Mathematical models of the dynamical properties of biological systems aim to improve our understanding of the studied system with the ultimate goal of being able to predict system responses in the absence of experimentation.
1 Why stochastic models?
2 General settings
3 Deterministic approach
4 Stochastic approach
5 Stochastic Simulation
6 Space models
Abstract

Many processes in cell and molecular biology are comprised of biochemical reaction networks.
It has proven useful to study these networks using computer simulations because they allow us to quantitatively investigate hypotheses about the networks.
Deterministic simulations are sufficient to predict average behaviors at the population level, but they cannot address questions about noise, random switching between stable states of the system, or the behaviors of systems with very few molecules of key species.
These topics are investigated with stochastic simulations.
In this first Bridges talk, we will review, in an intuitive, and hopefully comprehensive manner, some key Stochastic Simulation Algorithms used in Sistems Biology. We will give several illustrations of these methods.
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**Applications ([9])** [Systems Biology, Computational Biology, Immunology, etc.]
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Biology. Biochemical reaction networks (BRN).

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Applications ([9]) [Systems Biology, Computational Biology, Immunology, etc.]

- Molecule Synthesis and Degradation
- Enzymatic Reactions
- Receptor-Ligand Interaction
- Gene Expression and Regulation
- Ion Channel Dynamics and Ion Transport Across Membranes
- Immunological processes (inter and intra cellular)
- Epidemiological models
The cellular machinery differs a lot from the machines we see in our everyday life:

- Cells are microscopic reactors. On a microscopic level, individual molecules are constantly formed and destroyed by chemical reactions.
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- Proteins and other molecules tumble back and forth, diffuse, change their conformations, assemble and disassemble in permanent thermal movement.

- Biochemical reactions are probabilistic collisions between randomly moving molecules, with each event resulting in the increment or decrement of molecular species by integer amounts. They can be described mathematically by random processes: reactions happen unpredictably, and each sequence of random events leads to a different history of the system.
The amplified effect of fluctuations in a molecular reactant, or the compounded of fluctuations across many molecular reactants, referred to as molecular noise, often can accumulate as an observable phenotype.
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Furthermore, individual realizations of random processes can often be obtained by stochastic simulation.
On larger space and time scales, the microscopic processes translate into an effective macroscopic behavior, for instance, the dynamics of metabolic pathways governed by kinetic laws.
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On larger space and time scales, the microscopic processes translate into an effective macroscopic behavior, for instance, the dynamics of metabolic pathways governed by kinetic laws.

Random models provide a more detailed description than the deterministic kinetic models. Whenever the random fluctuations remain small, deterministic models provide a good and numerically cheap approximation.

However, random fluctuations can become important if molecule numbers are low, which typically happens in gene expression, or in models with nonlinear and unstable dynamics.
General settings

Consider a well-stirred system of “molecules” of $s$ species \( \{X_1, \cdots, X_s\} \), which interact through $r$ reaction channels \( \{R_1, \cdots, R_r\} \). We assume the system in thermal equilibrium and confined to a finite constant volume $V$. 
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Consider the following reaction network

\[
R_\mu : \sum_{i=1}^{s} \alpha_{i\mu} X_i \xrightarrow{\kappa_\mu} \sum_{i=1}^{s} \beta_{i\mu} X_i, \quad \mu = 1, 2, \cdots, r
\]
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\]

Define the **stoichiometric matrix** $S = (S_{i\mu})$, where

\[
S_{i\mu} = \beta_{i\mu} - \alpha_{i\mu}, \quad i = 1, \cdots, s; \mu = 1, \cdots, r
\]
General settings

Let:

\[ N_i(t) = \text{number of molecules of species } X_i \text{ present in instant } t \] (1)
General settings

Let:

\[ N_i(t) = \text{number of molecules of species } \mathcal{X}_i \text{ present in instant } t \]  

Aim. Compute the state vector time evolution

\[ \mathbf{N}(t) = (N_1(t), \ldots, N_s(t)), \text{ assuming the initial state } \mathbf{N}(0) = \mathbf{n}_0. \]
Why stochastic models?

General settings

- Let:
  \[ N_i(t) = \text{number of molecules of species } X_i \text{ present in instant } t \]  
  (1)

- **Aim.** Compute the state vector time evolution\n  \[ N(t) = (N_1(t), \cdots, N_s(t)), \text{ assuming the initial state } N(0) = n_o. \]

- We can also use other state variable descriptions
  \[ X(t) = (X_1(t), \cdots, X_s(t))^\top \text{ (real concentrations)} \]
  \[ Z(t) = (Z_1(t), \cdots, Z_r(t))^\top \text{ (event reaction counts on } [0, t]) \]
General settings

- each time reaction \( R_\mu \) triggers, the \( X_i \) state changes according to

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N_i \rightarrow N_i + S_{i\mu}
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- each time reaction $R_\mu$ triggers, the $X_i$ state changes according to

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$$\Delta N(t) = S\Delta Z(t)$$
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- each time reaction $R_\mu$ triggers, the $X_i$ state changes according to

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- The stoichiometry matrix therefore encodes important structural information about the reaction network. In particular, vectors in the left null-space of $S$ correspond to conservation laws in the network: any $s$-vector $a$ that satisfies $a^T S = 0$ has the property that $N(t)$ remains constant for all $t$. 

