STOCHASTIC CHEMICAL KINETICS

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A Chemically Reacting System consists of …

- Molecules of N ***chemical species*** $S_1,\ldots,S_N$.
  - Inside a volume Ω, at some temperature T.
- M "elemental" ***reaction channels*** $R_1,\ldots,R_M$.
  - We assume R_j to be a ***single instantaneous physical event*** that changes the population of at least one species.
  - In practice, "elemental" means that R_j must be one of two types:

    Unimolecular: $S_i \to$ something else,

    or

    Bimolecular: $S_i + S_{i'} \to$ something else.
  - All other types of reaction (trimolecular, reversible, etc.) are made up of a series of two or more elemental reactions. E.g.:

$$S_1 + S_2 + S_3 \to S_4 + S_5 \quad \text{is typically} \quad \begin{cases} S_1 + S_2 \rightleftharpoons S_{12} \\ S_{12} + S_3 \to S_4 + S_5 \end{cases}$$

Question: **How does a spatially homogeneous (or well-stirred) chemically reacting system evolve in time?**

The Trad Answer:

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 complete equilibrium.
- Implies the system evolves *continuously* and *deterministically*.
  - Yet molecules come in integer numbers and react stochastically.
- Is empirically accurate for large (test tube size) systems
- But is sometimes not adequate for very small (cell-size) systems.

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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

$$\mathbf{X}(t) \triangleq \left(X_1(t), \ldots, X_N(t) \right),$$

$X_i(t) \triangleq$ the *number* of S_i molecules at time t.

But this ***well-stirred simplification***, which . . .

- *ignores* the non-reactive collisions,
- *drastically truncates* the definition of the system's state,

. . . comes at a price:

$\mathbf{X}(t)$ *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*** $a_j(\mathbf{x})$: Given the system is in state $\mathbf{x}$,

  $a_j(\mathbf{x})\,dt \triangleq$ *probability* that one R_j event will occur in the next dt.

  - The *existence* and *form* of $a_j(\mathbf{x})$ follow from *molecular physics*.

- a ***state change vector*** $\boldsymbol{\nu}_j \equiv \left(\nu_{1j},\ldots,\nu_{Nj}\right)$:

  $\nu_{ij} \triangleq$ the *change* in X_i caused by one R_j event.

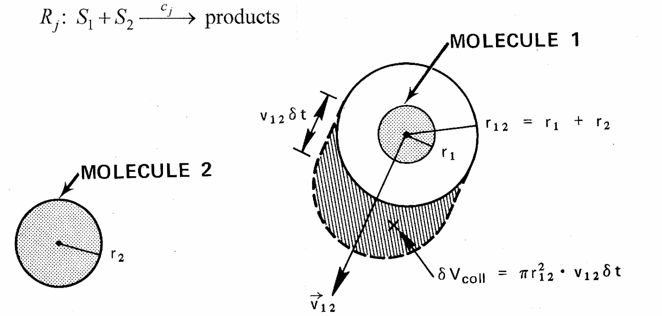
  - R_j induces $\mathbf{x} \to \mathbf{x} + \boldsymbol{\nu}_j$. $\left\{\nu_{ij}\right\} \equiv$ the "stoichiometric matrix."

Examples:

$$S_1 \xrightarrow{c_j} S_2 : \ \boldsymbol{\nu}_j = \left(-1, 1, 0, \ldots, 0\right); \ a_j(\mathbf{x})dt = \left(c_j dt\right) \times x_1 \Rightarrow a_j(\mathbf{x}) = c_j x_1$$

$$S_1 + S_2 \xrightarrow{c_j} 2S_2 : \ \text{same } \boldsymbol{\nu}_j; \ a_j(\mathbf{x})dt = \left(c_j dt\right) \times x_1 x_2 \Rightarrow a_j(\mathbf{x}) = c_j x_1 x_2$$

