



Aalto University

From discrete-state to continuous-state stochastic simulations of chemical reaction networks

Stochastic analysis and simulation of reactive and diffusive systems

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Discrete to continuous simulation

The stochastic simulation of reaction systems and its variations are discrete methods

In discrete simulations, we determined or estimated the mean and variance of process

- ↪ Those statistics were used to coarsely characterise full distributions
- ↪ (Needed because often those distributions are not fully known)

We now approximate the jump process $(N(t))_{t \geq 0}$ with a continuous process $(N^c(t))_{t \geq 0}$

- In principle, simulating (a path from) the continuous process should be faster

We consider a process whose expected values change with time

- ↪ We will say that the process is **drifting**

We consider a process whose (co)variance changes with time

- ↪ We will say that the process is **diffusing**

We use these concepts to develop an intuitive notion of stochastic differential equation

Drift and diffusion

From discrete-state to continuous-state stochastic simulations

Drift and diffusion

We start by describing drift and diffusion, locally, for a reactive system with $(N(t))_{t \geq 0}$

$$N(t) = N(t=0) + SZ(t)$$

Given a system in state $N(t)$ at time t , we know the copy-number at time $t + \Delta t$

$$\underbrace{N(t + \Delta t)}_{N_s \times 1} = \underbrace{N(t)}_{N_s \times 1} + \underbrace{S}_{N_s \times N_r} \underbrace{[Z(t + \Delta t) - Z(t)]}_{N_r \times 1}$$

$\underbrace{\hspace{10em}}_{N_s \times 1}$

We relate increments in copy-numbers with increments in reaction counts, in time

$$\begin{aligned} \Delta N(t) &= N(t + \Delta t) - N(t) \\ &= S [Z(t + \Delta t) - Z(t)] \\ &= S \Delta Z(t) \end{aligned}$$

We consider the increment process $(\Delta N(t))_{t \geq 0}$ in the copy-numbers, in $[t, t + \Delta t)$

- $\Delta N(t)$ is a random variable that we are interested to determine

Drift and diffusion (cont.)

The copy-number increment is a linear combination of reaction-count increments

$$\underbrace{\begin{bmatrix} \Delta N_1(t) \\ \vdots \\ \Delta N_{n_r}(t) \\ \vdots \\ \Delta N_{N_r}(t) \end{bmatrix}}_{\Delta N(t)} = \underbrace{\begin{bmatrix} S_{1,1} & \cdots & S_{1,n_r} & \cdots & S_{1,N_r} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ S_{n_s,1} & \cdots & S_{n_s,n_r} & \cdots & S_{n_s,N_r} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ S_{N_s,1} & \cdots & S_{N_s,n_r} & \cdots & S_{N_s,N_r} \end{bmatrix}}_S \underbrace{\begin{bmatrix} \Delta Z_1(t) \\ \vdots \\ \Delta Z_{n_r}(t) \\ \vdots \\ \Delta Z_{N_r}(t) \end{bmatrix}}_{\Delta Z(t)}$$

$N(t+\Delta t) - N(t)$ $Z(t+\Delta t) - Z(t)$

Drift and diffusion (cont.)

$$\underbrace{\Delta N(t)}_{N_s \times 1} = \underbrace{N(t + \Delta t)}_{N_s \times 1} - \underbrace{N(t)}_{N_s \times 1}$$

Given a system in state $N(t) = n(t)$ at time t , we define the **short-term (local) drift**

$$\underbrace{\mathbb{E} \left[\underbrace{\Delta N(t) \mid N(t) = n(t)}_{N_s \times 1} \right]}_{N_s \times 1} = \underbrace{\mathbb{E} \left[\underbrace{\Delta N(t)}_{N_s \times 1} \right]}_{N_s \times 1} \Big|_{n(t)} = \underbrace{\langle \underbrace{\Delta N(t)}_{N_s \times 1} \rangle}_{N_s \times 1} \Big|_{n(t)}$$

Local drift is the change of the mean value of the process during interval $[t, t + \Delta t)$

Drift and diffusion (cont.)

$$\underbrace{\Delta N(t)}_{N_s \times 1} = \underbrace{N(t + \Delta t)}_{N_s \times 1} - \underbrace{N(t)}_{N_s \times 1}$$

