Faster stochastic simulation —
Alternative formulations of the chemical Langevin equation

Bence Mélykúti[♥,♣] (Joint work with **Kevin Burrage**[♦] and **Konstantinos Zygalakis**[♠].)

[♥]Life Sciences Interface Doctoral Training Centre; [♣]Department of Statistics; [♦]Computing Laboratory; [♠]Mathematical Institute
University of Oxford, UK Website: www.stats.ox.ac.uk/~melykuti Email: bence.melykuti@keble.ox.ac.uk September 2009

|Abstract|

The chemical Langevin equation[1]*:*
- *multivariable Itô stochastic differential equation*
- *describes the dynamics of (bio)chemical reactions*
- *continuous and probabilistic (*chemical master equation *&* Gillespie's algorithm — *discrete, probabilistic;* ordinary differential equation models — *continuous, deterministic)*

n = no. of chemical species; m = no. of reaction channels; r = no. of pairs of reversible reactions

The original formulation: •*m independent standard Brownian motions*
•*including 2r Brownian motions for the reversible reactions*

Our formulation: •*omits one independent Brownian motion for each pair of reversible reactions*
•*that is, only r Brownian motions are used for the reversible reactions*

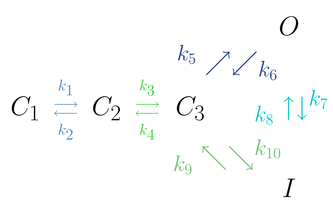
The result is faster simulation of the chemical Langevin equation.

|Applications|

Example 1: A K^+ channel

Transformations of human ether a-go-go related gene (HERG) encoded K^+ channels between three closed states (C_1, C_2, C_3), one open state (O) and one inactivation state (I)[2].

We model it as $n = 5$ chemical species (C_1, C_2, C_3, O, I) reacting through $m = 10$ reactions:



The chemical Langevin equation:

$$\mathrm{d}\begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \end{pmatrix} = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \end{bmatrix} \begin{pmatrix} k_1X_1 \\ k_2X_2 \\ k_3X_2 \\ k_4X_3 \\ k_5X_3 \\ k_6X_4 \\ k_7X_4 \\ k_8X_5 \\ k_9X_5 \\ k_{10}X_3 \end{pmatrix} \mathrm{d}t + g(X)\,\mathrm{d}B(t).$$

Originally one had

$$g^{\text{original}}(X)\,\mathrm{d}B(t) = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \end{bmatrix} \begin{bmatrix} \sqrt{k_1X_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sqrt{k_2X_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sqrt{k_3X_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \sqrt{k_4X_3} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sqrt{k_5X_3} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sqrt{k_6X_4} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_7X_4} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_8X_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_9X_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{k_{10}X_3} \end{bmatrix} \begin{pmatrix} \mathrm{d}B_1(t) \\ \mathrm{d}B_2(t) \\ \mathrm{d}B_3(t) \\ \mathrm{d}B_4(t) \\ \mathrm{d}B_5(t) \\ \mathrm{d}B_6(t) \\ \mathrm{d}B_7(t) \\ \mathrm{d}B_8(t) \\ \mathrm{d}B_9(t) \\ \mathrm{d}B_{10}(t) \end{pmatrix}.$$

We propose

$$g^{\text{new}}(X)\,\mathrm{d}B(t) = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 1 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \sqrt{k_1X_1 + k_2X_2} & 0 & 0 & 0 & 0 \\ 0 & \sqrt{k_3X_2 + k_4X_3} & 0 & 0 & 0 \\ 0 & 0 & \sqrt{k_5X_3 + k_6X_4} & 0 & 0 \\ 0 & 0 & 0 & \sqrt{k_7X_4 + k_8X_5} & 0 \\ 0 & 0 & 0 & 0 & \sqrt{k_9X_5 + k_{10}X_3} \end{bmatrix} \begin{pmatrix} \mathrm{d}B_1(t) \\ \mathrm{d}B_2(t) \\ \mathrm{d}B_3(t) \\ \mathrm{d}B_4(t) \\ \mathrm{d}B_5(t) \end{pmatrix}.$$

The number of Brownian motions is decreased by 50%.

Example 2: The Goldbeter–Koshland switch

A system of covalent modifications facilitated by two converter enzymes, E_1 and E_2[3]. E.g. a phosphorylation–dephosphorylation system.