R_j: $S_1 + S_2 \xrightarrow{c_j}$ products



$$\text{Prob}\left\{\text{collision in } dt\right\} = \frac{(\pi r_{12}^2)(\bar{v}_{12} dt)}{\Omega}. \quad \text{Prob}\left\{R_j \,|\, \text{collision}\right\} \equiv p_j.$$

$$a_j(\mathbf{x})\,dt \equiv \underbrace{\left(\frac{(\pi r_{12}^2)(\bar{v}_{12} dt)}{\Omega}\right) \times p_j}_{\substack{\text{Prob that a typical } S_1\text{-}S_2 \\ \text{pair reacts in next } dt}} \times x_1 x_2 = \underbrace{\left(\frac{\pi r_{12}^2 \bar{v}_{12} p_j}{\Omega}\right)}_{c_j} x_1 x_2\,dt = \underbrace{c_j x_1 x_2}_{a_j(\mathbf{x})}\,dt$$

$$R_j \text{ iff "}\textit{collisional K.E.}\text{"} > E_j \ \Rightarrow \ p_j = \exp\left(-\frac{E_j}{k_B T}\right) \text{ ... Arrhenius!}$$

Diffusional motion (well-stirred): $\pi r_{12}^2 \bar{v}_{12}$ is replaced by $4\pi r_{12}(D_1 + D_2)$

Two exact, rigorously derivable consequences . . .

- **1.** The ***chemical master equation*** (CME):

$$\frac{\partial P(\mathbf{x},t\,|\,\mathbf{x}_0,t_0)}{\partial t} = \sum_{j=1}^{M}\left[a_j(\mathbf{x}-\boldsymbol{\nu}_j)P(\mathbf{x}-\boldsymbol{\nu}_j,t\,|\,\mathbf{x}_0,t_0) - a_j(\mathbf{x})P(\mathbf{x},t\,|\,\mathbf{x}_0,t_0)\right].$$

- $P(\mathbf{x},t\,|\,\mathbf{x}_0,t_0) \triangleq \text{Prob}\left\{\mathbf{X}(t)=\mathbf{x},\text{ given }\mathbf{X}(t_0)=\mathbf{x}_0\right\}$ for $t \ge t_0$.
- Follows from the *probability* statement

$$P(\mathbf{x},t+dt\,|\,\mathbf{x}_0,t_0) = P(\mathbf{x},t\,|\,\mathbf{x}_0,t_0)\times\left[1-\sum_{j=1}^{M}\left(a_j(\mathbf{x})dt\right)\right] + \sum_{j=1}^{M}P(\mathbf{x}-\boldsymbol{\nu}_j,t\,|\,\mathbf{x}_0,t_0)\times\left(a_j(\mathbf{x}-\boldsymbol{\nu}_j)dt\right).$$

- But the CME is usually too hard to solve.

- Averages: $\left\langle f\left(\mathbf{X}(t)\right)\right\rangle \triangleq \sum_{\mathbf{x}} f(\mathbf{x})P(\mathbf{x},t\,|\,\mathbf{x}_0,t_0)$.

  If we multiply the CME through by $\mathbf{x}$ and then sum over $\mathbf{x}$, we find

$$\frac{d\left\langle \mathbf{X}(t)\right\rangle}{dt} = \sum_{j=1}^{M}\boldsymbol{\nu}_j\left\langle a_j\left(\mathbf{X}(t)\right)\right\rangle.$$

- ***If*** *there were* ***no fluctuations***,

$$\left\langle a_j\left(\mathbf{X}(t)\right)\right\rangle = a_j\left(\left\langle \mathbf{X}(t)\right\rangle\right) = a_j\left(\mathbf{X}(t)\right),$$

  and the above would reduce to:

$$\frac{d\mathbf{X}(t)}{dt} = \sum_{j=1}^{M}\boldsymbol{\nu}_j a_j\left(\mathbf{X}(t)\right).$$

  - **This is the reaction-rate equation (RRE).**
  - It's usually written in terms of the *concentration* $\mathbf{Z}(t) \triangleq \mathbf{X}(t)/\Omega$.

- **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 $\mathbf{X}(t)$.