Given a system in state $N(t) = n(t)$ at time t , we define the **short-term (local) diffusion**

$$\begin{aligned} \mathbb{E} \left[\underbrace{\left(\underbrace{\underbrace{\Delta N(t)}_{N_s \times 1} - \underbrace{\langle \Delta N(t) \rangle_{n(t)}}_{N_s \times 1}}_{N_s \times 1} \right) \left(\underbrace{\underbrace{\Delta N(t)}_{N_s \times 1} - \underbrace{\langle \Delta N(t) \rangle_{n(t)}}_{N_s \times 1}}_{N_s \times 1} \right)^T}_{1 \times N_s} \right]_{n(t)} &= \mathbb{E} \left[\underline{\Delta N(t)} \underline{\Delta N(t)}^T \right]_{n(t)} \\ &= \langle \underline{\Delta N(t)} \underline{\Delta N(t)}^T \rangle_{n(t)} \end{aligned}$$

Local diffusion is the change of the covariance of the process during interval $[t, t + \Delta t]$

Drift and diffusion (cont.)

We start by characterising individual short-time (Δt) reaction-count increments $\Delta Z_{n_r}(t)$

Given the state $n(t)$, we determined the waiting time S_{n_r} until the next reaction \mathcal{R}_{n_r}

The probability that reaction \mathcal{R}_{n_r} does not occur in the next interval Δt

- (Provided no other reactions occur and the state does not change)

$$\mathbb{P}[S_{n_r} > \Delta t \mid N(t) = n(t)] = \exp \left[- \underbrace{h_{n_r}(n(t))}_{\text{rate/propensity}} \Delta t \right]$$

Taking the Taylor expansion around the short interval Δt , we get

$$\begin{aligned} \mathbb{P}[S_{n_r} > \Delta t \mid N(t) = n(t)] &= \exp[-h_{n_r}(n(t)) \Delta t] \\ &= 1 - h_{n_r}(n(t)) \Delta t \quad (\text{neglecting h.o.t.}) \end{aligned}$$

Drift and diffusion (cont.)

$$\mathbb{P}[S_{n_r} > \Delta t \mid N(t) = n(t)] = 1 - h_{n_r}(n(t)) \Delta t$$

The probability of occurrence of a reaction \mathcal{R}_{n_r} in Δt is the complementary probability

$$\mathbb{P}[S_{n_r} \leq \Delta t \mid N(t) = n(t)] = h_{n_r}(n(t)) \Delta t$$

For vanishingly small intervals, it is improbable that a reaction occurs more than once

Drift and diffusion (cont.)

$$\mathbb{P}[S_{n_r} \leq \Delta t \mid N(t) = n(t)] = h_{n_r}(n(t))$$

Let us consider the probability of two occurrences of reaction \mathcal{R}_{n_r} during $[t, t + \Delta t)$

- The occurrence of \mathcal{R}_{n_r} in $[t, t + \alpha\Delta t)$ and another \mathcal{R}_{n_r} in $[t + \alpha\Delta t, t + \Delta t)$
- ($\alpha \in (0, 1)$ joins the time of the two non-overlapping events)

We can write

$$\underbrace{\mathbb{P}[S_{n_r} \leq \alpha\Delta t \mid N(t) = n(t)]}_{h_{n_r}(n(t))\alpha\Delta t} \times \underbrace{\mathbb{P}[S_{n_r} \leq (1-\alpha)\Delta t \mid N(t) = n(t) + S_{-,n_r}]}_{h_{n_r}(n(t)+S_{-,n_r})(1-\alpha)\Delta t} = 0$$

Drift and diffusion (cont.)

While the system is in state $N(t) = n(t)$, the probability of one single reaction \mathcal{R}_{n_r}

$$\mathbb{P}[S_{n_r} \leq \Delta t \mid N(t) = n(t)] = h_{n_r}(n(t)) \Delta t$$

This is also the probability of a **unit increment** in the reaction-count of reaction \mathcal{R}_{n_r}

$$\mathbb{P}[Z_{n_r}(t + \Delta t) - Z_{n_r}(t) = 1 \mid N(t) = n(t)] = h_{n_r}(n(t)) \Delta t$$

