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Computing probability landscape of stochastic networks through Discrete Chemical Master Equation: Understanding Maintenance of Epigenetic State of Phage Lambda

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Abstract Computational studies of biological networks can help to identify components and wirings responsible for observed phenotypes. Stochasticity plays important roles in many biological networks when molecular concentrations are in the range of 0.1 uM to 10nM (about 100 to 10 copies in a cell). However, studying stochastic networks controlling many biological processes is challenging. Similar to Schrodinger's equation in quantum mechanics, the chemical master equation (CME) provides a basic framework for understanding stochastic networks, and the time varying landscape probability distribution over the full microstates, i.e., the combination of copy numbers of molecular species, provide a full characterization of the network dynamics. Whereas progress in solving Schrodinger's equation extends to systems of hundreds of particles, the CME cannot be solved exactly, except for simple toy problems with few molecular species. Here we describe a method called direct chemical master equation (dCME) to compute directly the full steady-state probability landscape of stochastic network of moderate size. Our method is based an algorithm that can exhaustively enumerate the microstates of a molecular network of small copy numbers under the condition that the net gain in newly synthesized molecules is modest. This algorithm works for networks of arbitrary reaction stoichiometry, and is optimal in both storage and time complexity. It provides a reduction of the state space with a factor of 10^8 - 10^{20} compare to a naive method. We apply the dCME method to study the lysogeny maintenance network in phage lambda. Results show that wild type phage lambda can maintain a constant level of repressor over a wide range of repressor degradation rate, and is stable against UV irradiation, ensuring heritability of the lysogenic state. Furthermore, it can switch efficiently to the lytic state once repressor degradation increases past a high threshold by a small amount. We find that beyond bistability and nonlinear dimerization, cooperativity between repressors bound to O_R1 and O_R2 is required for stable and heritable epigenetic state of lysogeny that can switches efficiently. Mutants of phage lambda lack stability and do not possess a high threshold. Instead, they are leaky and respond to gradual changes in degradation rate. Our computation faithfully reproduces the hair triggers for UV-induced lysis observed in mutants and the limitation in robustness against mutation. Analysis of altered wirings further suggests a simpler prototype-circuit for lysogeny maintenance. Our landscape approach computed from dCME is general and can be applied to study broad issues in systems biology.

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