João Nuno Tavares and Ricardo Cruz
Stochastic Simulation in Biology
Assuming very big numbers, we can approximate $N$, $X$ and $Z$ by real ($t$-smooth dependent) numbers $n$, $x$ and $z$ and write ODE's

\[
\dot{n}(t) = S\dot{z}(t), \quad \dot{x}(t) = S\frac{\dot{z}(t)}{V},
\]
Assuming very big numbers, we can approximate $N$, $X$ and $Z$ by real ($t$-smooth dependent) numbers $n$, $x$ and $z$ and write ODE’s:

$$\dot{n}(t) = S\dot{z}(t), \quad \dot{x}(t) = S\frac{\dot{z}(t)}{V},$$

However, these ODE’s are only useful if we can establish a relationship between the derivative $\dot{z}(t)$ and the variables $n$ or $x$.

$$\dot{z}(t) = \hat{\nu}(n) = V\nu(x)$$
Usually we adopt the so called **mass-action law (MAL)**

\[
\hat{\nu}_\mu(n) = \hat{k}_\mu \prod_{i=1}^{s} n_i^{\alpha_{i\mu}}, \quad \nu_\mu(x) = k_\mu \prod_{i=1}^{s} x_i^{\alpha_{i\mu}}
\]

which leads to **RRE (reaction rate equations)** according to MAL

\[
\dot{n}(t) = S \hat{\nu}(n(t)), \quad \dot{x}(t) = S \nu(x(t)),
\]
An example: Lotka-Volterra Predator-prey model

Species: $X_1=$prey; $X_2=$predator. $n_1(t), n_2(t)$ the corresponding copy numbers. The number $n_A$ of food items is assumed unchanged.

▶ The reaction network and action-mass conversion rates are

\[
\begin{align*}
X_1 + A & \xrightarrow{\hat{k}_1} 2X_1 \\
X_1 + X_2 & \xrightarrow{\hat{k}_2} 2X_2 \\
X_2 & \xrightarrow{\hat{k}_3} 0
\end{align*}
\]

\[
\begin{align*}
\hat{v}_1 &= \hat{k}_1 n_1 n_A \\
\hat{v}_2 &= \hat{k}_2 n_1 n_2 \\
\hat{v}_3 &= \hat{k}_3 n_2
\end{align*}
\]

▶ We will see later the SSA.
An example: Lotka-Volterra Predator-prey model
An example: SIRS epidemic model

The reaction network and action-mass conversion rates are

\[
\begin{align*}
S + I & \xrightarrow{\hat{k}_1} 2I & \hat{\nu}_1 &= \hat{k}_1 n_S n_I \\
I & \xrightarrow{\hat{k}_2} R & \hat{\nu}_2 &= \hat{k}_2 n_I \\
R & \xrightarrow{\hat{k}_3} S & \hat{\nu}_3 &= \hat{k}_3 n_R 
\end{align*}
\]

The RRE’s are

\[
\begin{align*}
\dot{n}_S &= -\hat{k}_1 n_S n_I + \hat{k}_3 n_R \\
\dot{n}_I &= \hat{k}_1 n_S n_I - \hat{k}_2 n_I \\
\dot{n}_R &= \hat{k}_2 n_I - \hat{k}_3 n_R 
\end{align*}
\]

We will see later the SSA.
An example: SIRS epidemic model
An example: Michaelis-Menten enzyme kinetics

The reaction network is

\[
S + E \rightleftharpoons C \\
C \rightarrow P + E
\]

where \(S\) is the substance which is transformed by the reaction, \(E\) is the enzyme which facilitates the reaction, \(C\) is an intermediary species and \(P\) the final product.
An example: Gene regulation

where the gene $G$ is transcribed to the mRNA $M$ with rate constant $k_m$, the mRNA is translated to the protein $P$ with rate constant $k_p$, and the protein binds to (and represses) the gene with rate constant $k_b$ and unbinds back with rate constant $k_u$. The mRNA and protein are degraded with respective rate constants $k_m^-$ and $k_p^-$. 
An example: Gene regulation