Given state $n(t)$, the distribution of reaction-count increments $\Delta Z_{n_r}(t)$ in $[t, t + \Delta t)$

$$\mathbb{P}[\Delta Z_{n_r} = \delta z_{n_r} \mid N(t) = n(t)] = \begin{cases} h_{n_r}(n(t)) \Delta t, & \delta z_{n_r} = 1 \\ 1 - h_{n_r}(n(t)) \Delta t, & \delta z_{n_r} = 0 \\ 0, & \delta z_{n_r} > 1 \end{cases}$$

Drift and diffusion (cont.)

$$\mathbb{P}[\Delta Z_{n_r} = \delta z_{n_r} \mid N(t) = n(t)] = \begin{cases} h_{n_r}(n(t)) \Delta t, & \delta z_{n_r} = 1 \\ 1 - h_{n_r}(n(t)) \Delta t, & \delta z_{n_r} = 0 \\ 0, & \delta z_{n_r} > 1 \end{cases}$$

For a vanishingly small Δt , copy-numbers and propensities remain virtually constant

↪ As changes in propensity are negligible, reactions events in Δt are independent

The probability $\mathbb{P}[\Delta Z_{n_r} = \delta z_{n_r} \mid N(t) = n(t)]$ of that a certain number of reactions fired in the interval Δt is, by definition, well approximated by a Poisson distribution

- (Given that the probability for a reaction event remained constant)

Propensities $h_{n_r}(N(t))$ only depend on non-negative integer powers of copy-numbers

- Copy-numbers practically never change by more than two, per reaction event

The number of occurring reactions needs be much smaller than copy-numbers

Drift and diffusion (cont.)

The (conditional) expected value of short-term Poissonian reaction-count increments

$$\begin{aligned}\langle \Delta Z_{n_r}(t) \rangle_{n(t)} &= \sum_{\delta z_{n_r} \in \{0,1,>1\}} \delta z_{n_r} \mathbb{P}[\Delta Z_{n_r} = \delta z_{n_r} \mid N(t) = n(t)] \\ &= h_{n_r}(n(t)) \Delta t\end{aligned}$$

Similarly, for its variance we have

$$\left\langle \left(\underbrace{\Delta Z_{n_r}(t) - \langle \Delta Z_{n_r}(t) \rangle_{n(t)}}_{\underline{\Delta} Z_{n_r}(t)} \right)^2 \right\rangle_{n(t)} = h_{n_r}(n(t)) \Delta t$$

The propensity $h_{n_r}(n(t))$ is interpreted as a mean conversion rate, given $N(t) = n(t)$

Drift and diffusion (cont.)

Short-term reaction-count increments $\{\Delta Z_{n_r}(n(t))\}_{n_r=1}^{N_r}$ follow a Poisson distribution

- ↪ Jointly, $\Delta Z(t) = (\Delta Z_1(t), \dots, \Delta Z_{N_r}(t))$ is a collection of Poisson variables
- ↪ The component variables can be assumed to be mutually independent
 - (Reasonably, as reactions progress independently during Δt)

Let $h(n(t)) = (h_1(n(t)), \dots, h_{N_r}(n(t)))^T$ be the vector collecting the propensities

The mean vector and the covariance matrix for the reaction-count increments,

$$\begin{aligned}\langle \Delta Z(t) \rangle_{n(t)} &= h(n(t)) \Delta t \\ \langle \underline{\Delta} Z(t) \underline{\Delta} Z(t)^T \rangle_{n(t)} &= \begin{bmatrix} h_1(n(t)) & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & h_{N_r}(n(t)) \end{bmatrix} \Delta t \\ &= H_D(n(t)) \Delta t\end{aligned}$$

The non-diagonal elements of the covariance matrix are all zero

- Reactions $\{\mathcal{R}_{n_r}\}$ progress independently during Δt

The chemical Langevin equations

From discrete-state to continuous-state stochastic simulations

The chemical Langevin equation

The short-time drift is the (conditional) expectation of the reaction-count increment

$$\langle \Delta N(t) \rangle_{n(t)}$$

To determine the short-time drift, we have the relation

$$\Delta N(t) = S \Delta Z(t)$$

Taking conditional expectations, we get

$$\begin{aligned} \langle \Delta N(t) \rangle_{n(t)} &= S \langle \Delta Z(t) \rangle_{n(t)} \\ &= S \underbrace{h(n(t)) \Delta t} \end{aligned}$$

$$= \underbrace{\begin{bmatrix} S_{1,1} & \cdots & S_{1,n_r} & \cdots & S_{1,N_r} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ S_{n_s,1} & \cdots & S_{n_s,n_r} & \cdots & S_{n_s,N_r} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ S_{N_s,1} & \cdots & S_{N_s,n_r} & \cdots & S_{N_s,N_r} \end{bmatrix}}_{h_S(n(t))} \begin{bmatrix} h_1(n(t)) \\ \vdots \\ h_{n_r}(n(t)) \\ \vdots \\ h_{N_r}(n(t)) \end{bmatrix} \Delta t$$

