A Chemically Reacting System

- Molecules of $N$ chemical species $S_1, \ldots, S_N$.
  - In a volume $\Omega$, at temperature $T$.
  - Different conformations or excitation levels are considered different species if they behave differently.

- $M$ “elemental” reaction channels $R_1, \ldots, R_M$.
  - each $R_j$ describes a single instantaneous physical event, which changes the population of at least one species. Thus, $R_j$ is either
    $\emptyset \rightarrow S_i$,
    or
    $S_i \rightarrow$ something else,
    or
    $S_i + S_r \rightarrow$ something else.
**Question:** How does this 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.
- Implies the system evolves *continuously* and *deterministically*.
- Empirically accurate for large systems.
- Often not adequate for small systems.

* * *

The question deserves a more carefully considered answer.

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**Molecular Dynamics (MD)**

- The most exact way of describing the system’s evolution.
- 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 positions of the molecules (and also maintain thermal equilibrium).
- The non-reactive collisions merely serve to keep the system well-stirred or spatially homogeneous for the reactive collisions.
- Can describe the state of the system by $X(t) \triangleq (X_1(t), \ldots, X_N(t))$,
  $$X_i(t) \triangleq \text{the number of } S_i \text{ molecules at time } t.$$ 

But this well-stirred simplification, which . . .

- ignores the non-reactive collisions,
- truncates the definition of the system’s state,
  . . . comes at a price:

  $X(t)$ must be viewed as a stochastic process.

- In fact, the system was never deterministic to begin with!
  Even if molecules moved according to classical mechanics . . .
  - monomolecular reactions always involve QM.
  - bimolecular reactions require collisions, whose extreme sensitivity to initial conditions renders them essentially random.
  - bimolecular reactions usually involve QM too.
- But stochastic processes can be handled.
For well-stirred systems, each $R_j$ is completely characterized by:

- a **propensity function** $a_j(\mathbf{x})$: Given the system in state $\mathbf{x}$,
  
  $a_j(\mathbf{x}) \, dt \triangleq \text{the probability that one } R_j \text{ event will occur in the next } dt$.
  
  - The existence and form of $a_j(\mathbf{x})$ follow from kinetic theory.
  
  - $a_j(\mathbf{x})$ is roughly equal to, but is not derived from, the RRE “rate”.

- a **state change vector** $\nu_j \equiv (v_{ij}, \ldots, v_{iN_j})$: $v_{ij} \triangleq \text{the change in the number of } S_i \text{ molecules caused by one } R_j \text{ event}$.
  
  - $R_j$ induces $\mathbf{x} \to \mathbf{x} + \nu_j$. 

  \[ \{ v_{ij} \} \equiv \text{the “stoichiometric matrix.”} \]

*E.g.*

\[
S_1 + S_2 \xrightarrow{c_2} 2S_1 \quad \Rightarrow \quad \begin{cases} 
    a_1(\mathbf{x}) = c_1 x_1 x_2, & \mathbf{v}_1 = (+1,-1,0,...,0) \\
    a_2(\mathbf{x}) = c_2 \frac{x_1(x_1-1)}{2}, & \mathbf{v}_2 = (-1,+1,0,...,0) 
\end{cases}
\]
Two exact, rigorously derivable consequences . . .

1. The chemical master equation (CME):
\[
\frac{\partial P(x,t|x_0,t_0)}{\partial t} = \sum_{j=1}^{M} \left[ a_j(x - \nu_j)P(x - \nu_j,t|x_0,t_0) - a_j(x)P(x,t|x_0,t_0) \right].
\]
- Gives \( P(x,t|x_0,t_0) \doteq \text{Prob}\{X(t) = x \text{ given } X(t_0) = x_0\} \) for \( t \geq t_0 \).
- The CME 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 it’s practically always intractable (analytically and numerically).

- With \( \langle f(X(t)) \rangle \doteq \sum_x f(x)P(x,t|x_0,t_0) \), can show from CME that
\[
\frac{d}{dt} \langle X(t) \rangle = \sum_{j=1}^{M} \nu_j \langle a_j(X(t)) \rangle.
\]
- If there were no fluctuations, we would have
\[
\langle f(X(t)) \rangle = f\left(\langle X(t) \rangle \right) = f(X(t)),
\]
and the above would reduce to the reaction-rate equation (RRE):
\[
\frac{dX(t)}{dt} = \sum_{j=1}^{M} \nu_j a_j(X(t)).
\]
(Usually written in terms of the concentration \( Z(t) \doteq X(t)/\Omega \).)
- 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 $X(t)$.
   - Approach: Generate the time to the next reaction and the index of that reaction.
   - Theoretical justification: With $p(\tau, j|x, t)$ defined by
     $$p(\tau, j|x, t) d\tau \triangleq \text{prob, given } X(t) = x, \text{that the next reaction will occur in } [t+\tau, t+\tau+d\tau], \text{and will be an } R_j,$$
     can prove that
     $$p(\tau, j|x, t) = a_j(x) \exp\left(-a_0(x) \tau\right), \quad \text{where } a_0(x) \triangleq \sum_{j=1}^{M} a_j(x).$$
     This implies that the time $\tau$ to the next reaction event is an exponential random variable with mean $1/a_0(x)$, and the index $j$ of that reaction is an integer random variable with prob $a_j(x)/a_0(x)$.