The reaction network is

\[
\begin{align*}
G & \xrightarrow{k_m} G + M & \nu_1 = k_m x_G & \text{transcription} \\
M & \xrightarrow{k_p} M + P & \nu_2 = k_p x_M & \text{translation} \\
G + P & \xrightarrow{k_b} G \cdot P & \nu_3 = k_b x_G x_P & \text{binding} \\
G \cdot P & \xrightarrow{k_u} G + P & \nu_4 = k_u (x_G^{\text{total}} - x_G) & \text{unbinding} \\
M & \xrightarrow{k_m^-} \emptyset & \nu_5 = k_m^- x_M & \text{degradation} \\
P & \xrightarrow{k_p^-} \emptyset & \nu_6 = k_p^- x_P & \text{degradation}
\end{align*}
\]
An example: HIV infection

The reaction network is

\[
\begin{align*}
\emptyset & \xrightarrow{s} T \\
T & \xrightarrow{\delta} \emptyset \\
T + V & \xrightarrow{\kappa} T^* \\
T^* & \xrightarrow{\eta} NV \\
V & \xrightarrow{\gamma} \emptyset
\end{align*}
\]

where $T$ is a CD4+ T-cell, $V$ is virus and $T^*$ is an infected active T-cell. Referring to concentrations \(\text{copies}/\mu L\), we have the RRE's

\[
\begin{align*}
\dot{x}_T &= s - \delta x_T - \kappa x_V x_T \\
\dot{x}_{T^*} &= \kappa x_V x_T - \eta x_{T^*} \\
\dot{x}_V &= N \eta x_{T^*} - \gamma x_V
\end{align*}
\]
Even though the deterministic approach has proven very successful, it comes with some issues:

1. Small particle numbers in cellular subsystems (e.g. in signaling pathways) lead to random fluctuations which can change the dynamic behavior considerably.
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2. Bi- or multi-stable systems can not be described adequately.
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3. Stochasticity itself can be an important property of the system, e.g. in evolution, noise-induced amplification of signals or noise-driven divergence of cell fates.
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3. Stochasticity itself can be an important property of the system, e.g. in evolution, noise-induced amplification of signals or noise-driven divergence of cell fates.

4. For very small particle numbers (e.g. single genes) the concept of continuous concentrations is not appropriate.
Fundamental assumptions

- Hypothesis 1. The chemical system is under thermal equilibrium conditions.
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- **Hypothesis 1.** The chemical system is under thermal equilibrium conditions.

- **Hypothesis 2.** The chemical system is such that, at any time $t$, the concentration of each species is homogeneous in the reaction vessel (i.e., does not depend on space). Homogeneity is in fact achieved if nonreactive collisions are much more frequent than reactive ones, which ensures diffusion processes proceed at much higher rate than any reaction in the system.
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- **Hypothesis 1.** The chemical system is under thermal equilibrium conditions.

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- **Hypothesis 3.** In a bimolecular reaction, the time to the occurrence of the reaction is largely determined by the time to the reactive collision whereas the time necessary for the chemical transformation of the colliding species into the reaction products is negligible.
To each reaction channel $R_{\mu}$ we associate two quantities:

- the vector $\vartheta_{\mu} = S \cdot \mu$ - stoichiometric matrix column $\mu$. Thus, if the system is in state $n$ and if reaction $R_{\mu}$ triggers, the system changes instantly its state to $n + \vartheta_{\mu}$.
To each reaction channel $\mathcal{R}_\mu$ we associate two quantities:

1. the vector $\vartheta_\mu = S_\mu$ - stoichiometric matrix column $\mu$. Thus, if the system is in state $n$ and if reaction $\mathcal{R}_\mu$ triggers, the system changes instantly its state to $n + \vartheta_\mu$.

2. the propensity or hazard $h_\mu(n, c_\mu)$, defined by

$$h_\mu(n, c_\mu) dt = \text{probability that, assuming that } N(t) = n, \text{reaction } \mathcal{R}_\mu \text{triggers in interval } [t, t + dt) \text{ somewhere in volume } V.$$  

Here $c_\mu$ is the stochastic rate constant.  

(2)
Examples of reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Propensity $h_\mu(n, c_\mu)$</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\emptyset \rightarrow X_1$</td>
<td>$c_1$</td>
<td>Inflow</td>
</tr>
<tr>
<td>$X_1 \rightarrow \emptyset$</td>
<td>$c_2 n_1$</td>
<td>Degradation</td>
</tr>
<tr>
<td>$X_1 + X_2 \rightarrow X_3$</td>
<td>$c_3 n_1 n_2$</td>
<td>Catalysis</td>
</tr>
<tr>
<td>$2X_1 \rightarrow X_2$</td>
<td>$c_4 n_1(n_1 - 1)/2$</td>
<td>Dimerisation</td>
</tr>
<tr>
<td>$3X_1 \rightarrow X_3$</td>
<td>$c_5 n_1(n_1 - 1)(n_1 - 2)/6$</td>
<td>Trimerisation</td>
</tr>
</tbody>
</table>
The first thing we can do is to deduce a master equation (Kolmogoroff-Chapmann).