Vector $h_S(n(t))$ is the **drift per unit time**, or **drift rate**, with components

$$h_{S n_s}(n(t)) = \sum_{n_r=1}^{N_r} S_{n_s, n_r} h_{n_r}(n(t))$$

The chemical Langevin equation (cont.)

Similarly, for the short-term diffusion we can write

$$\begin{aligned}
 \left\langle \underline{\Delta N}(t) \underline{\Delta N}(t)^T \right\rangle_{n(t)} &= \langle \Delta N(t) \Delta N(t)^T \rangle_{n(t)} - \langle \Delta N(t) \rangle_{n(t)} \langle \Delta N(t) \rangle_{n(t)}^T \\
 &= S \left[\langle \Delta Z(t) \Delta Z(t)^T \rangle_{n(t)} - \langle \Delta Z(t) \rangle_{n(t)} \langle \Delta Z(t) \rangle_{n(t)}^T \right] S^T \\
 &= S \left\langle \underline{\Delta Z}(t) \underline{\Delta Z}(t)^T \right\rangle_{n(t)} S^T \\
 &= S [H_D(n(t)) \Delta t] S^T \\
 &= \underbrace{S [H_D(n(t))] S^T}_{B(n(t))} \Delta t
 \end{aligned}$$

Matrix $B(n(t))$ is the **diffusion per unit time**, or **diffusion rate**, with elements

$$B_{n_s, n'_s}(n(t)) = \sum_{n_r=1}^{N_r} S_{n_s, n_r} S_{n'_s, n_r} h_{n_r}(n(t))$$

The chemical Langevin equation (cont.)

We have expressions for the mean reaction-count and mean copy-number increments

$$\begin{aligned}
 \langle \Delta Z(t) \rangle_{n(t)} &= h(n(t)) \Delta t \\
 \langle \Delta N(t) \rangle_{n(t)} &= h_S(n(t)) \Delta t
 \end{aligned}$$

Individually, reaction-count increment $\Delta Z_{n_r}(t)$ of reaction \mathcal{R}_{n_r} is a Poisson variable

- Conditional on the state being $n(t)$, the expected value of the variable

$$\langle \Delta Z_{n_r}(t) \rangle_{n(t)} = h_{n_r}(n(t)) \Delta t$$

A Poissonian variable can be well approximated by a variable with a normal distribution

- The larger the parameter of the Poisson variable, the better the approximation
- (This parameter is also the mean and the variance of the distribution)

The chemical Langevin equation (cont.)

Let Δt be large enough for mean reaction-count increment $\langle \Delta Z_{n_r}(t) \rangle_{n(t)}$ to be large

$$\rightsquigarrow h_{n_r}(n(t)) \Delta t \gg 1$$

This condition is practically verified for systems with sufficiently large copy-numbers

Under these conditions, $\Delta Z_{n_r}(n(t))$ can be approximated by a normal variable

- The mean and the variance remain the same for each reaction

$$\Delta Z_{n_r}(n(t)) \sim \mathcal{N}\left(h_{n_r}(n(t)) \Delta t, (h_{n_r}(n(t)) \Delta t)^{1/2}\right)$$

The chemical Langevin equation (cont.)

$$\Delta Z_{n_r}(n(t)) \sim \mathcal{N}\left(\underbrace{h_{n_r}(n(t)) \Delta t}_{\mu}, \underbrace{(h_{n_r}(n(t)) \Delta t)^{1/2}}_{\sigma}\right)$$

