

## Characterizing the Stochastic Decisions of Biomolecular Systems with Probability Gradients

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Randomness is inherent to all forms of biomolecular computation: at any given instant, the choice of which reaction fires next is a matter of chance. Certain biomolecular systems appear to exploit this randomness for evolutionary advantage, choosing between different outcomes with a probability distribution – in effect, hedging their bets with a portfolio of responses that is carefully tuned to the environmental conditions. Examples include the lysis/lysogeny decision of the *lambda phage*<sup>1</sup> and the *pap pili* epigenetic response of bacteria.<sup>2</sup>

Characterizing the probabilistic behavior of such systems is a challenging problem from a computational standpoint. The standard approach is to use stochastic simulation, as proposed by Gillespie.<sup>3</sup> In each trial, reactions are executed at random based on propensity calculations. The probability distribution of the outcomes is estimated by averaging the results.

The drawback of stochastic simulation is the prohibitive computation time that is required. In order to obtain an accurate estimate, a large number of trials must be performed, each trial consisting of a long chain of reaction events. Furthermore, by averaging the results, such a simulation produces only coarse-grained statistics that provide little insight into the dynamics of the stochastic behavior. For instance, in a system with a bimodal response (say lysis vs. lysogeny), we can expect each trajectory eventually to veer in one direction or the other. Is this decision gradual or abrupt? If it is gradual, then the behavior might be due to straight-forward stochastic competition; if it is abrupt, then there may be interesting dynamics at play.

The broad thrust of our research is to develop analysis techniques that: (1) are computationally efficient, and (2) provide fine-grained statistics for characterizing the behavior of biomolecular systems. In this work, we describe a conceptually simple, yet effective, metric: the *probability gradient*. For each point in the state space, the probability gradient is a vector corresponding to the *expected value* of transitions. More precisely, consider a system consisting of  $N$  types of molecules  $\{X_1, \dots, X_N\}$ . The state of the system is

$$[x_1, \dots, x_N] \in \mathbb{N}^N,$$

where  $x_i$  is the number of molecules of type  $X_i$ . Suppose that, from a given state  $\vec{S}$ , there are  $M$  possible transitions. Suppose that the  $j$ -th transition occurs with probability  $p_j$  and is characterized by the vector

$$\vec{V}_j = [v_{1,j}, \dots, v_{N,j}] \in \mathbb{Z}^N,$$

where  $v_{i,j}$  is the change in the number of molecules of type  $X_i$  that this transition produces. The gradient is computed as

$$\vec{G} = \sum_{j=1}^M p_j \vec{V}_j.$$

For the *first-order* gradient, we consider the transitions resulting from a single reaction firing; for the *m-th order* gradient, we consider the transitions resulting from all possible sequences of  $m$  reactions firing.

The gradient allows us to characterize the topology of the state space. If the gradient is small in magnitude, then we are likely in a “flat” region with considerable uncertainty in the outcome; if it is large in magnitude, then we are likely in a “canyon” progressing rapidly toward a decision. If the outcome is nearly certain, then a trajectory can be terminated early, reducing the computation time. Furthermore, profiling the probability gradient allows us to detect abrupt changes in the topology – indicating the decision points of the system.

1. A. Arkin, J. Ross, and H. McAdams, “Stochastic Kinetic Analysis of Developmental Pathway Bifurcation in Phage Lambda-Infected E. Coli Cells,” *Genetics* 149: 1633–48 (1998).
2. A. Hernday, M. Krabbe, B. Braaten, and D. Low, “Self-perpetuating Epigenetic Pili Switches in Bacteria,” *PNAS* 99: 16470–76 (2002).
3. D. Gillespie, “Exact Stochastic Simulation of Coupled Chemical Reactions,” *Physical Chemistry* 81: 2340–61 (1977).