Let

$$P(n, t) = \text{Prob}\{N(t) = n|N(0) = n_0\}$$

We write $P(n, t + dt)$ as the sum of the probabilities of the number of ways in which the network can arrive in state $n$ at time $t + dt$

$$P(n, t + dt) = o(dt) + \left(1 - \sum_{\mu=1}^{r} h_\mu(n, c_\mu)dt\right) P(n, t) +$$

$$+ \sum_{\mu=1}^{r} h_\mu(n - \mathcal{V}_\mu, c_\mu)dt \ P(n - \mathcal{V}_\mu, t)$$
The Chemical Master Equation (CME) is a fundamental concept in stochastic modeling of chemical systems. It describes the probability evolution of a system undergoing reactions over time.

1. The first quantity in is the probability that the system undergoes no reactions in \([t, t + dt)\).

2. The term \(h_\mu(n - \vartheta_\mu, c_\mu)P(n - \vartheta_\mu, t)\ dt\) is the probability that the system is one \(R_\mu\) reaction removed from state \(n\) at time \(t\) and then undergoes such a reaction in \([t, t + dt)\).

- \(k_{2n1n2}\): Reaction \(n1 \rightarrow n2\)
- \(k_{3n2}\): Reaction \(n2 \rightarrow n1\)
- \(k_{1nA(n1-1)}\): Reaction \(n1 \rightarrow n2\)
- \(k_{1nAn1}\): Reaction \(n1 \rightarrow n1\)
- \(k_{2(n1+1)(n2-1)}\): Reaction \(n1 \rightarrow n2\)

State transitions of the Lotka–Volterra model.
The CME is then

$$\frac{dP(n, t)}{dt} = \sum_{\mu=1}^{r} \left[ h_\mu(n - \vartheta_\mu, c_\mu) \ P(n - \vartheta_\mu, t) - h_\mu(n, c_\mu) \ P(n, t) \right]$$
Why stochastic models?

General settings

Deterministic approach

Stochastic approach

Stochastic Simulation

Space models

Chemical Master Equation (CME)

The CME is then

\[
\frac{dP(n, t)}{dt} = \sum_{\mu=1}^{r} \left[ h_{\mu}(n - \vartheta_{\mu}, c_{\mu}) P(n - \vartheta_{\mu}, t) - h_{\mu}(n, c_{\mu}) P(n, t) \right]
\]

▶ This a set of linear, autonomous ODEs. One ODE for each possible \(n\)-state of the system. Solution of the \(n\) th equation at time \(t\) gives the probability of system being in that particular state at time \(t\).
The CME is then

\[
dP(n, t) \quad dt = \sum_{\mu=1}^{r} \left[ h_{\mu}(n - \vartheta_{\mu}, c_{\mu}) \cdot P(n - \vartheta_{\mu}, t) - h_{\mu}(n, c_{\mu}) \cdot P(n, t) \right]
\]

This a set of linear, autonomous ODEs. One ODE for each possible \( n \)-state of the system. Solution of the \( n \) th equation at time \( t \) gives the probability of system being in that particular state at time \( t \).

Unfortunately, the CME is only tractable for a handful of cases. Hence, for most systems of interest, an analysis via the CME will not be possible and then stochastic simulation techniques will present the only practical approach to gaining insight into a system’s dynamics.
Gillespie Algorithm (SSA)

Typically, the CME is too high dimensional to deal with computationally. The SSA gets around this issue by computing single realizations of the state vector rather than an entire probability distribution.
Typically, the CME is too high dimensional to deal with computationally. The SSA gets around this issue by computing single realizations of the state vector rather than an entire probability distribution.

The key point to design SSA is to compute the joint density function for the two random variables \( \mu \) and \( \tau \). We can prove that this joint density is the product of two individual density functions.

- **Next reaction index** \( \mu \) - discrete pdf \( \frac{h_\mu(n, c_\mu)}{h_0(n, c)} \), ie, choose one of the reactions with the rule that the chance of picking the \( \mu \)th reaction is proportional to its propensity \( h_\mu(n, c_\mu) \).

Here \( h_0(n, c) = \sum_{\mu=1}^{r} h_\mu(n, c_\mu) \).