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

- $p(\tau, j|\mathbf{x},t)\,d\tau \triangleq$ probability, given $\mathbf{X}(t)=\mathbf{x}$, that the *next* reaction will occur in $[t+\tau, t+\tau+d\tau)$, *and* will be R_j.

$$= P_0(\tau)\times a_j(\mathbf{x})d\tau\,,\quad P_0(\tau)\triangleq \Pr(\textit{no}\text{ reactions in time }\tau)\,.$$

$$P_0(\tau+d\tau)=P_0(\tau)\times\left(1-a_0(\mathbf{x})d\tau\right),\quad\text{where}\quad a_0(\mathbf{x})\triangleq\sum_1^M a_{j'}(\mathbf{x})\,.$$

Implies $\dfrac{dP_0(\tau)}{d\tau}=-a_0(\mathbf{x})P_0(\tau).$ Solution: $P_0(\tau)=\mathrm{e}^{-a_0(\mathbf{x})\tau}$.

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

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

The "Direct" Version of the SSA

1. In state **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 τ and j according to

- $\tau=\dfrac{1}{a_0(\mathbf{x})}\ln\left(\dfrac{1}{r_1}\right)$,
- j = 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 $\mathbf{x}\leftarrow\mathbf{x}+\boldsymbol{\nu}_j$.

4. Record $(\mathbf{x},t)$. Return to Step **1**, or else end the simulation.

A Simple Example: $S_1 \xrightarrow{c_1} 0$.

$a_1(x_1) = c_1 x_1, \quad \nu_1 = -1$. Take $X_1(0) = x_1^0$.

<u>RRE</u>: $\dfrac{dX_1(t)}{dt} = -c_1 X_1(t)$. Solution is $X_1(t) = x_1^0 \, \mathrm{e}^{-c_1 t}$.

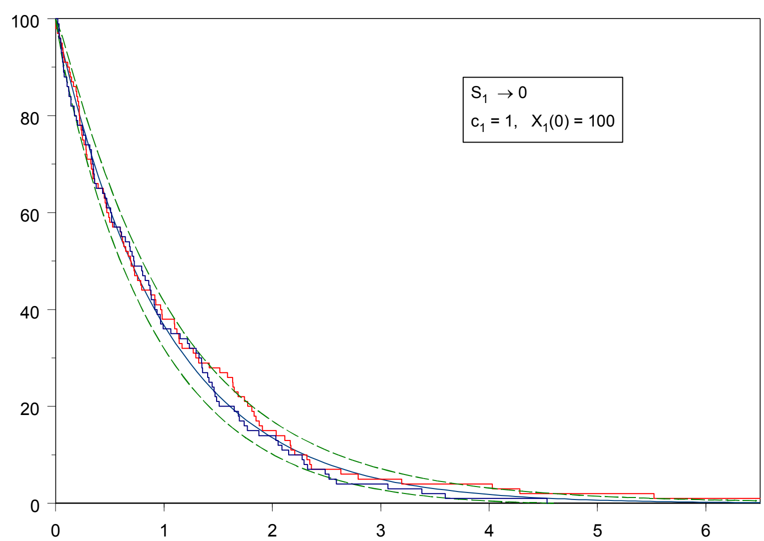
<u>CME</u>: $\dfrac{\partial P(x_1,t\,|\,x_1^0,0)}{\partial t} = c_1\Big[(x_1+1)P(x_1+1,t\,|\,x_1^0,0) - x_1 P(x_1,t\,|\,x_1^0,0)\Big]$.

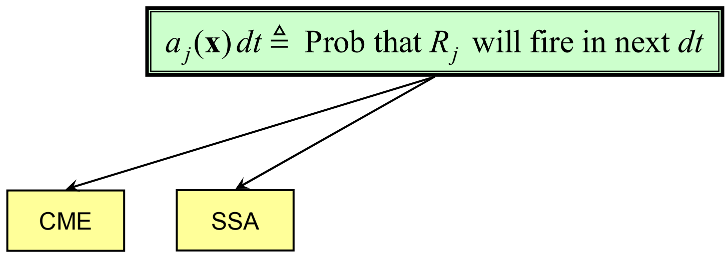
Solution: $P(x_1,t\,|\,x_1^0,0) = \dfrac{x_1^0\,!}{x_1!(x_1^0-x_1)!}\,\mathrm{e}^{-c_1 x_1 t}\left(1-\mathrm{e}^{-c_1 t}\right)^{x_1^0-x_1} \quad (x_1 = 0,1,\ldots,x_1^0)$

which implies $\langle X_1(t)\rangle = x_1^0\,\mathrm{e}^{-c_1 t}$, $\mathrm{sdev}\{X_1(t)\} = \sqrt{x_1^0\,\mathrm{e}^{-c_1 t}\left(1-\mathrm{e}^{-c_1 t}\right)}$.