It is well-known that a normal variable $\mathcal{N}(\mu, \sigma)$ can be written as the sum of its mean μ and the standard normal variable $\mathcal{N}(0, 1)$ multiplied by its standard deviation σ

$$\mathcal{N}(\mu, \sigma) = \mu + \sigma \mathcal{N}(0, 1)$$

From approximating the reaction-count increment of reaction \mathcal{R}_{n_r} as a normal variable,

$$\begin{aligned} \Delta Z_{n_r}(n(t)) &= h_{n_r}(n(t)) \Delta t + [h_{n_r}(n(t)) \Delta t]^{1/2} \mathcal{N}_{n_r}(0, 1) \\ &= \underbrace{h_{n_r}(n(t)) \Delta t}_{\text{Deterministic}} + \left[\underbrace{h_{n_r}(n(t))^{1/2}}_{\text{Deterministic}} \right] \underbrace{\sqrt{\Delta t} \mathcal{N}_{n_r}(0, 1)}_{\text{Stochastic}} \end{aligned}$$

$\sqrt{\Delta t} \mathcal{N}_{n_r}(0, 1)$ is a Wiener increment $\Delta W_{n_r}(t)$ of a univariate Brownian motion $W_{n_r}(t)$

$$\sqrt{\Delta t} \mathcal{N}(0, 1) = \underbrace{W_{n_r}(t + \Delta t) - W_{n_r}(t)}_{\Delta W_{n_r}(t)}$$

The chemical Langevin equation (cont.)

Jointly, the independent reaction-count increments $\{\Delta Z_{n_r}(n(t))\}_{n_r=1}^{N_r}$ take the form

$$\begin{aligned} \Delta Z(n(t)) &= \begin{bmatrix} h_1(n(t)) \Delta t \\ \vdots \\ h_{N_r}(n(t)) \Delta t \end{bmatrix} + \begin{bmatrix} \sqrt{h_1(n(t)) \Delta t} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sqrt{h_{N_r}(n(t)) \Delta t} \end{bmatrix} \mathcal{N}(0, I_{N_r}) \\ &= \underbrace{\begin{bmatrix} h_1(n(t)) \Delta t \\ \vdots \\ h_{N_r}(n(t)) \Delta t \end{bmatrix}}_{\text{Deterministic}} + \underbrace{\begin{bmatrix} h_1(n(t))^{1/2} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & h_{N_r}(n(t))^{1/2} \end{bmatrix}}_{\text{Deterministic}} \underbrace{\sqrt{\Delta t} \mathcal{N}(0, I_{N_r})}_{\text{Stochastic}} \end{aligned}$$

$\sqrt{\Delta t} \mathcal{N}(0, I_{N_r})$ is a Wiener increment $\Delta W_R(t)$ of multivariate Brownian motions $W_R(t)$

$$\sqrt{\Delta t} \mathcal{N}(0, I_{N_r}) = \underbrace{W_R(t + \Delta t) - W_R(t)}_{\Delta W_R(t)}$$

The chemical Langevin equation (cont.)

$$\Delta Z_{n_r}(n(t)) = h_{n_r}(n(t)) \Delta t + \left[h_{n_r}(n(t))^{1/2} \right] \sqrt{\Delta t} \mathcal{N}_{n_r}(0, 1)$$

When considering the copy-number increment of the n_s -th species, we have

$$\begin{aligned} \Delta N_{n_s}(t) &= \underbrace{N_{n_s}(t + \Delta t) - N_{n_s}(t)}_{S_{n_s, -} \Delta Z(n(t))} \\ &= \sum_{n_r=1}^{N_r} S_{n_s, n_r} [Z_{n_r}(t + \Delta t) - Z_{n_r}(t)] \\ &= \sum_{n_r=1}^{N_r} S_{n_s, n_r} \Delta Z_{n_r}(t) \\ &= \sum_{n_r=1}^{N_r} S_{n_s, n_r} \left[h_{n_r}(n(t)) \Delta t + h_{n_r}(n(t))^{1/2} \sqrt{\Delta t} \mathcal{N}_{n_r}(0, 1) \right] \\ &= \sum_{n_r=1}^{N_r} S_{n_s, n_r} [h_{n_r}(n(t)) \Delta t] + \sum_{n_r=1}^{N_r} S_{n_s, n_r} \left[h_{n_r}(n(t))^{1/2} \sqrt{\Delta t} \mathcal{N}_{n_r}(0, 1) \right] \end{aligned}$$

The chemical Langevin equation (cont.)