- **Time \( \tau \) until next reaction.** With exponential pdf \( h_0(n, c)e^{-h_0(n,c)\tau} \).
Gillespie Algorithm (SSA)

1. Initialize in $t = 0$, with molecular numbers $n = (n_1, \cdots, n_s)$ and stochastic constant rates $c = (c_1, \cdots, c_r)$.

2. For each $\mu = 1, \cdots, r$, compute $h_\mu(n, c_\mu)$, based in actual state $n$, and $h_0(n, c)$. STOP if $h_0 = 0$.

4. Simulate time $\tau$ until next reaction $\tau \sim \text{Exp}(h_0(n, c))$.

5. Simulate the type $\mu$ of next reaction using $\left(h_\mu(n, c_\mu)/h_0(n, c)\right)_{\mu=1,\cdots,r}$.

6. Update time $t = t + \tau$.

7. Update state $n$ according to $n = n + \vartheta_\mu$.

8. If $t < t_{\text{max}}$, go to step 2.
\(\tau\)-leaping

Assume that there exists \(\tau > 0\) that satisfies the following **Leap condition**: “\(\forall \mu, h_\mu(n, c_\mu) \approx \text{constant in interval } [t, t+\tau]\)”.

- We then can show that each reaction count number is Poisson with mean (and variance) \(h_\mu(n, c_\mu)\tau\).
- So, we can leap the system by \(\tau\) time units

\[
N(t + \tau) = n + \sum_{\mu=1}^{r} P_\mu(h_\mu(n, c_\mu)\tau) \, \vartheta_\mu
\]

with \(N(t) = n\) and \(P_\mu(m_\mu)\) independent Poisson RV with mean (and variance) \(m_\mu = h_\mu(n, c_\mu)\tau\).
1. Initialize in $t = 0$, with molecular numbers $\mathbf{n} = (n_1, \cdots, n_s)$ and stochastic constant rates $c = (c_1, \cdots, c_r)$.

2. For each $\mu = 1, \cdots, r$, compute $h_\mu(\mathbf{n}, c_\mu)$, based in actual state $\mathbf{n}$, and $h_0(\mathbf{n}, c)$. STOP if $h_0 = 0$.

3. Simulate rv’s $\{p_\mu\}_{\mu=1}^r$ from RVMs $\{\mathcal{P}_\mu(h_\mu(\mathbf{n}, c_\mu)\tau)\}_{\mu=1}^r$.

4. Update

$$\mathbf{N}(t + \tau) = \mathbf{n} + \sum_{\mu=1}^r p_\mu \vartheta_\mu$$

and $t = t + \tau$.

5. Go to step 1.
Langevin equation (CLE)

- Assume that we choose $\tau$ so that

$$h_\mu(n, c_\mu) \tau >> 1, \quad \forall \mu$$

- Then

$$\mathcal{P}_\mu(h_\mu(n, c_\mu) \tau) \approx h_\mu(n, c_\mu) \tau + \sqrt{h_\mu(n, c_\mu) \tau} \mathcal{N}_\mu(0, 1)$$

- and substituting, we get the update (Euler-Maruyama)

$$Y(t + \tau) = Y(t) + \tau \sum_{\mu=1}^{r} \vartheta_\mu h_\mu(Y(t), c_\mu) + \sqrt{\tau} \sum_{\mu=1}^{r} \vartheta_\mu \sqrt{h_\mu(Y(t), c_\mu)} \mathcal{N}_\mu(0, 1)$$
Why we call this “diffusion approximation”?

▶ Drift. When the average value of a stochastic process changes with time, we say that the process has a drift.
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- **Drift.** When the average value of a stochastic process changes with time, we say that the process has a drift.

- **Diffusion.** When the (co)variance, a measure of spread of the distribution, changes with time, we say that the process has diffusion.
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- **Diffusion.** When the (co)variance, a measure of spread of the distribution, changes with time, we say that the process has diffusion.

- Let $\Delta Z_{\mu}(t) = Z_{\mu}(t + \Delta t) - Z_{\mu}(t)$ be the short time $R_{\mu}$-reaction count increment. Then

$$
(\Delta Z_{\mu})_n \approx h_{\mu}(n, c_{\mu}) \Delta t + \sqrt{h_{\mu}(n, c_{\mu}) \Delta t} \mathcal{N}_{\mu}(t)
$$
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- Let $\Delta Z_\mu(t) = Z_\mu(t + \Delta t) - Z_\mu(t)$ be the short time $R_\mu$-reaction count increment. Then

  $$(\Delta Z_\mu)_n \approx h_\mu(n, c_\mu) \Delta t + \sqrt{h_\mu(n, c_\mu) \Delta t} N_\mu(t)$$

and since $(\Delta N_i)_n = S (\Delta Z_\mu)_n$, we obtain

$$(\Delta N_i)_n \approx \sum_{\mu=1}^{r} S_i\mu h_\mu(n, c_\mu) \Delta t + \sum_{\mu=1}^{r} S_i\mu \sqrt{h_\mu(n, c_\mu) \Delta t} N_\mu(t)$$
CLE. Langevin equation

