Stochastic Chemical Reaction Networks

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1 Background

- Chemical Reactions
- Standard Model
- Stoichiometric Compatibility Classes
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2 Stochastic Models
   - Small-Scale Considerations
   - Gillespie Algorithm
   - Chemical Master Equation
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3 Interesting Systems
   - Lotka-Volterra System
   - The Block
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Chemical kinetics is the study of the rates/dynamics resulting from systems of such reactions.
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If many reactant molecules are involved (e.g. chemical reactor), we consider the reactant *concentrations.*
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We will keep track of

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The concentrations are approximately *continuous* with respect to each occurrence of a reaction.

The reaction constant \( k \) represents the *average occurrence rate* of the reaction per time.
Consider the general system

\[ C_i \xrightarrow{k_i} C'_i, \quad i = 1, \ldots, r. \]
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This system is governed by the system of autonomous, polynomial, ordinary differential equations

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- \( x^{z_i} = \prod_{j=1}^{m} (x_j)^{z_{ij}} \) is the mass-action term.
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This has the governing dynamics

\[
\begin{bmatrix}
\dot{x}_1 \\
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\end{bmatrix} = k_1 \begin{bmatrix}
-1 \\
2
\end{bmatrix} x_1 + k_2 \begin{bmatrix}
1 \\
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\end{bmatrix} x_2^2,
\]

where \( x_1 \) and \( x_2 \) are the concentrations of \( A_1 \) and \( A_2 \) respectively.
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The (positive) equilibrium set is given by

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E = \left\{ x \in \mathbb{R}^2_+ \mid x_2 = \sqrt{\frac{k_1}{k_2}} x_1 \right\}.
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For any \( k_1, k_2, x_1, x_2 \) we have \( f(x) \in S \) where

\[
S = \text{span} \left\{ \begin{bmatrix} 1 \\ -2 \end{bmatrix} \right\}.
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Figure: Previous system with $k_1 = k_2 = 1$. 
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**Definition**

The **stoichiometric subspace** $S \subset \mathbb{R}^m$ is given by

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**Theorem**

Solutions \( x(t) \) of (1) are restricted to stoichiometric compatibility classes such that

\[
x(t) \in (S + x_0) \cap \mathbb{R}_+^m \quad \forall t \geq 0.
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A few considerations:

- Differences between states is *large* - i.e. continuity of concentrations breaks down.
- Each occurrence of a reaction matters - i.e. we cannot average into a lump parameter $k_i$.
- We cannot tell when reactions will occur - i.e. the model is *stochastic/probabilistic* instead of deterministic.
There are two general approaches to analyzing purely stochastic chemical kinetics systems:

1. Evaluating sample trajectories/realizations.
2. Analyzing the chemical master equation (models the probability distribution over the admissible states as a function of time).

Evaluating sample trajectories is simple to do numerically but not particularly insightful. Solving the chemical master equation is typically several orders of magnitude beyond impossible.
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An algorithm for evaluating sample trajectories was developed by Doob (1945) and Gillespie (1977) [1]:

1. Initialize reactant numbers $n_i(0)$. 
2. Determine time $\tau$ until next reaction. 
3. Determine next reaction. 
4. Step forward $\tau$, update system and return to step 2. 

Typically carried out for a finite number of iterations or for a fixed amount of time.
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Consider the Michaelis-Menten enzyme reaction

\[ S + E \overset{k_1^+}{\rightleftharpoons} SE \overset{k_2}{\rightarrow} P + E \]

Models the conversion of some substrate $S$ into some product $P$ via the enzyme $E$. The deterministic model is a limiting case for $n_i \rightarrow \infty$ keeping $n_i / V$ constant.
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Figure: Comparison of deterministic and stochastic Michaelis-Menten enzyme mechanism (S = red, E = blue, SE = green, P = yellow).
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We are typically interested in questions such as:

1. What is the probability that $X_i = n_i$, $X_i \geq n_i$, etc., at time $t$?

2. Does the system have steady states?

If we sample enough trajectories we can build curves of best fit and confidence intervals but we will still miss many details.

