# Stochastic Simulation of Bio-molecular Networks in Dynamic Environments

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***Short Abstract* — Simulation algorithms have become indispensable tools in modern quantitative biology, providing deep insight into many biochemical systems including gene regulatory networks. However, current stochastic simulation approaches handle the effects of fluctuating extracellular signals and upstream processes poorly, either failing to give qualitatively reliable predictions or being very inefficient computationally. Here, we introduce the Extrande method, a novel approach for simulation of bio-molecular networks embedded in the dynamic environment of the cell and its surroundings. The method is accurate and computationally efficient, and hence fills an important gap in the field of stochastic simulation. We employ it to study a bacterial decision-making network and demonstrate that robustness to fluctuations from upstream signaling places strong constraints on the design of networks determining cell fate.**

***Keywords* — Stochastic simulation, biochemical networks, fluctuating environment, time-varying propensities.**

DYNAMIC simulation is an essential and widespread approach for studying models of bio-molecular networks in cell biology [1]. Often such models need to take into account biochemical stochasticity [2] as well as the effects of interactions with other fluctuating processes in the cell and/or with signals arising extracellularly [3].

The stochastic simulation algorithm (SSA) [4] allows the random timing of reactions in the network model to be taken into account (often known as intrinsic noise). However, the SSA assumes constant propensities between reactions and cannot be used when other processes interacting with the network cause its propensities to fluctuate between reaction occurrences. Here, we introduce a new approach relaxing this assumption, which we call *Extrande*. The method allows stochastic simulation of a bio-molecular network of interest embedded in the dynamic, fluctuating environment of the cell and its surroundings.

There are two existing approaches to stochastic simulation of reaction networks subject to dynamic, fluctuating inputs. The first class of algorithms [5-7] simply implements the SSA, under the approximation that the input remains constant between the occurrences of any two reactions. We term these collectively the naive method. The second class of algorithms [8-10] involves step-wise numerical integration of reaction propensities until a target value for the integral is reached. We term these collectively the integral method. The naive method can yield qualitatively misleading predictions (even when dynamic inputs change relatively slowly) while the integral method can impose large and impractical computational burdens due to numerical integration of propensities.

We demonstrate the clear advantages of *Extrande* in terms of speed and accuracy using two illustrative case studies. In the first case study, we study how various biological sources, including effects related to circadian oscillations, chromatin remodeling, the cell cycle, and pulsatile transcription factors, affect variation in gene expression levels across cells and over time. In the second case study, we use *Extrande* to study how fluctuations in the protein componentry of signal transduction networks affect downstream networks determining cell fate. We find that robustness to fluctuations from upstream signaling places strong constraints on the design of networks determining cell fate.

Acknowledgements: MV acknowledges support under an MRC

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## REFERENCES

[1] Karr JR, Sanghvi JC, Macklin DN, Gutschow MV, Jacobs JM, et al. (2012) A whole-cell computational model predicts phenotype from genotype. Cell 150: 389–401.

[2] Eldar A, Elowitz MB (2010) Functional roles for noise in genetic circuits. Nature 467: 167–173.

[3] Bowsher CG, Voliotis M, Swain PS (2013) The fidelity of dynamic signaling by noisy biomolecular networks. PLoS Comput Biol 9: e1002965.

[4] Gillespie DT (1976) A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J Comp Phys 22: 403–434.

[5] Rand U, Rinas M, Schwerk J, Nohren GN, Linnes M, et al. (2012) Multi-layered stochasticity and paracrine signal propagation shape the type-I interferon response. Mol Syst Biol 8: 1–13.

[6] Gillespie DT (1976) A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J Comp Phys 22: 403–434.

[7] Guerriero ML, Pokhilko A, Fernandez AP, Halliday KJ, Millar AJ, et al. (2012) Stochastic properties of the plant circadian clock. J R Soc Interface 9: 744–756.

[8] Anderson DF (2007) A modified next reaction method for simulating chemical systems with time dependent propensities and delays. J Chem Phys 127: 214107.

[9] Shahrezaei V, Ollivier JF, Swain PS (2008) Colored extrinsic fluctuations and stochastic gene expression. Mol Syst Biol 4: 196.

[10] Johnston IG, Gaal B, Neves RPd, Enver T, Iborra FJ, et al. (2012) Mitochondrial variability as a source of extrinsic cellular noise. PLoS Comput Biol 8: e1002416.