- The increment vector then takes the form

\[(\Delta N)_n \approx A(n) \Delta t + D(n) \sqrt{\Delta t} \mathcal{N}(t)\]

- The factor \(\sqrt{\Delta t} \mathcal{N}(t)\) in the second summation on the right can be recognized as the Wiener increment,

\[\Delta \mathcal{W} = \mathcal{W}(t + \Delta t) - \mathcal{W}(t) = \sqrt{\Delta t} \mathcal{N}(t)\]

of an \(r\) vector \(\mathcal{W}(t)\) of independent standard Brownian motions, or standard Wiener processes.

- Finally we obtain the CLE

\[dY(t) = \underbrace{A(Y)(t))}_{\text{drift-rate function}} \, dt + \underbrace{D(Y)(t))}_{\text{diffusion-rate function}} \, d\mathcal{W}(t)\]
This SDE (CLE equation) represents the diffusion process that most closely matches the dynamics of the associated Markov Jump Process (MJP), and can be shown to approximate the Stochastic Kinetic Network (SKM) increasingly well in high concentration scenarios.
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However, it should be noted that the approximation breaks down in low-concentration scenarios, and therefore should not be expected to work well for models involving species with very low copy-number. This is quite typical for many SKN’s; yet the approximation often turns out to be adequate for inferential purposes in practice.
Summary

We summarize the high-level differences between the CME, CLE, and RRE philosophies.
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▶ **Chemical Master Equation.** A set of linear, autonomous ODEs. One ODE for each possible state of the system. Solution of the \( n \)th equation at time \( t \) gives the probability of system being in that particular state at time \( t \).
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▶ Chemical Master Equation. A set of linear, autonomous ODEs. One ODE for each possible state of the system. Solution of the $n$th equation at time $t$ gives the probability of system being in that particular state at time $t$.

▶ Chemical Langevin Equation. A set of nonlinear, autonomous SDEs. One SDE for each chemical species. Solution of the $i$th equation at time $t$ is a real-valued random variable representing the amount of species $i$ at time $t$. 
Why stochastic models?
General settings
Deterministic approach
Stochastic approach
Stochastic Simulation
Space models

Summary

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- **Chemical Master Equation.** A set of linear, autonomous ODEs. One ODE for each possible state of the system. Solution of the $n$th equation at time $t$ gives the probability of system being in that particular state at time $t$.

- **Chemical Langevin Equation.** A set of nonlinear, autonomous SDEs. One SDE for each chemical species. Solution of the $i$th equation at time $t$ is a real-valued random variable representing the amount of species $i$ at time $t$.

- **Reaction Rate Equations.** A set of nonlinear, autonomous ODEs. One ODE for each chemical species. Solution of the $i$th equation at time $t$ is a real number representing the concentration of species $i$ at time $t$. 
Logical structure of stochastic chemical kinetics. Everything follows from the fundamental premise at the top via the laws of probability theory.
Computational Experiment. Michaelis-Menten system

Reaction network

\[ \mathcal{R}_1 : \quad S + E \xrightarrow{c_1} C \]
\[ \mathcal{R}_2 : \quad C \xrightarrow{c_2} S + E \]
\[ \mathcal{R}_3 : \quad C \xrightarrow{c_3} P + E \]

Stoichiometry vectors

Species ordering \((S, E, C, P)\):

\[ \vartheta_1 = \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix}, \quad \vartheta_2 = \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \end{pmatrix}, \quad \vartheta_3 = \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix}, \]

Propensities

\( \mathcal{R}_1 : h_1(n, c) = c_1 n_S(t) n_E(t) ; \)
\( \mathcal{R}_2 : h_2(n, c) = c_2 n_C(t) ; \)
\( \mathcal{R}_3 : h_3(n, c) = c_3 n_C(t) \)
Computational Experiment. Michaelis-Menten system

- **Initial data and constant rates (deterministic)**

\[
\begin{pmatrix}
    x_S(0) \\
    x_E(0) \\
    x_C(0) \\
    x_P(0)
\end{pmatrix} = \begin{pmatrix}
    5 \times 10^{-7} M \\
    2 \times 10^{-7} M \\
    0 M \\
    0 M
\end{pmatrix}, \quad k_1 = 10^6, \ k_2 = 10^4, \ k_3 = 10^{-1}
\]