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The “Direct” Version of the SSA

1. With the system in state $x$ at time $t$, evaluate $a_0(x) \triangleq \sum_{j=1}^{M} a_j(x)$.
2. Draw two unit-interval uniform random numbers $r_1$ and $r_2$, and compute $\tau$ and $j$ according to
   - $\tau = \frac{1}{a_0(x)} \ln \left(\frac{1}{r_1}\right)$,
   - $j = \text{the smallest integer satisfying } \sum_{j=1}^{j} a_j(x) > r_2 a_0(x)$.
3. Replace $t \leftarrow t + \tau$ and $x \leftarrow x + \nu_j$.
4. Record $(x, t)$. Return to Step 1, or else end the simulation.
A Simple Example: \( S_1 \rightarrow 0 \).

\[ a_1(x_i) = c_1 x_i, \quad \nu = -1. \text{ Take } X_i(0) = x_i^0. \]

RRE: \( \frac{dX_i(t)}{dt} = -c_1 X_i(t) \). Solution is \( X_i(t) = x_i^0 e^{-c_1 t} \).

CME: \( \frac{\partial P(x,t|x_i^0,0)}{\partial t} = c_1 \left[ (x_i + 1) P(x_i + 1,t|x_i^0,0) - x_i P(x_i,t|x_i^0,0) \right] \).

Solution: \( P(x,t|x_i^0,0) = \frac{x_i^0!}{x_i! (x_i^0 - x_i)!} e^{-c_1 t} \left( 1 - e^{-c_1 t} \right)^{x_i^0 - x_i} \) (\( x_i = 0,1,\ldots,x_i^0 \))

which implies \( \langle X_i(t) \rangle = x_i^0 e^{-c_1 t}, \text{ sdev} \{ X_i(t) \} = \sqrt{x_i^0 e^{-c_1 t} \left( 1 - e^{-c_1 t} \right)} \).

SSA: Given \( X_i(t) = x_i \), generate \( \tau = \frac{1}{c_1 x_i} \ln \left( \frac{1}{r} \right) \), then update:

\[ t \leftarrow t + \tau, \quad x_i \leftarrow x_i - 1. \]
$\hat{S}_1 \to 0$
$c_1 = 1, \ X(0) = 100$
The SSA . . .

- Is **exact**.
- Is equivalent to (but is not derived from) the CME.
- Does **not** entail approximating “$dt$” by “$\Delta t$”.
- Is **procedurally simple**, even when the CME is intractable.
- Has been redesigned to be faster and more efficient for very large systems (though more complicated to code) by Gibson and Bruck.

- **Remains too slow for most practical problems**: Simulating every reaction event, **one** at a time, is just too much work if any reactant is present in very large numbers.
We would be willing to sacrifice a little exactness . . .

. . . if that would buy us a faster simulation.

One way of doing this: **Tau-Leaping**

- **Approximately** advances the process by a *pre-selected* time \( \tau \), which may encompass *more than one* reaction event.
- The size of \( \tau \) is limited by the **Leap Condition**: *The changes induced in the propensity functions during \( \tau \) must be “small”.*
- If \( \tau \) can also be taken large enough to encompass many reaction events, tau-leaping will be faster than the SSA.
- Real speed-ups of 100× obtained for some simple model systems.
- **But must use with care.** Not as automatic and foolproof as the SSA.

