STOCHASTIC CHEMICAL KINETICS

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Rethinking Chemical Kinetics

A Chemically Reacting System consists of …

- Molecules of \( N \) chemical species \( S_1, \ldots, S_N \).
  - Inside a volume \( \Omega \), at some temperature \( T \).
- \( M \) “elemental” reaction channels \( R_1, \ldots, R_M \).
  - \( R_j \) describes a single instantaneous physical event, which changes the population of at least one species.
  - “Elemental” means that \( R_j \) is one of two types:
    \[ S_i \rightarrow \text{something else (unimolecular),} \]
    or
    \[ S_i + S_r \rightarrow \text{something else (bimolecular).} \]
  - All other types (trimolecular, reversible, etc.) are made up of a series of two or more elemental reactions.
How does a chemically reacting system evolve in time?

The traditional answer, for spatially homogeneous systems:

“According to the reaction rate equation (RRE).”

- A set of coupled, first-order ODEs.
- Derived using ad hoc, phenomenological reasoning.
  - Is more than the “mass action equations” of thermodynamics, which apply only to systems in equilibrium.
- Implies the system evolves continuously and deterministically, even though molecules come in integer numbers and react stochastically.
- Is empirically accurate for large (test tube size) systems.
- But is often not adequate for very small (cell-size) systems.

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Let’s take a fresh look at this question.

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Doing it “right”: Molecular Dynamics

- The most exact way of describing the system’s evolution.
- The “motion picture” approach: Tracks the position and velocity of every molecule in the system.
- Simulates every collision, non-reactive as well as reactive.
- Shows changes in species populations and their spatial distributions.
- But . . . it’s unfeasibly slow for nearly all realistic systems.
A great simplification occurs if successive reactive collisions tend to be separated in time by very many non-reactive collisions.

- The overall effect of the non-reactive collisions is to randomize:
  - the velocities of the molecules (Maxwell-Boltzmann distribution).
  - the positions of the molecules (spatially uniform or well-stirred),
- Then, instead of having to describe the system’s state as the position, velocity and species of each molecule, we need only give
  \[ X(t) \triangleq (X_1(t), \ldots, X_N(t)), \]
  \[ X_i(t) \triangleq \text{the number of } S_i \text{ molecules at time } t. \]

But this well-stirred simplification, which . . .
  - ignores the non-reactive collisions,
  - truncates the definition of the system’s state,
  . . . comes at a price:

  \[ X(t) \text{ must now be viewed as a stochastic process.} \]

- But in fact, the system was never deterministic to begin with.
  Even if molecules moved according to classical mechanics . . .
    - Unimolecular reactions always involve randomness (QM).
    - Bimolecular reactions usually do too.
    - A system of many colliding molecules is so sensitive to initial conditions that, for all practical purposes, it evolves “randomly”.
    - The system is not isolated. It’s in a heat bath, which keeps it “at temperature \( T \)” – via essentially random interactions.
For well-stirred systems, each $R_j$ is completely characterized by …

- a **propensity function** $a_j(x)$: Given the system is in state $x$, $a_j(x)dt \equiv \text{probability}$ that one $R_j$ event will occur in the next $dt$.
  - The **existence and form** of $a_j(x)$ follow from molecular physics.

- a **state change vector** $v_j \equiv (v_{ij}, \ldots, v_{nj})$:
  - $v_{ij} \equiv \text{the change in } X_i \text{ caused by one } R_j \text{ event}$. $R_j$ induces $x \rightarrow x + v_j$. \{v_{ij}\} = \text{the “stoichiometric matrix.”}

**Examples:**

$$S_1 + S_2 \xrightarrow{c_2} 2S_1 : \begin{cases} a_1(x) = c_1 x_1 x_2, & \nu_1 = (+1, -1, 0, \ldots, 0) \\ a_2(x) = c_2 \frac{x_1(x_1 - 1)}{2}, & \nu_2 = (-1, +1, 0, \ldots, 0) \end{cases}$$

$$\text{Prob -collision in } \frac{(\pi r_{12}^2)(v_{12}dt)}{\Omega} \times \{v_{12}\} \times x_1 x_2 = \left(\frac{\pi r_{12}^2}{\Omega} \frac{(v_{12}p_j(v_{12}))_{\nu_{12}}}{c_j}\right) x_1 x_2 dt = \frac{8k_B T}{\pi m_{12}} \frac{E_f}{k_B T} \exp \left( -\frac{E_f}{k_B T} \right) \text{Arrhenius}$$
Two exact, rigorously derivable consequences . . .

