

Determining the validity of Hill functions in stochastic simulations

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The non-elementary reaction functions (e.g. Michaelis-Menten or Hill functions) are used to reduce the model of biochemical network. Such deterministic reductions are frequently a basis for heuristic stochastic models in which non-elementary reaction functions are used as propensities of Gillespie algorithm. Despite their popularity, it remains unclear when such stochastic reductions are valid. Here, we first identify the validity condition for using non-elementary reaction functions for the stochastic simulations. This provides a simple and computationally inexpensive way to test the accuracy of reduced stochastic model.

Keywords – multi-scale stochastic system, stochastic simulation, Hill-function, Michaelis-Menten function

I. INTRODUCTION

BIOCHEMICAL systems are often regulated by processes that evolve on widely differing timescales. Simulating the fastest of these processes is computationally expensive and often not of direct interest. Thus, to replace the fast processes, non-elementary reaction functions (e.g. the Michaelis-Menten or Hill function) have been used. This approach is simple, computationally inexpensive, and has been used widely in both deterministic and stochastic simulations [1-3].

While the deterministic reductions have been theoretically justified [4], it is not clear when their stochastic counterparts will be accurate. Many previous modeling results rely on the assumption that the results of stochastic simulations can be accepted if their deterministic counterparts are valid. However, a number of recent examples show that this is not necessarily the case [5-7].

In this study [8], we show that the validity of these approximations is closely related, but in a more subtle way than previously assumed. This insight provides a simple and concrete method for testing the validity of using non-elementary functions for the propensity functions in stochastic simulations.

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II. RESULTS

We find that discrepancies between the stochastic and the deterministic reduction stem from the fact that, due to the random fluctuations, the stochastic system explores a wider range of states than its deterministic counterpart. Our analysis and simulations show that the stochastic reduction is accurate only when the corresponding deterministic reduction is accurate over a range that covers the most likely states of the stochastic system.

This finding implies that, for testing the validity of stochastic reduction, it is sufficient to examine the validity of deterministic reduction *post facto* -- after the corresponding stochastic simulations of the reduced model reveal the range of status that need to be tested.

III. CONCLUSION

Our work first develops a simple and general method to test the validity of stochastic models that include non-elementary propensity functions. If the validity condition is satisfied, we can perform accurate and computationally inexpensive stochastic simulation without converting the non-elementary functions to the elementary functions (e.g. mass action kinetics). Considering the popularity of Michaelis-Menten or Hill functions in various biological models, our results will provide a useful tool to a large modeling community.

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