We can do better - in fact, we can model the evolution of these probabilities explicitly!
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We can do better - in fact, we can model the evolution of these probabilities *explicitly*!
We will let $P(n; t) = P(X_1 = n_1, \ldots, X_m = n_m; t)$ and
\[
\lambda_i(n) = \frac{k_i}{\sqrt{|z_i| - 1}} \prod_{j=1}^{m} \frac{n_j!}{(n_j - z_{ij})!}
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denote the propensity function of $i^{th}$ reaction at state $n$. 
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The chemical master equation is given by

$$
\frac{dP(n; t)}{dt} = \sum_{i \in I} \lambda_i(n + z_i - z'_i)P(n + z_i - z'_i; t) - P(n; t) \sum_{i \in O} \lambda_i(n)
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We will let $P(n; t) = P(X_1 = n_1, \ldots, X_m = n_m; t)$ and

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where $I$ are the reactions which lead into a given state...
We will let $P(n; t) = P(X_1 = n_1, \ldots, X_m = n_m; t)$ and

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where $I$ are the reactions which lead into a given state and $O$ are the reactions which lead from a given state.
Reconsider the earlier system

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Consider the states \((2, 0), (1, 2), \) and \((0, 4)\)...
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Consider the states \((2, 0), (1, 2),\) and \((0, 4),\) for which we have

\[
\frac{dP(2, 0; t)}{dt} = \frac{2k_2}{V} P(1, 2; t) - 2k_1 P(2, 0; t)
\]

\[
\frac{dP(1, 2; t)}{dt} = \frac{12k_2}{V} P(0, 4; t) + 2k_1 P(2, 0; t) - \left( k_1 + \frac{2k_2}{V} \right) P(1, 2; t)
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\frac{dP(0, 4; t)}{dt} = k_1 P(1, 2; t) - \frac{12k_2}{V} P(0, 4; t).
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\frac{dP(0, 4; t)}{dt} = k_1 P(1, 2; t) - \frac{12k_2}{V} P(0, 4; t).
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This can be solved explicitly!
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Less-than-nice features about the CME:

1. It is typically *massive* (for unbounded systems, it is infinite-dimensional).
2. Mass-action term must be computed for each state.
3. Connections between states can be complicated near the boundary.
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Modeling chemical kinetics systems stochastically can qualitatively change the dynamics of a system.
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Consider the Lotka-Volterra predator-prey system ($A_1$ is the prey, $A_2$ is the predator)

$$A_1 \xrightarrow{k_1} 2A_1$$

$$A_1 + A_2 \xrightarrow{k_2} 2A_2$$

$$A_2 \xrightarrow{k_3} 0.$$
Modeling chemical kinetics systems stochastically can qualitatively change the dynamics of a system.

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1 First “reaction”: growth of prey
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\]

1. First “reaction”: growth of prey
2. Second “reaction”: predator eats prey
3. Third “reaction”: death of predator
For all positive rate constant values, this system has a unique positive steady state which is orbited by stable trajectories.
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For the corresponding stochastic system, however...
The stable equilibrium concentration is no longer stable! (In fact, none of the stable periodic orbits are stable.)
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Furthermore, extinction events which were not possible in the continuous, deterministic system are now possible.
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Furthermore, extinction events which were not possible in the continuous, deterministic system are now possible.

Although it is unlikely for either the predator or the prey to go extinct, it is *irreversible* — carried over a long enough time scale, extinction is the inevitable outcome of the system!
Horn and Jackson consider the following system in their seminal paper “General Mass Action Kinetics” [2]:

\[
\begin{align*}
2A_1 + A_2 \overset{1}{\underset{\epsilon}{\rightarrow}} 3A_1 \\
\epsilon \uparrow & \quad \Downarrow \epsilon \\
3A_2 \overset{1}{\leftarrow} A_1 + 2A_2.
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1. \( \epsilon \geq 1/6 \): one stable equilibrium.
2. \( 0 < \epsilon < 1/6 \): two stable and one unstable equilibria.
3. \( \epsilon = 0 \): two stable boundary equilibria.
Figure: Block system with (a) $\epsilon \geq 1/6$, (b) $0 < \epsilon < 1/6$, and (c) $\epsilon = 0$. 
Let’s restrict our attention to the case $0 < \epsilon < 1/6$. 
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Trajectories can *jump* from one side to the other!
Figure: Block system with $\epsilon = 0.12$. 
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For small systems, these distributions can be computed explicitly.

We expect areas of high density near where trajectories spend most of their time, and in fact...
Figure: Stationary distribution for the Block System with ten states and the value $\epsilon = 1$. 
Figure: Stationary distribution for the Block System with ten states and the value $\epsilon = 0.5$. 
Figure: Stationary distribution for the Block System with ten states and the value $\epsilon = 0.2$. 
Figure: Stationary distribution for the Block System with ten states and the value $\epsilon = 0.15$. 
Figure: Stationary distribution for the Block System with ten states and the value $\epsilon = 0.1$. 
Thanks for coming out!