1. The chemical master equation (CME):

\[
\frac{\partial P(x,t|x_0,t_0)}{\partial t} = \sum_{j=1}^{M} [a_j(x - \nu_j)P(x - \nu_j,t|x_0,t_0) - a_j(x)P(x,t|x_0,t_0)].
\]

- \( P(x,t|x_0,t_0) \triangleq \text{Prob}\{X(t) = x, \text{given} X(t_0) = x_0\} \) for \( t \geq t_0 \).
- Follows from the probability statement

\[
P(x,t+dt|x_0,t_0) = P(x,t|x_0,t_0) \times \left[ 1 - \sum_{j=1}^{M} (a_j(x)dt) \right] + \sum_{j=1}^{M} P(x-\nu_j,t|x_0,t_0) \times (a_j(x-\nu_j)dt).
\]

- But the CME is usually too hard to solve.

- Averages:

\[
\langle f(X(t)) \rangle \triangleq \sum_{x} f(x)P(x,t|x_0,t_0).
\]

If we multiply the CME through by \( x \) and then sum over \( x \), we find

\[
\frac{d\langle X(t) \rangle}{dt} = \sum_{j=1}^{M} \nu_j \langle a_j(X(t)) \rangle.
\]

- If there were no fluctuations,

\[
\langle a_j(X(t)) \rangle = a_j(\langle X(t) \rangle) = a_j(X(t)),
\]

and the above would reduce to:

\[
\frac{dX(t)}{dt} = \sum_{j=1}^{M} \nu_j a_j(X(t)).
\]

- This is the reaction-rate equation (RRE).
- It’s usually written in terms of the concentration \( Z(t) \triangleq X(t)/\Omega \).

- But as yet, we have no justification for ignoring fluctuations.
2. The **stochastic simulation algorithm** (SSA):

A procedure for constructing **sample paths or realizations** of \( X(t) \).

**Idea:** Generate properly distributed random numbers for
- the time \( \tau \) to the next reaction,
- the index \( j \) of that reaction.

- \( p(\tau, j|\mathbf{x}, t)d\tau \triangleq \text{probability, given } X(t) = \mathbf{x}, \text{ that the next reaction} \]
  \[
  \text{will occur in } [t+\tau, t+\tau+d\tau), \text{ and will be } R_j.
  \]
  \[
  = P_0(\tau)\times a_j(\mathbf{x})d\tau, \quad P_0(\tau) \triangleq \Pr(\text{no reactions in time } \tau).
  \]

\[
P_0(\tau + d\tau) = P_0(\tau)\times(1-a_0(\mathbf{x})d\tau), \quad \text{where } a_0(\mathbf{x}) \triangleq \sum_{j=1}^{M} a_j(\mathbf{x}).
\]

Implies \[ \frac{dP_0(\tau)}{d\tau} = -a_0(\mathbf{x})P_0(\tau). \quad \text{Solution: } P_0(\tau) = e^{-a_0(\mathbf{x})\tau}. \]

\[
\therefore p(\tau, j|\mathbf{x}, t) = e^{-a_0(\mathbf{x})\tau} a_j(\mathbf{x}) = a_0(\mathbf{x}) \frac{e^{-a_0(\mathbf{x})\tau}}{a_0(\mathbf{x})} \times \frac{a_j(\mathbf{x})}{a_0(\mathbf{x})}.
\]

Thus,
- \( \tau \) is an exponential random variable with mean \( 1/a_0(\mathbf{x}), \)
- \( j \) is an integer random variable with probabilities \( a_j(\mathbf{x})/a_0(\mathbf{x}). \)

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**The “Direct” Version of the SSA**

1. In state \( \mathbf{x} \) at time \( t \), evaluate \( a_1(\mathbf{x}), \ldots, a_M(\mathbf{x}) \), and \( a_0(\mathbf{x}) \equiv \sum_{j=1}^{M} a_j(\mathbf{x}). \)