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**Basics of Tau-Leaping**

- Some math: The *Poisson random variable* \( \mathcal{P}(a, \tau) \triangleq \) the number of events that will occur in time \( \tau \), given that the probability of an event occurring in any \( dt \) is \( adt \).
- So, with \( \mathbf{X}(t) = \mathbf{x} \), if \( \tau \) is such that \( a_j(\mathbf{x}) = \) constant in \([t, t+\tau]\), then the number of \( R_j \) reactions that will occur in \([t, t+\tau]\) is *approximately* \( \mathcal{P}\left( a_j(\mathbf{x}), \tau \right) \); hence,

\[
\mathbf{X}(t+\tau) \triangleq \mathbf{x} + \sum_{j=1}^{M} \mathcal{P}\left( a_j(\mathbf{x}), \tau \right) \mathbf{v}_j .
\]

- Often feasible because . . .
  - Reliable procedures exist for generating samples of \( \mathcal{P}(a, \tau) \).
  - A way has been found to estimate in advance the *largest* \( \tau \) for a specified degree of adherence to the Leap Condition.
The Tau-Leap Simulation Algorithm

1. In state $x$ at time $t$, choose $\tau$ so that the expected change in every propensity function in $[t,t+\tau]$ is $\leq \epsilon a_j(x)$. (This can be done.)

2. Generate the number of firings $k_j$ of channel $R_j$ in $[t,t+\tau]$ as $k_j = P \left( a_j(x), \tau \right)$ ($j = 1, \ldots, M$).

3. Leap: Replace $t \leftarrow t + \tau$ and $x \leftarrow x + \sum_{j=1}^{M} k_j \nu_j$.

4. Record $(x,t)$. Then return to Step 1, or else end the simulation.
Decaying-Dimerizing Reaction Set

- $S_1 \rightarrow 0 \quad c_1 = 1$
- $S_1 + S_1 \rightarrow S_2 \quad c_2 = 0.002$
- $S_2 \rightarrow S_1 + S_1 \quad c_3 = 0.5$
- $S_2 \rightarrow S_3 \quad c_4 = 0.04$

- Explicit Tau Leaping Run ($\epsilon = 0.03$)
- 1 leap per plotted dist.
- Initially: $X_1 = 100,000; \quad X_2 = X_3 = 0.$
- Last reaction at $T = 44.52.$
- Final $X(3) = 17,033.$
- 592 leaps total.

Decaying-Dimerizing Reaction Set

$R_1: \quad S_1 \rightarrow 0 \quad A_1 = C_1^* X_1$
$R_2: \quad S_1 + S_1 \rightarrow S_2 \quad A_2 = C_2^* X_1(X_1-1)/2$
$R_3: \quad S_2 \rightarrow S_1 + S_1 \quad A_3 = C_3^* X_2$
$R_4: \quad S_2 \rightarrow S_3 \quad A_4 = C_4^* X_2$

Plots of $A_j/A_0$, where $A_0 = A_1 + A_2 + A_3 + A_4.$
Exact SSA run. 500 reactions per plotted point.
3 x 10,000 Simulation Runs

$t=0$: $X_1=4150$, $X_2=39565$, $X_3=3445$

Gaussian-windowed histograms of $X_1$ at $t=10$

- Exact SSA (32 hours).
- Tau-leaping, $\epsilon=0.02$, (11 minutes).
- Tau-leaping, $\epsilon=0.03$, (6.5 minutes).

3 x 10,000 Simulation Runs

$t=0$: $X_1=4150$, $X_2=39565$, $X_3=3445$

Gaussian-windowed histograms of $X_2$ at $t=10$

- Exact SSA
- Tau-leaping ($\epsilon=0.02$)
- Tau-leaping ($\epsilon=0.03$)
We can push Tau-Leaping further . . .

• Some more math: $\mathcal{P}(a, \tau)$ has mean and variance $a\tau$. And when $a\tau \gg 1$, can approximate $\mathcal{P}(a, \tau) \approx \mathcal{N}(a\tau, a\tau) \equiv a\tau + \sqrt{a\tau}\mathcal{N}(0,1)$.

• So, with $X(t) = x$, suppose we can choose $\tau$ to satisfy the Leap Condition, and also the conditions $a_j(x) \tau \gg 1$, $\forall j$. Then

$$X(t + \tau) \approx x + \sum_{j=1}^{M} \mathcal{P}(a_j(x), \tau) \nu_j$$

can be further approximated to

$$X(t + \tau) \approx x + \sum_{j=1}^{M} \nu_j a_j(x) \tau + \sum_{j=1}^{M} \nu_j \sqrt{a_j(x)} \mathcal{N}_j(0,1) \sqrt{\tau}.$$  

• Valid iff $\tau$ is chosen small enough to satisfy the Leap Condition, yet large enough that every $R_f$ fires many more times than once in $\tau$.