- In a volume \( V = 10^{-15} L \), this corresponds to molecular data

\[
\begin{pmatrix}
    n_S(0) \\
    n_E(0) \\
    n_C(0) \\
    n_P(0)
\end{pmatrix} = \begin{pmatrix}
    \lfloor 5 \times 10^{-7} N_A V \rfloor \\
    \lfloor 2 \times 10^{-7} N_A V \rfloor \\
    0 \\
    0
\end{pmatrix} = \begin{pmatrix}
    312 \\
    125 \\
    0 \\
    0
\end{pmatrix}
\]

\[
c_1 = \frac{10^6}{N_A V}, \ c_2 = 10^{-4}, \ c_3 = 10^{-1}
\]

where \( N_A \approx 6.023 \times 10^{23} \) is **Avogadro number**.
Open Challenges

Stochastic modeling of biological dynamics, especially at the cellular level, is increasingly making its way to the mainstream of quantitative biology investigation. The CME and its accompanying SSA have proven to be invaluable computational tools for such studies. There are, however, many challenges that need to be addressed in order to make stochastic modeling a widely applicable tool for realistic biological problems.
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▶ Efficient Stochastic Simulation and Analysis for Systems Evolving at Disparate Temporal and Spatial Scales.
Open Challenges

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- Efficient Stochastic Simulation and Analysis for Systems Evolving at Disparate Temporal and Spatial Scales.
- Efficient Spatiotemporal Simulations. Biological networks in practice consist of components that interact in a three-dimensional space and are not necessarily distributed homogeneously as they diffuse between different cellular compartments.
Open Challenges

- **Holistic understanding of biological systems.**
  Understanding of biological systems often involves the probing of cellular biochemical networks in the context of the cell, of cells in the context of a tissue, and of a tissue in the context of the organism. How to account for and move between these spatial scales remains an open problem for stochastic modeling.
Open Challenges

- **Holistic understanding of biological systems.** Understanding of biological systems often involves the probing of cellular biochemical networks in the context of the cell, of cells in the context of a tissue, and of a tissue in the context of the organism. How to account for and move between these spatial scales remains an open problem for stochastic modeling.

- **Parametrization and Sensitivity Analysis of Stochastic Models.** Stochastic models of biological systems typically depend on a set of kinetic parameters whose values are often unknown or fluctuate due to an uncertain environment. These parameters determine the dynamic behavior of the model, and changes in them may alter the system’s output in nonintuitive ways.
Next steps

Space as the final frontier in stochastic simulations of biological systems.
In the his 1976 paper [4], Gillespie writes two algorithms: • **Direct Method (DM)** that we have explored before and which requires 2 random numbers per iteration. • **First Reaction Method (FRM)** which will be exemplified therefore:

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
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<th>$t = 0$</th>
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<tbody>
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$t = 0.20$, $R_2$

$t = 0.20 + 0.60$, $R_1$
First Reaction Method

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\[ 0.75 \quad 0.20 \quad 1.20 \]
\[ t = 0 \]
\[ 0.60 \quad 0.63 \quad 1.30 \]
\[ t = 0.20 + 0.60, R_1 \]

- algorithm: generate \( t_i \) for each reaction \( i \), based on its propensities → choose smallest \( t_i \)
- requires \( \nu \) random numbers (number of reactions)
- Gillespie proved it to be compatible (yet slower) than DM
First Reaction Method

1. Initialization: initial conditions.
2. Calculate reaction propensities $h_i(x, c_i)$, for $i = 1, 2, \cdots, \nu$.
3. Simulate a time to the next reaction $i$, $t_i \sim \text{Exp}(h_i(x, c_i))$, for $i = 1, 2, \cdots, \nu$.
4. Let $j$ be the index of the smallest time $t_i$.
5. Set $t := t + t_j$.
6. Update the state $x$ according to the reaction with index $j$. That is, set $x := x + S^{(j)}$.
7. If $t < T_{\text{max}}$, return to step 2.
The former algorithm was improved by Gibson and Bruck [3] in what they called **Next Reaction Method (NRM)**:

\[
\begin{array}{ccc}
R_1 & R_2 & R_3 \\
0.60 & 0.20 & 1.30 \\
\end{array}
\Rightarrow
\begin{array}{ccc}
R_2 & R_1 & R_3 \\
0.20 & 0.60 & 1.30 \\
\end{array}
\]

\[R_2, \ t := 0.20\]

\[
\begin{array}{ccc}
R_2 & R_1 & R_3 \\
0.63 & 0.60 & 1.30 \\
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\Rightarrow
\begin{array}{ccc}
R_1 & R_2 & R_3 \\
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\]

\[R_1, \ t := t + 0.60, \quad t = t + 0.43\]

- Generate times only for reactions whose propensities have been affected by the current one.
- Always keep \( t_i \) in absolute time by adding current time:
  \[ t_i := t + \text{Exp}(h_i(x, c_i)) \].
Next Reaction Method