2. Draw two unit-interval uniform random numbers \( r_1 \) and \( r_2 \), and compute \( \tau \) and \( j \) according to

   - \( \tau = \frac{1}{a_0(\mathbf{x})} \ln \left( \frac{1}{r_1} \right), \)
   - \( j \) is the smallest integer satisfying \( \sum_{k=1}^{j} a_k(\mathbf{x}) > r_2 a_0(\mathbf{x}). \)

3. Replace \( t \leftarrow t + \tau \) and \( \mathbf{x} \leftarrow \mathbf{x} + \nu_j. \)

4. Record \( (\mathbf{x}, t) \). Return to Step 1, or else end the simulation.
A Simple Example: $S_i \rightarrow 0$.

$a_i(x_i) = c_i x_i, \quad v_i = -1$. Take $X_i(0) = x_i^0$.

RRE: $\frac{dX_i(t)}{dt} = -c_i X_i(t)$. Solution is $X_i(t) = x_i^0 e^{-c_it}$.

CME: $\frac{\partial P(x_i,t|x_i^0,0)}{\partial t} = c_i \left[ (x_i + 1)P(x_i + 1,t|x_i^0,0) - x_i P(x_i,t|x_i^0,0) \right]$.

Solution: $P(x_i,t|x_i^0,0) = \frac{x_i^0!}{x_i^0(x_i^0 - x_i)!} e^{-c_i t} \left( 1 - e^{-c_i t} \right)^{x_i^0 - x_i} (x_i = 0, 1, \ldots, x_i^0)$

which implies $\{X_i(t)\} = x_i^0 e^{-c_i t}, \quad \text{sdev} \{X_i(t)\} = \sqrt{x_i^0 e^{-c_i t} \left( 1 - e^{-c_i t} \right)}$.

SSA: Given $X_i(t) = x_i$, generate $\tau = \frac{1}{c_i x_i} \ln \left( \frac{1}{r} \right)$, then update:

$t \leftarrow t + \tau, \quad x_i \leftarrow x_i - 1.$
The SSA . . .

- Is exact.
- Does not entail approximating “$df$” by “$Δf$”.
- Is logically on par with the CME (but is not a method for numerically solving the CME).
- Is procedurally simple, even when the CME is intractable.
- Comes in a variety of implementations …
  - Direct Method (Gillespie, 1976)
  - First Reaction Method (Gillespie, 1976)
  - Next Reaction Method (Gibson & Bruck, 2000)
  - First Family Method (Lok, 2003)
  - Modified Direct Method (Cao, Li & Petzold, 2004)
  - Sorting Direct Method (McCollum, et al. 2006)

- Remains too slow for most practical problems: Simulating every reaction event one at a time just takes too much time if any reactants are present in very large numbers.
We would be willing to sacrifice a little exactness . . .
. . . if that would buy us a faster simulation.

_Tau-Leaping_

- **Approximately** advances the process by a _pre-selected_ time \( \tau \), which may encompass _more than one_ reaction event.

- **Key:** The definition of “the Poisson random variable with mean \( a \tau \)”:
  \[ \mathcal{P}(a \tau) \triangleq \text{the number of events} \] that will occur in a time \( \tau \), _given_ that the probability of an event in any \( dt \) is \( adt \) where \( a \) can be any positive _constant_.

- With \( X(t) = x \), let us choose \( \tau \) _small enough_ to satisfy the _Leap Condition:_ Each \( a_j(x) \approx \text{constant} \) in \([t, t+\tau]\).

- Then: The number of \( R_j \) firings in \([t, t+\tau]\) \( \approx \mathcal{P}(a_j(x)\tau) \).

\[
X(t + \tau) \approx x + \sum_{j=1}^{M} \mathcal{P}(a_j(x)\tau) v_j
\]

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*_Practical Implementation of Tau-Leaping_*

- We have _two control parameters_, \( \epsilon \) and \( n_c \):
  - **To satisfy the Leap Condition**, restrict \( \tau \) so that \( |A_j a_j|/a_j \leq \epsilon, \forall j \).
  - **To avoid populations <0**, allow only one firing of all _critical_ reactions (\( \triangleq \) reactions that are within \( n_c \) firings of exhausting any reactant).