• It’s not always possible to find such a $\tau$! But it usually is if all the reactant populations are “sufficiently large”.
\[ X(t + \tau) = x + \sum_{j=1}^{M} \nu_j a_j(x) \tau + \sum_{j=1}^{M} \nu_j \sqrt{a_j(x)} \mathcal{N}_j(0,1) \sqrt{\tau} \]

- Is called the **Langevin leaping formula**.
- It’s **faster** than ordinary tau-leaping.
- It **directly implies** (and is entirely equivalent too) a SDE called the **chemical Langevin equation** (CLE):

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

\( \Gamma_j \)'s are “Gaussian white noises”, \( \mathbb{E}[\Gamma_j(t) \Gamma_j(t')] = \delta_{jj'} \delta(t - t') \).

- Our **discrete stochastic** process \( X(t) \) has now been **approximated** as a **continuous stochastic** process.
- Again, the CLE can’t always be invoked. But it usually can **if all the reactant molecular populations are “sufficiently large”**.

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**The Thermodynamic Limit**

**Def:** All \( X_i \to \infty \), and \( \Omega \to \infty \), with \( X_i/\Omega \) constant.

- Can prove that, in this limit, **all** propensity functions **grow linearly** with the system size.
- So as we approach this limit, 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), while the **stochastic** term grows like \( \sqrt{\text{system size}} \).

- This establishes the well know rule-of-thumb: **Relative fluctuations scale as the inverse square root of the system size**.
- **Very near** the thermodynamic limit, the CLE approximates to

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

the **reaction rate equation** (RRE)! \( X(t) \) has now become a **continuous deterministic** process. And we’ve **derived** the RRE!
Summarizing . . .

Start with Molecular Dynamics
- The Gold Standard.
- “State” = positions and velocities of all the molecules.
- Simulates all collisions, non-reactive as well as reactive.
- But is way too slow.

The “well-stirred” simplification gives the CME/SSA
- Assumes the non-reactive collisions occur frequently enough to keep the system well-stirred (spatially homogeneous) for the reactive collisions.
- Simulates only the reactive collisions.
- “State” = the molecular populations of all the species, \( X(t) \).
- \( X(t) \) is a discrete stochastic process.

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The Spectrum of Analytical Approaches for Well-Stirred Systems

\[
\begin{align*}
a_j(x) &= \text{const} \\
\forall j \in [t, t+\tau], \forall j &\quad \tau \gg 1 \\
X_i &\to \infty, \Omega \to \infty \\
\end{align*}
\]

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Is it simply a matter of picking the “right tool” from this spectrum?
Not quite.
Complications from “Multiscale”

- Some $R_j$ occur very much more frequently than others.
- Some $X_i$ are very much larger than others.
- Fast & slow & small & large usually all occur coupled – not easy to separate.
- Leads to dynamical stiffness, which usually restricts $\tau$ to the smallest time scale in the system.
- One recently proposed fix: Implicit tau-leaping – a stochastic adaptation of the implicit numerical solution method for stiff ODEs.
- Other proposed fixes: stochastic versions of the quasi-steady state and partial equilibrium approximation methods of deterministic chemical kinetics.

Spatially Inhomogeneous Systems

- Spatial homogeneity does not require that all equal-size subvolumes of $\Omega$ contain the same number of molecules!
- The CME and SSA require only that the center of a randomly chosen $S_i$ molecule be found with equal probability at any point inside $\Omega$.
- A system consisting of only one molecule can be “well-stirred”.
  
  - But the well-stirred assumption can’t always be made.

In that case, we must do something different; however, the traditional reaction-diffusion equation (RDE) is not always the answer:

- The RDE (like the RRE) is continuous and deterministic.
- It assumes that each $d\Omega$ contains a spatially homogeneous mixture of infinitely many molecules.
- Not the case in most cellular systems, where spatial inhomogeneity arises not from slow mixing but rather from compartmentalization caused by highly heterogeneous structures within the cell.
We can formulate a spatially inhomogeneous CME/SSA: Subdivide $\Omega$ into $K$ spatially homogeneous subvolumes $\{\Omega_k\}$. Mathematically is the same as in the homogeneous case, except now we have

- $KN$ species $\{S_{ik}\}$, and $KM$ chemical reactions $\{R_{jk}\}$,
- plus a whole bunch of diffusive transfer reactions $\{R_{diff}^{i,j,k}\}$.

**Challenges:**

- Enormous increases in the numbers of species and reactions, so simulations will run orders of magnitude slower.
- No unambiguous definition of spatial homogeneity, hence no clear criterion for making the partitioning $\Omega \rightarrow \{\Omega_k\}$.
- Dynamically altering the $\{\Omega_k\}$ will probably be necessary, and will require bookkeeping that is complicated and time-consuming.
- Conflicting ways to compute the diffusive transfer rate constants.