<u>SSA</u>: Given $X_1(t) = x_1$, generate $\tau = \dfrac{1}{c_1 x_1}\ln\left(\dfrac{1}{r}\right)$, then update:

$$t \leftarrow t + \tau, \quad x_1 \leftarrow x_1 - 1.$$





The SSA . . .

- Is exact. It does *not* entail approximating "*dt*" by "Δt".
- 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 τ, which may encompass *more than one* reaction event.
- *Key*: The "Poisson random variable with mean $a\tau$" can be defined:
  $\mathcal{P}(a\tau) \equiv$ the ***number of events*** that will occur in a time τ,
  when the probability of an event in any dt is $a\,dt$,
  provided a is a positive ***constant***.
- With $\mathbf{X}(t) = \mathbf{x}$, let us choose τ *small enough* to satisfy the

  Leap Condition: Each $a_j(\mathbf{x}) \approx$ ***constant*** in $[t, t+\tau]$.

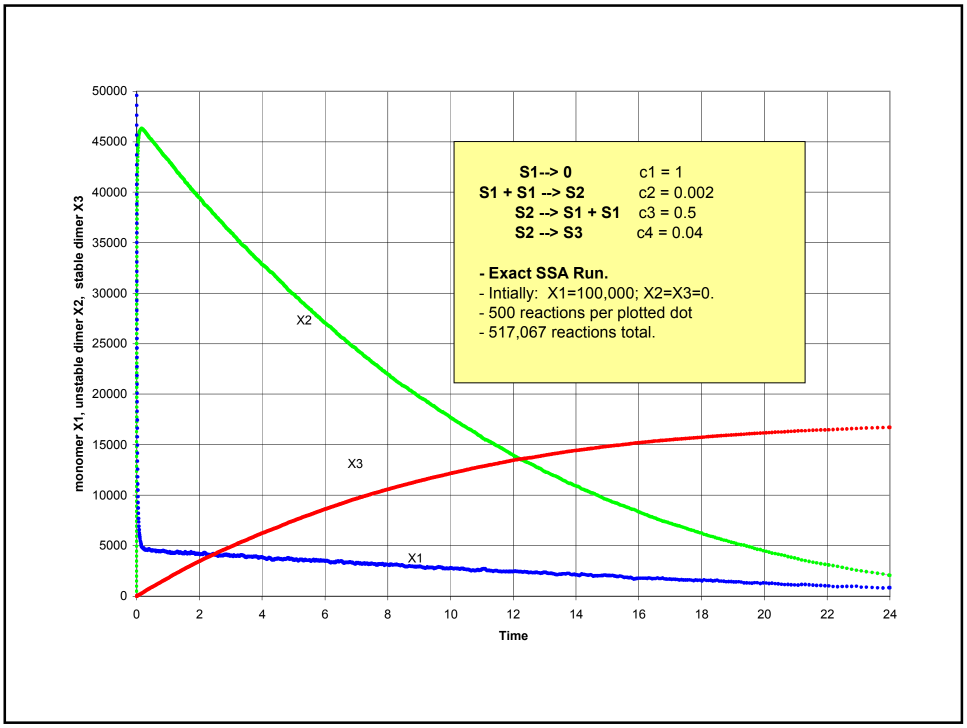
- Then the number of R_j firings in $[t, t+\tau]$ will be $\approx \mathcal{P}\left(a_j(\mathbf{x})\tau\right)$. So …