Jointly, the independent copy-number increments $\{\Delta N_{n_s}(n(t))\}_{n_s=1}^{N_s}$ take the form

$$\begin{aligned}\Delta N(n(t)) &= \underbrace{\underbrace{S}_{N_s \times N_r} \underbrace{h(n(t))}_{N_r \times 1}}_{h_S(\cdot)} \Delta t + \underbrace{\underbrace{S}_{N_s \times N_r} \underbrace{H_D(n(t))}_{N_r \times N_r}}_{D_R(\cdot)} \underbrace{\sqrt{\Delta t} \mathcal{N}(0, I_{N_r})}_{\Delta W_R(t)} \\ &= \underbrace{h_S(n(t))}_{N_s \times 1} \Delta t + \underbrace{D_R(n(t))}_{N_s \times N_r} \underbrace{\Delta W_R(t)}_{N_r \times 1}\end{aligned}$$

We can now set $\Delta t = dt$, $\Delta N(n(t)) = dN^c(t)$ and replace $\sqrt{dt} \mathcal{N}(0, I_{N_r})$ with $dW_R(t)$

$$dN^c(t) = h_S(N^c(t)) dt + D_R(N^c(t)) dW_R(t)$$

This is the chemical Langevin equation (CME)

↪ An Itô stochastic differential equation

The chemical Langevin equation (cont.)

$$dN^c(t) = h_S(N^c(t)) dt + D_R(N^c(t)) dW_R(t)$$

By dividing by dt , the equation can be written in the equivalent ‘white-noise form’¹

$$\frac{dN^c(t)}{dt} = h_S(N^c(t)) + D_R(N^c(t)) \frac{dW_R(t)}{dt}$$

The N_r elements of process $\left(\frac{dW_R(t)}{dt}\right)_{t \geq 0}$ are independent Gaussian processes

¹Expressions of this form are not precise because the solution $(N^c(t))_{t \geq 0}$ are usually not differentiable and the left-hand-side is not well defined.

The chemical Langevin equation (cont.)

It is also possible to derive an alternative form of the chemical Langevin equation

↪ A form with independent Brownian motions $\Delta W_{n_s}(t)$ for each species

Increments $\Delta N(t)$ in copy-number are combinations of Gaussian variables $\Delta Z(t)$

$$\Delta N(t) = S \Delta Z(t)$$

Therefore, also process $(\Delta N(t))_{t \geq 0}$ is a Gaussian process with N_s elements

The copy-number increment $\Delta N(t)$ is a Gaussian variable,

$$\Delta N(t) = \langle \Delta N(t) \rangle_{n(t)} + \left\langle \underline{\Delta N}(t) \underline{\Delta N}(t)^T \right\rangle_{n(t)}^{1/2} \mathcal{N}(0, I_{N_s})$$

A square root $M^{1/2}$ of a square matrix M is the matrix such that $M = M^{1/2} (M^{1/2})^T$

The chemical Langevin equation (cont.)

$$\Delta N(n(t)) = \langle \Delta N(t) \rangle_{n(t)} + \left\langle \underline{\Delta N}(t) \underline{\Delta N}(t)^T \right\rangle_{n(t)}^{1/2} \mathcal{N}(0, I_{N_s})$$

We derived the expression for the short-time drift

$$\begin{aligned} \langle \Delta N(t) \rangle_{n(t)} &= Sh(n(t)) \Delta t \\ &= h_S(n(t)) \Delta t \end{aligned}$$

Similarly, for the short time diffusion

$$\begin{aligned} \left\langle \underline{\Delta N}(t) \underline{\Delta N}(t)^T \right\rangle_{n(t)} &= S [H_D(n(t))] S^T \Delta t \\ &= B(n(t)) \Delta t \end{aligned}$$

After substituting, we get

$$\begin{aligned} \Delta N(n(t)) &= h_S(n(t)) \Delta t + [B(n(t)) \Delta t]^{1/2} \mathcal{N}(0, I_{N_s}) \\ &= \underbrace{h_S(n(t)) \Delta t}_{N_s \times 1} + \underbrace{B(n(t))^{1/2}}_{\underbrace{N_s \times N_s}_{D_S(\cdot)}} \sqrt{\Delta t} \mathcal{N}(0, I_{N_s}) \end{aligned}$$