1. Initialization: initial conditions.
2. Let $j$ be the index of the smallest $t_i$.
3. Set $t := t_j$.
4. Update $\mathbf{x}$ according to reaction with index $j$.
5. Update $h_j(\mathbf{x}, c_j)$ according to the new state $\mathbf{x}$ and simulate a new time $t_j := t + \text{Exp}(h_j(\mathbf{x}, c_j))$.
6. For each reaction $i(\neq j)$ whose hazard is changed by reaction $j$:
   a) Update $h'_i = h_i(\mathbf{x}, c_i)$ (but temporarily keep the old $h_i$).
   b) Set $t_i := t + (h_i/h'_i)(t_i - t)$.
   c) Forget the old $h_i$.
7. If $t < T_{\text{max}}$, return to step 2.
Next Reaction Method

- Requires extra structures for:
  - **a)** graph identifying reactions whose propensities may have been affected by current reaction.
  - **b)** event queue structure to keep $t_i$ sorted, avoiding performing a full sort.

- It may actually be faster than the **Direct Method** (DM), depending on details of the model (DM always requires 2 random numbers; the model may require only 1 or more under NRM) and implementation (structures used).

- Iterations also have the potential to be run in parallel. (Wilkinson, 2005)
For spatial modeling, one algorithm is **Next Subvolume Method (NSM)** by Elf and Ehrenberg [2].
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This method modifies **Next Reaction Method**, so that it uses “subvolumes” instead.

Each subvolume is a homogeneous mixture under the **Direct Method**.

We may in fact look at these subvolumes as reactions, where each molecule is subject to diffusion to another subvolume, according to a diffusion rate (its $h_i$):

$$ I_1 : A_{(1,1)} \xrightarrow{D_1} A_{(2,1)} $$
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\[
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Each spatial diffusion affects only 2 subvolumes, so only 2 times need to be regenerated (like in **DM**).
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Each spatial diffusion affects only 2 subvolumes, so only 2 times need to be regenerated (like in **DM**).

Can potentially represent any spatial geometry (2D, 3D, graph)
Next Subvolume Method

1. For each subvolume $k$, calculate rates $r_k$ and $s_k$, and generate $t_k \sim \text{Exp}(D_k(r_k + s_k))$. Sort vector $t$.

2. For the smallest time $\tau$ of subvolume $\lambda$, choose either a reaction event if $\text{rand} < \frac{r_\lambda}{(r_\lambda + s_\lambda)}$, or a diffusion event.

3. If reaction:
   - a) Reuse the previous random number to determine which reaction occurred, as in the DM.
   - b) Recalculate $r_\lambda$, $s_\lambda$ and $t_\lambda$ for this subvolume.

4. If diffusion:
   - a) Reuse the previous random number to determine which molecule diffused away, given their respective diffusion rates.
   - b) Another random number chooses a neighbor $\gamma$ based on the connectivity matrix.
   - c) Recalculate $r$, $s$ and $t$ for both subvolumes $\lambda$ and $\gamma$.

5. Go back to step 2.
Lotka-Volterra simulation

Using this method, we simulate Lotka-Volterra predator-prey model, in a 50x50 grid, by initially spreading around 100 $X_1$ (sheep) and 50 $X_2$ (wolves), using the reaction rates $C = (0.2, 0.5, 0.1)$ and diffusion rates $D = (1, 5)/3^2$, and the reaction network as:

$$
\begin{align*}
X_1 & \xrightarrow{C_1} 2X_1 \\
X_1 + X_2 & \xrightarrow{C_2} 2X_2 \\
X_2 & \xrightarrow{C_3} \emptyset 
\end{align*}
$$
Lotka-Volterra simulation

Legend: Green=(0,X1,0,X2), White=(>0,X1,0,X2), Black=(0,X1,>0,X2), Red=(>0,X1,>0,X2)
The authors found that:

- the Gillespie simulation has larger peaks than the Langevin one
- the particle tracking simulation shows larger and fewer bursts than does the Gillespie simulation because it accurately treats diffusion at all length scales (this difference can be reduced by using smaller subvolumes)
Mathematical methods often employed in kinetic studies: ODEs, PDEs, SPDEs, SDEs; MC, Monte Carlo; SSA, Gillespie-type stochastic simulation approach; $k_{\text{react}} =$ rate of biochemical processes; $k_{\text{diff}} =$ rate of diffusion processes.
The world is governed by deterministic laws

We need exogenous stochasticity to keep our models simple
[9, pp.2]

Using stochastic methods matter more when working with fewer molecules/agents
Why stochastic models?

Deterministic approach

Stochastic approach

Stochastic Simulation

Space models

References