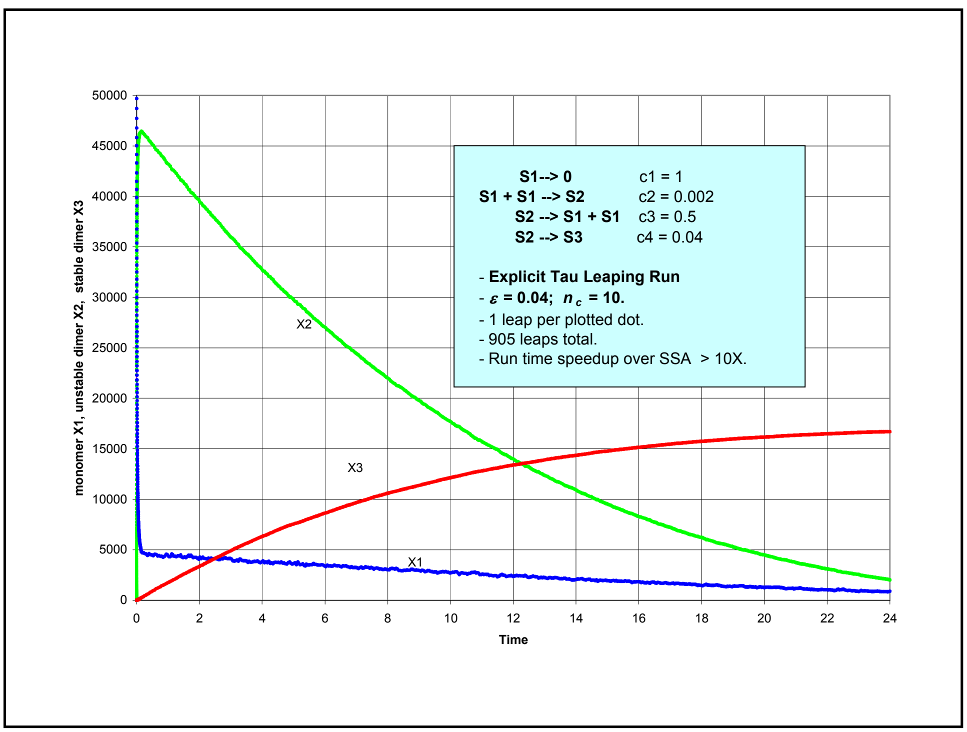
$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \mathcal{P}_j\left(a_j(\mathbf{x})\tau\right) \boldsymbol{\nu}_j$$

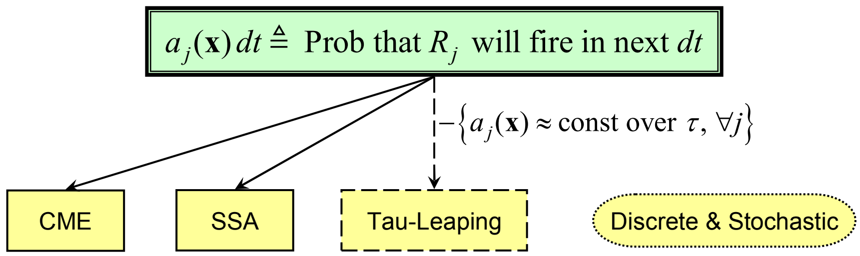
$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \mathcal{P}_j\left(a_j(\mathbf{x})\tau\right) \boldsymbol{\nu}_j$$

- Practical Considerations for Implementing Tau-Leaping -

- **Finding the largest τ that satisfies the Leap Condition.**
  - Accomplished via an accuracy control parameter ε.
  - We estimate the largest τ for which $\left|\Delta_\tau a_j / a_j\right| \le \varepsilon, \forall j$.
- **Avoiding negative populations, and segueing to the SSA**.
  - Accomplished via a second control parameter n_c.
  - We call any reaction that is within n_c firings of exhausting any reactant a ***critical*** reaction. Then we tau-leap *no farther* than the *next* firing of a critical reaction.
  - Becomes the SSA when ***all*** reactions are classified critical.


