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Not all Parameters Matter: Local and Global Sensitivity Analysis applied to Phage Lambda Lysis/Lysogeny Models

Mathematical models are increasingly prevalent in systems biology with the goal of providing predictions and insight that may be less accessible by intuition alone. However, analysis of these models can be challenging because they are often defined by a large number of parameters and non-linear interactions between components. While brute-force numerical simulations have been used for analyzing models, the large-variation in parameters and the very large parameter space make the analysis difficult.

Here we consider methods to rationally explore model dynamics using recent innovations in the area of sensitivity analysis (SA). In particular, we utilize a recent technique called 'Sloppy-stiff' SA method to quantify how changes in parameter values affect model output[1]. This method is realized through calculating partial derivatives of a cost function dependent on the output dynamics at a local point in parameter space. We extend the local analysis to look globally by sampling in a large range of biologically feasible parameter space to demonstrate that results from any particular local SA may not match the global trends. Looking globally gives us a distribution of the importance of parameters in the space.

To illustrate how different parameters differentially contribute to the overall dynamics of models, we apply SA to models of the lysis/lysogeny decision for phage Lambda infecting *E. coli*. The underlying gene regulatory network is believed to be bistable corresponding to two different phenomenological outcomes. After infection there can either be an immediate production and release of new viruses through a bursting of the bacterial cell (lysis), or the viral DNA can incorporate itself with the bacterial DNA and lay dormant (lysogeny) until a more favorable time to undergo lysis. Experiments have demonstrated that the lysogenic outcome is more likely when more phages infect a given cell[2,3] and lysogeny is also more likely with decreasing cell volume[4]. Theory suggests that this change in behavior is mediated by a change in viral genome concentration[5] along with stochastic effects[3]. However, the relationship between network parameters and cell fate outcome remains unresolved. Here, we utilize SA to evaluate candidate models of cell fate determination and determine the relative importance of parameters to cell fate outcome.

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