We model it as $n = 6$ chemical species $(S, E_1, C_1, P, E_2, C_2)$ reacting through $m = 6$ reactions:

$$S + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} C_1 \xrightarrow{k_3} P + E_1,$$
$$P + E_2 \underset{k_5}{\overset{k_4}{\rightleftarrows}} C_2 \xrightarrow{k_6} S + E_2,$$

The chemical Langevin equation:

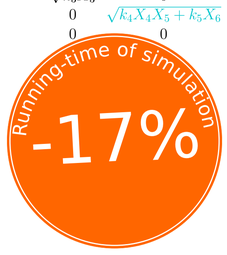
$$\mathrm{d}\begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ X_5 \\ X_6 \end{pmatrix} = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ -1 & 1 & 1 & 0 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 & 1 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix} \begin{pmatrix} k_1X_1X_2 \\ k_2X_3 \\ k_3X_3 \\ k_4X_4X_5 \\ k_5X_6 \\ k_6X_6 \end{pmatrix} \mathrm{d}t + g(X)\,\mathrm{d}B(t).$$

Originally one had

$$g^{\text{original}}(X)\,\mathrm{d}B(t) = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ -1 & 1 & 1 & 0 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 & 1 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix} \begin{bmatrix} \sqrt{k_1X_1X_2} & 0 & 0 & 0 & 0 & 0 \\ 0 & \sqrt{k_2X_3} & 0 & 0 & 0 & 0 \\ 0 & 0 & \sqrt{k_3X_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & \sqrt{k_4X_4X_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & \sqrt{k_5X_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & \sqrt{k_6X_6} \end{bmatrix} \begin{pmatrix} \mathrm{d}B_1(t) \\ \mathrm{d}B_2(t) \\ \mathrm{d}B_3(t) \\ \mathrm{d}B_4(t) \\ \mathrm{d}B_5(t) \\ \mathrm{d}B_6(t) \end{pmatrix}.$$

We propose

$$g^{\text{new}}(X)\,\mathrm{d}B(t) = \begin{bmatrix} -1 & 0 & 0 & 1 \\ -1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \sqrt{k_1X_1X_2 + k_2X_3} & 0 & 0 & 0 \\ 0 & \sqrt{k_3X_3} & 0 & 0 \\ 0 & 0 & \sqrt{k_4X_4X_5 + k_5X_6} & 0 \\ 0 & 0 & 0 & \sqrt{k_6X_6} \end{bmatrix} \begin{pmatrix} \mathrm{d}B_1(t) \\ \mathrm{d}B_2(t) \\ \mathrm{d}B_3(t) \\ \mathrm{d}B_4(t) \end{pmatrix}.$$



The number of Brownian motions is decreased by 33%.

|Theory|

Stoichiometry matrix S is $n \times m$, and the propensities $a(X)$ are an m-dimensional vector. All n-variable Itô stochastic differential equations

$$\mathrm{d}X_t = f(X_t)\,\mathrm{d}t + g(X_t)\,\mathrm{d}B(t),$$

for which

$$f(X) = Sa(X) \qquad \text{and} \qquad g(X)g(X)^T = S\,\mathrm{diag}(a(X))S^T$$

give chemical Langevin equations which have the same finite-dimensional distributions, thus means and covariances. Gillespie's solution[1] is just one of many alternatives: $g(X) = S\,\mathrm{diag}(\sqrt{a(X)})$.

Using one Brownian motion for each pair of reversible reactions

Two vectors $y_1, y_2 \in \mathbb{R}^n \setminus \{0\}$ represent the same *direction*, if there is a $\lambda \in \mathbb{R} \setminus \{0\}$ such that $y_1 = \lambda y_2$.

Theorem Let s be the number of different directions given by the columns of S. There exist matrices $J \in \mathbb{R}^{m\times s}$ and $V \in \mathbb{R}^{s\times m}$ such that $V\,\mathrm{diag}(a(X))V^T \in \mathbb{R}^{s\times s}$ is diagonal with only nonnegative entries and

$$g(X) = SJ\sqrt{V\,\mathrm{diag}(a(X))V^T}$$

gives a chemical Langevin equation with s independent standard Brownian motions, $m-\dim(\mathrm{Ker}\,S) \le s \le m$.

