}{cccccc} \phi & E & S & E+S & ES & E+P \end{array} \\ \begin{bmatrix} -\bar{k}_3-\bar{k}_4 & k_3 & k_4 & 0 & 0 & 0 \\ \bar{k}_3 & -k_3 & 0 & 0 & 0 & 0 \\ \bar{k}_4 & 0 & -k_4 & & & \\ 0 & 0 & 0 & -k_1 & \bar{k}_1 & 0 \\ 0 & 0 & 0 & k_1 & -\bar{k}_1-\bar{k}_2 & k_2 \\ 0 & 0 & 0 & 0 & \bar{k}_2 & -k_2 \end{bmatrix} \end{array}$$

The linkage classes show up as the 2 "blocks"

We can check that the rate equations can be written as

$$\frac{d}{dt}\begin{pmatrix} x_E \\ x_S \\ x_{ES} \\ x_P \end{pmatrix} = YA \begin{pmatrix} 1 \\ x_E \\ x_S \\ x_E x_S \\ x_{ES} \\ x_E x_P \end{pmatrix} \equiv YA\Psi$$

The dynamics takes place in species space while the network is a relation on complexes

The dynamics takes place via reactions which can be also represented as vectors.

$E+S \rightleftharpoons ES \rightleftharpoons E+P$; $E \rightleftharpoons \phi \rightleftharpoons S$

$E+S \to ES$ can be represented as $\begin{bmatrix} -1 \\ -1 \\ 1 \\ 0 \end{bmatrix}$

$ES \to E+P \Rightarrow \begin{bmatrix} 1 \\ 0 \\ -1 \\ 1 \end{bmatrix}$

$E \to \phi \Rightarrow \begin{bmatrix} -1 \\ 0 \\ 0 \\ 0 \end{bmatrix}$

$\phi \to S \Rightarrow \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}$

All other reactions give vectors which are not independent of above.

$\Rightarrow$ we define

$s \equiv$ span of stoichiometric subspace $= \text{span}_{\{\cancel{\nu_K' \to \nu_K \in R}\}} \{\nu_K' - \nu_K\}$

In our example $s = 4$, which is the dimension of species space ($\Rightarrow$ no conserved quantities)

- what if there are conserved quantities?

$E+S \rightleftharpoons ES \rightleftharpoons E+P$

$s = 2$

So dynamics moves around in a 2-d subspace of the 4-d species space.

2 conserved quantities

(1) $x_E + x_{ES} = \text{const}$

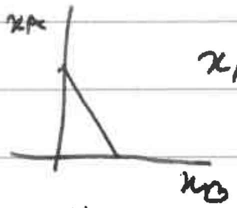
(2) $x_S + x_{ES} + x_P = \text{const}$

$$(1) \rightarrow \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \end{bmatrix}$$

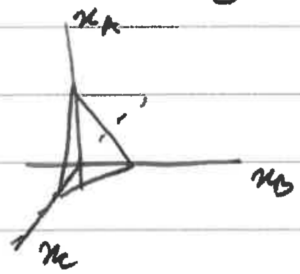
$$(2) \rightarrow \begin{bmatrix} 0 \\ 1 \\ 1 \\ 1 \end{bmatrix}$$

we can check that (1) & (2) are $\perp$ to the reaction vectors $\begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix}$ & $\begin{pmatrix} 1 \\ 0 \\ -1 \\ 1 \end{pmatrix}$

Eg.



$x_A + x_B = \text{const}$ $[A \rightleftharpoons B]$



$x_A + x_B + x_C = \text{const}$

$[A \rightleftharpoons B \rightleftharpoons C]$

From this, we can now compute the "deficiency"

$$\delta = |c| - \ell - s$$

$|c| \rightarrow$ # of complexes

$\ell \rightarrow$ # linkage classes

$s \rightarrow$ dimension of stoichiometric subspace

we'll see $\delta \geq 0$