- We take \( \tau = \min(\tau', \tau^*) \), where:
  - \( \tau' \) maximally satisfies the Leap Condition for firings of the _non-critical_ reactions. (We have a fairly efficient way to estimate \( \tau' \).)
  - \( \tau^* \) is the time to the _next critical_ reaction. (Generate \( \tau^* \) by applying the SSA to the _critical_ reactions.)

- **For each non-critical** \( R_j \), generate \( k_j \) as a sample of \( \mathcal{P}(a_j(x)\tau) \).

- **If** \( \tau' < \tau^* \): Set the \( k_j \)'s for all the _critical_ \( R_j \)'s to 0.
  - **If** \( \tau^* \leq \tau' \): Use the SSA to determine which critical reaction fires, set its \( k_j \) to 1, and set all other critical \( k_j \)'s to 0.

- **Leap:** \( t \leftarrow t + \tau \) and \( x \leftarrow x + \sum_{j=1}^{M} k_j v_j \).
  - **Becomes the SSA if all reactions are critical** \( (n_c \to \infty) \).
monomer X1, unstable dimer X2, stable dimer X3

- Exact SSA Run.
- Initially: X1=100,000; X2=X3=0.
- 500 reactions per plotted dot
- 517,067 reactions total.

Explicit Tau Leaping Run
- $\epsilon = 0.04$; $n_c = 10$.
- 1 leap per plotted dot.
- 905 leaps total.
- Run time speedup over SSA > 10X.
\[ a_j(x) \, dt \triangleq \text{Prob that } R_j \text{ will fire in next } dt \]

\[ \{ a_j(x) \approx \text{const over } \tau, \forall j \} \]

CME \quad SSA \quad Tau-Leaping \quad Discrete & Stochastic

**Speeding up Tau-Leaping: The Langevin Equation**

- Two math facts:
  - If \( m \gg 1 \), then \( P(m) \approx N(m,m) \).
  - \( N(m,\sigma^2) = m + \sigma N(0,1) \).
- So, with \( X(t) = x \), suppose we can choose \( \tau \) small enough to satisfy the Leap Condition, yet also large enough that \( a_j(x) \, \tau \gg 1, \forall j \).

Then . . .

\[ X(t+\tau) \doteq x + \sum_{j=1}^{M} p_j \left( a_j(x) \tau \right) \nu_j \]

\[ \doteq x + \sum_{j=1}^{M} N_j \left( a_j(x) \tau, a_j(x) \tau \right) \nu_j \]

\[ \doteq x + \sum_{j=1}^{M} \left[ a_j(x) \tau + \sqrt{a_j(x) \tau} N_j(0,1) \right] \nu_j \]

\[ \text{✓ } X(t+\tau) \doteq x + \sum_{j=1}^{M} \nu_j a_j(x) \tau + \sum_{j=1}^{M} \nu_j \sqrt{a_j(x)} \, N_j(0,1) \sqrt{\tau} . \]
\[ \mathbf{X}(t + \tau) \approx \mathbf{x} + \sum_{j=1}^{M} \nu_j a_j(\mathbf{x}) \tau + \sum_{j=1}^{M} \nu_j \sqrt{a_j(\mathbf{x})} \mathcal{N}(0,1) \sqrt{\tau} \]

- This is the **Langevin leaping formula**.
- It’s faster than the ordinary tau-leaping formula, because
  - \( a_j(\mathbf{x}) \tau \gg 1 \) means *lots* of reaction events get leapt over in \( \tau \);
  - *normal* random numbers can be generated faster than Poissons.
- It directly implies, and is entirely equivalent to, a SDE called the **chemical Langevin equation** (CLE):

\[
\frac{d\mathbf{X}(t)}{dt} \Delta \sum_{j=1}^{M} \nu_j a_j(\mathbf{X}(t)) + \sum_{j=1}^{M} \nu_j \sqrt{a_j(\mathbf{X}(t))} \Gamma_j(t) .
\]

- *Gaussian white noise*: \( \Gamma(t) \Delta \lim_{dt \to 0^+} \frac{\mathcal{N}(0,1)}{\sqrt{dt}} \equiv \lim_{dt \to 0^+} \mathcal{N} \left( 0, \frac{1}{dt} \right) .
\)
- Satisfies \( \langle \Gamma_j(t) \Gamma_j(t') \rangle = \delta_{jj} \delta(t-t') \).