The square root $D_S = B^{1/2}$ can be computed from the eigenvalue decomposition of B

The chemical Langevin equation (cont.)

$$\Delta N(n(t)) = h_S(n(t)) \Delta t + D_S(n(t)) \underbrace{\sqrt{\Delta t} \mathcal{N}(0, I_{N_s})}_{\Delta W_S(t)}$$

$\sqrt{\Delta t} \mathcal{N}(0, I_{N_s})$ is a Wiener increment $\Delta W_S(t)$ of multivariate Brownian motions $W_S(t)$

$$\sqrt{\Delta t} \mathcal{N}(0, I_{N_s}) = \underbrace{W_S(t + \Delta t) - W_S(t)}_{\Delta W_S(t)}$$

We can now set $\Delta t = dt$, $\Delta N(n(t)) = dN^c(t)$ and replace $\sqrt{dt} \mathcal{N}(0, I_{N_s})$ with $dW_S(t)$

$$dN^c(t) = h_S(N^c(t)) dt + D_S(N^c(t)) dW_S(t)$$

This is another chemical Langevin equation (CME)

- Another Itô stochastic differential equation

The chemical Langevin equation (cont.)

$$\begin{aligned} dN^c(t) &= N(t + t) - N(t) \\ &= h_S(N^c(t)) dt + D_R(N^c(t)) dW_R(t) \\ &= h_S(N^c(t)) dt + D_S(N^c(t)) dW_S(t) \end{aligned}$$

For any initial condition $N^c(0) = N_0^c$, the solutions to the SDEs are stochastic processes

Generating sample paths from the stochastic differential equations is relatively fast

- ↪ The first equation requires N_r random numbers
- ↪ The second one requires N_s random numbers

The choice between the two depends by the number of reactions relative to species

The chemical Langevin equation (cont.)

It was pointed out that noise in a jump process is ‘internal’ (inherent to the mechanism by which the state evolves) and cannot be dissociated from its equations of motion

In contrast, the noise in the chemical Langevin equation (and in other continuous Markov processes) seems ‘external’ (independent corrections to the deterministic drift)

- (Though Gillespie claims that the source is internal)

The chemical Langevin equation is not without limitations

- They generally predict negative concentrations
- (Though, with small probability)

Some other common shortcomings encountered in practice

- May not exhibit multi-stability, when present
- Inaccurate for systems far from equilibrium

Brownian motions

From discrete-state to continuous-state stochastic simulations

Brownian motion

A standard Brownian motion (or Wiener process) is a stochastic process $(W(t))_{t \geq 0}$

- The process starts at zero,

$$W(t=0) = 0$$

- For any $t, s \geq 0$,

$$W(t+s) - W(t) \sim \sqrt{s}\mathcal{N}(0, 1)$$

That is,

$$\langle (W(t+s) - W(t)) \rangle = 0$$

$$\langle (W(t+s) - W(t))(W(t+s) - W(t))^T \rangle = s$$

- For any $0 \leq t_1 < t_2 < t_3 < t_4$,

$$(W(t_2) - W(t_1)) \perp (W(t_4) - W(t_3))$$

That is,

$$\langle (W(t_4) - W(t_3))(W(t_2) - W(t_1))^T \rangle = 0$$

It can be understood as an idealisation of a rapidly varying and irregular function $W(t)$

Brownian motion (cont.)

Like Poisson processes, Brownian motions have stationary and independent increments

- The sample paths of Poissonian motions are discontinuous functions of t
- The sample paths of Brownian motions are continuous functions of t

All the finite-dimensional distributions $(W(t_1), \dots, W(t_N))$ of $(W(t))_{t \geq 0}$ are Gaussian

$\rightsquigarrow (W(t))_{t \geq 0}$ is a Gaussian process

The expectation function, for all $t > 0$

$$\begin{aligned} \langle W(t) \rangle &= \mu_W(t) \\ &= 0 \end{aligned}$$

The covariance function, for any $s \leq t$

$$\begin{aligned} \langle (W(t) - \mu_W(t))(W(s) - \mu_W(s))^T \rangle &= \text{cov}(t, s) \\ &= \min(t, s) \\ &= s \end{aligned}$$

The sample paths of a Brownian motion are nowhere differentiable functions of t