S1--> 0 c1 = 1
S1 + S1 --> S2 c2 = 0.002
S2 --> S1 + S1 c3 = 0.5
S2 --> S3 c4 = 0.04
- Exact SSA Run.
- Intially: X1=100,000; X2=X3=0.
- 500 reactions per plotted dot
- 517,067 reactions total.
X1
X2
X3
monomer X1, unstable dimer X2, stable dimer X3
Time
0
5000
10000
15000
20000
25000
30000
35000
40000
45000
50000
0 2 4 6 8 10 12 14 16 18 20 22 24


S1--> 0 c1 = 1
S1 + S1 --> S2 c2 = 0.002
S2 --> S1 + S1 c3 = 0.5
S2 --> S3 c4 = 0.04
- Explicit Tau Leaping Run
- ε = 0.04; n c = 10.
- 1 leap per plotted dot.
- 905 leaps total.
- Run time speedup over SSA > 10X.
X1
X2
X3
monomer X1, unstable dimer X2, stable dimer X3
Time
0
5000
10000
15000
20000
25000
30000
35000
40000
45000
50000
0 2 4 6 8 10 12 14 16 18 20 22 24



Speeding up Tau-Leaping: The Langevin Equation

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

Then . . . $$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \mathcal{P}_j\left(a_j(\mathbf{x})\tau\right)\boldsymbol{\nu}_j$$

$$\doteq \mathbf{x} + \sum_{j=1}^{M} \mathcal{N}_j\left(a_j(\mathbf{x})\tau, a_j(\mathbf{x})\tau\right)\boldsymbol{\nu}_j$$

$$\doteq \mathbf{x} + \sum_{j=1}^{M} \left[a_j(\mathbf{x})\tau + \sqrt{a_j(\mathbf{x})\tau}\,\mathcal{N}_j(0,1)\right]\boldsymbol{\nu}_j$$

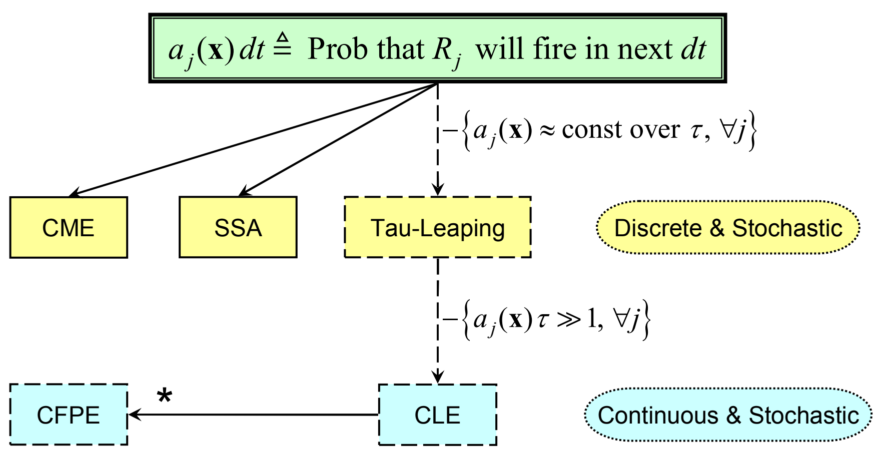
❖ $$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\mathbf{x})\tau + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\mathbf{x})}\,\mathcal{N}_j(0,1)\sqrt{\tau}\ .$$

$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\mathbf{x})\tau + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\mathbf{x})}\,\mathcal{N}_j(0,1)\sqrt{\tau}$$

- 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 τ;
  - *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):

$$\frac{d\mathbf{X}(t)}{dt} \doteq \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\mathbf{X}(t)) + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\mathbf{X}(t))}\,\Gamma_j(t) \ .$$

  - *Gaussian white noise*: $\Gamma(t) \triangleq \lim_{dt\to 0^+} \frac{\mathcal{N}(0,1)}{\sqrt{dt}} \equiv \lim_{dt\to 0^+} \mathcal{N}\left(0, \frac{1}{dt}\right)$.
  - Satisfies $\left\langle \Gamma_j(t)\,\Gamma_{j'}(t') \right\rangle = \delta_{jj'}\,\delta(t-t')$.
- Our *discrete stochastic* process $\mathbf{X}(t)$ has now been *approximated* as a *continuous stochastic* process.