- Our *discrete stochastic* process \( \mathbf{X}(t) \) has now been *approximated* as a *continuous stochastic* process.

\[ \textit{a}_j(\mathbf{x}) \text{dt} \equiv \text{Prob that } R_j \text{ will fire in next } \text{dt} \]

\[ \{ \textit{a}_j(\mathbf{x}) \approx \text{const over } \tau, \forall j \} \]

\[ \{ \textit{a}_j(\mathbf{x}) \tau \gg 1, \forall j \} \]

\[ \{ \text{CFPE} \rightarrow \text{CLE} \} \]

\[ \{ \text{CME, SSA, Tau-Leaping } \rightarrow \text{Discrete & Stochastic} \} \]

\[ \{ \text{CFPE, CLE } \rightarrow \text{Continuous & Stochastic} \} \]

\[ \star \rightarrow \text{J. Chem. Phys. } 113:297 \text{ (2000)} \]
\[ \star \rightarrow \text{Am. J. Phys. } 64:1246 \text{ (1996)} \]
\[ \star \rightarrow \text{J. Phys. Chem. A } 106:5063 \text{ (2002)} \]
The Thermodynamic Limit

**Def:** All $X_i \to \infty$, and $\Omega \to \infty$, with $X_i/\Omega$ constants.

- $a_j = c_j x_1 - x_1$
- $a_j = c_j x_1 x_2 - \Omega^{-1} x_1 x_2 - x_2$

In the thermodynamic limit, all $a_j$'s grow like (system size).

- In the thermodynamic limit, we see that in the CLE

\[
\frac{dX(t)}{dt} = \sum_{j=1}^{M} \nu_j a_j(X(t)) + \sum_{j=1}^{M} \nu_j \sqrt{a_j(X(t))} \Gamma_j(t),
\]

- the deterministic term grows like (system size),
- the stochastic term grows like (system size)$^{1/2}$.

- **Rule of Thumb:** Relative fluctuations die off as (system size)$^{-1/2}$.
- **At the thermodynamic limit** the stochastic term disappears, leaving

\[
\frac{dX(t)}{dt} = \sum_{j=1}^{M} \nu_j a_j(X(t)) \quad \text{the RRE \ldots derived!}
\]

$X(t)$ has now become a **continuous deterministic** process.

- $a_j(x) dt \triangleq \text{Prob that } R_j \text{ will fire in next } dt$

\[
\{a_j(x) \approx \text{const over } \tau, \forall j\}
\]

- $a_j(x) \tau \gg 1, \forall j$

\[
\{CME, SSA, \tau\text{-Leaping}\}
\]

- $\{\text{Discrete & Stochastic}\}$

\[
\{\text{CLE}\}
\]

- $\{\text{Continuous & Stochastic}\}$

\[
\{\text{RRE}\}
\]

- $\{\text{Continuous & Deterministic}\}$

- $\{X_i \to \infty, \ \Omega \to \infty\}$

- $\{X_i/\Omega = \text{const}_i, \forall i\}$
Complications from “Stiffness”

- Some $R_j$ may be very fast, others very slow.
- Some $X_i$ may be very fast, others very slow.
- “Fast” and “slow” are interconnected – not easy to separate.
- Often manifests as dynamical stiffness, a known ODE problem.
- SSA still works, and is exact. But it’s agonizingly slow.
- Tau-leaping remains accurate, but the Leap Condition restricts $\tau$ to the shortest (fastest) time scale of the system. Still very slow.

- **One approach:** Implicit Tau-Leaping
  - A stochastic adaptation of the implicit Euler method for ODEs.
- **Another approach:** The Slow-Scale Stochastic Simulation Algorithm
  - skips over the fast reactions and simulates only the slow reactions, using specially modified propensity functions. An adaptation of the partial equilibrium / quasi steady-state method for RREs.

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