Proof (sketch) Permute the columns of $S \in \mathbb{R}^{n\times m}$ such that $S = [S_1\ S_2]$, where $S_1 \in \mathbb{R}^{n\times s}$ has one representative column vector for each direction given by the columns of S. The columns that are left (S_2) are each a constant multiple of one column in S_1. Partition $A(X) = \mathrm{diag}(a(X))$ accordingly. $S_2 = S_1M$ with a matrix $M = [v^{(1)}\ \dots\ v^{(m-s)}] \in \mathbb{R}^{s\times(m-s)}$ which has one nonzero entry in each column. The definitions are

$$J = \begin{bmatrix} I_s \\ 0 \end{bmatrix} \in \mathbb{R}^{m\times s} \qquad \text{and} \qquad V = \begin{bmatrix} I_s & M \end{bmatrix} \in \mathbb{R}^{s\times m}.$$

Then $SJV = S$ holds. This implies for the above $g(X)$ that $g(X)g(X)^T = S\,\mathrm{diag}(a(X))S^T$ indeed. The actual form of g is

$$g(X) = [S_1\ S_2]\begin{bmatrix} \sqrt{A_1(X) + MA_2(X)M^T} \\ 0 \end{bmatrix} = S_1\sqrt{A_1(X) + MA_2(X)M^T} = S_1\sqrt{A_1(X) + \sum_{j=1}^{m-s}(A_2(X))_{jj}v^{(j)}v^{(j)T}}.$$

The minimal formulation

Theorem There exist state-dependent matrices $U_1(X) \in \mathbb{R}^{m\times(m-\dim(\mathrm{Ker}\,S))}$ and $D_1(X) \in \mathbb{R}^{(m-\dim(\mathrm{Ker}\,S))\times(m-\dim(\mathrm{Ker}\,S))}$ such that D_1 is diagonal with only nonnegative entries and

$$g(X) = U_1(X)D_1(X)^{1/2}$$

gives a chemical Langevin equation with $n - \dim(\mathrm{Ker}\,S^T) = m - \dim(\mathrm{Ker}\,S)$ independent standard Brownian motions. Any chemical Langevin equation requires at least this many Brownian motions. This formulation is usually computationally less favourable than the previous one.

Proof (sketch) $S\,\mathrm{diag}(a(X))S^T$ is a symmetric square matrix for all X. It can be diagonalised by a change of basis with an orthonormal matrix $U(X)$ of which the columns are eigenvectors of $S\,\mathrm{diag}(a(X))S^T$:

$$S\,\mathrm{diag}(a(X))S^T = U(X)D(X)U(X)^T.$$

Partition the eigenvectors based on whether they belong to zero eigenvalue ($U_0(X)$) or some nonzero eigenvalue ($U_1(X)$) and arrange them such that $U(X) = [U_1(X)\ U_0(X)]$. Then

$$D(X) = \begin{bmatrix} D_1(X) & 0 \\ 0 & 0 \end{bmatrix}.$$

With the above $g(X)$

$$g(X)g(X)^T = U(X)D(X)^{1/2}D(X)^{1/2}U(X)^T = S\,\mathrm{diag}(a(X))S^T.$$

This factorisation is minimal indeed, since the rank of $g(X)$ cannot be less than the rank of $S\,\mathrm{diag}(a(X))S^T = g(X)g(X)^T$, that is, $n - \dim(\mathrm{Ker}\,(S\,\mathrm{diag}(a(X))S^T))$. If for all X and each reaction channel j, $a_j(X) > 0$ (e.g. X is strictly positive), then $\dim(\mathrm{Ker}\,(S\,\mathrm{diag}(a(X))S^T)) = \dim(\mathrm{Ker}\,S^T)$. Also, $n - \dim(\mathrm{Ker}\,S^T) = m - \dim(\mathrm{Ker}\,S)$.

References

[1] Daniel T. Gillespie. The chemical Langevin equation. *Journal of Chemical Physics*, 113(1):297–306, Jul 2000.

[2] T. Brennan, M. Fink, and B. Rodriguez. Multiscale modelling of drug-induced effects on cardiac electrophysiological activity. *European Journal of Pharmaceutical Sciences*, 36:62–77, 2009.

[3] Albert Goldbeter and Daniel E. Koshland. An amplified sensitivity arising from covalent modification in biological systems. *Proceedings of the National Academy of Sciences USA*, 78(11):6840–6844, Nov 1981.

*Details for computational benchmarking

Rate constants: Example 1: $k_1 = \cdots = k_{10} = 0.1$; Example 2: $k_1 = 0.05$, $k_2 = 0.1$, $k_3 = 0.1$, $k_4 = 0.01$, $k_5 = 0.1$, $k_6 = 0.1$.

Initial state: Example 1: $(100, 50, 100, 50, 100)$; Example 2: $(110, 100, 30, 30, 100, 30)$.

Time horizon: $[0, 5]$, step size: 0.005.

No. of realisations: 10 000 in MATLAB with the Euler–Maruyama method.

|Acknowledgements for financial support|

EPSRC Engineering and Physical Sciences Research Council

RoSB net A Network in Synthetic Biology co-funded by BBSRC, EPSRC, AHRC and ESRC