* - J. Chem. Phys. **113**:297 (2000)
- Am. J. Phys. **64**:1246 (1996)
- J. Phys. Chem. A **106**:5063 (2002)

The Thermodynamic Limit

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

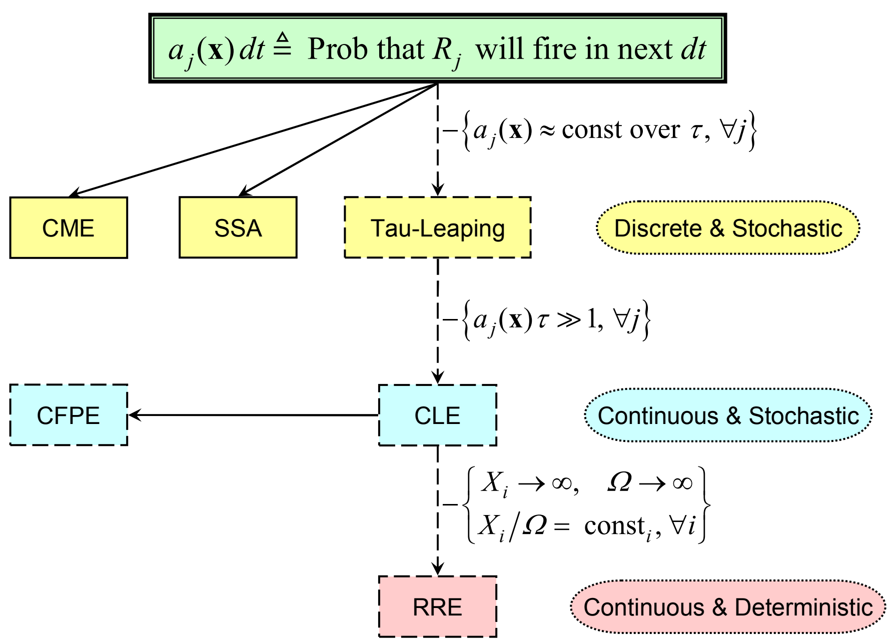
- $\left.\begin{array}{l} a_j = c_j x_1 \sim x_1 \\ a_j = c_j x_1 x_2 \sim \Omega^{-1} x_1 x_2 \sim x_2 \end{array}\right\} \Rightarrow \left\{ \begin{array}{l} \text{In the thermodynamic limit,} \\ \textbf{all } a_j\text{'s grow like (system size).} \end{array}\right.$
- So in the thermodynamic limit, we see that in the CLE

$$\frac{d\mathbf{X}(t)}{dt} \doteq \sum_{j=1}^{M} \boldsymbol{\nu}_j \, a_j\left(\mathbf{X}(t)\right) + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j\left(\mathbf{X}(t)\right)} \, \Gamma_j(t) \ ,$$

  - the *deterministic* term grows like (system size),
  - the *stochastic* term grows like $(\text{system size})^{1/2}$.
- $\Rightarrow$ Rule of Thumb: ***Relative fluctuations die off as*** $\boldsymbol{(\textbf{\textit{system size}})^{-1/2}}$.
- **At the thermodynamic limit** the stochastic term disappears, leaving

$$\frac{d\mathbf{X}(t)}{dt} \doteq \sum_{j=1}^{M} \boldsymbol{\nu}_j \, a_j\left(\mathbf{X}(t)\right) \quad \ldots \text{ the } \textbf{RRE} \ldots \textbf{\textit{derived!}}$$

$\mathbf{X}(t)$ has now become a ***continuous deterministic*** process.



A Spectrum of Descriptive Mathematical Modes
(for **well-stirred** systems)

$a_j(\mathbf{x}) \approx \text{const}$ in $[t, t+\tau], \forall j$	$a_j(\mathbf{x})\tau \gg 1$ $\forall j$	$X_i \to \infty$, $\Omega \to \infty$ $X_i/\Omega \to \text{const}_i$	
CME/SSA →	**Tau-Leaping** →	**CLE/CFPE** →	**RRE**
exact	approximate	approximate	approximate
discrete	discrete	continuous	continuous
stochastic	stochastic	stochastic	deterministic

increasing numbers of molecules →

Another Multi-Scale Problem

- Some reactions/species 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 τ to the shortest (fastest) time scale of the system. So even it's too 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 "rapid equilibrium" / "quasi steady-state" methods for RREs.