Equation-free computation for rule-based models of biochemical reaction networks

Nathan Lemons[12], Aric Hagberg[1], and William S. Hlavacek[3]

***Short Abstract* — Because of the combinatorial potential of biomolecular interactions, rule-based models tend to correspond to large-scale chemical reaction networks, which are often impractical to represent using a model with a traditional form, and most rule-based models can only be simulated using particle-based kinetic Monte Carlo techniques, which are computationally expensive. We demonstrate how equation-free computation can be used to accelerate simulation of a rule-based model through projective integration and provide access to the derivatives of two different types of macroscopic variables. These variables can be defined without identifying processes occurring on different time scales, which is the usual basis for definition of the macroscopic variables used in equation-free computation. The approach demonstrated should enable diverse derivative-based methods of numerical analysis to be brought to bear on rule-based models.**

INTRODUCTION

There is significant interest in modeling biomolecular interactions involved in cellular information processing at the level of chemical kinetics. Models specified in terms of rules are equivalent to models for chemical kinetics having traditional forms, such as models consisting of coupled ordinary differential equations. Most rule-based models can only be simulated using agent-based kinetic Monte Carlo techniques, which are computationally expensive. We demonstrate how equation-free computation can be used to accelerate simulation of a rule-based model through projective integration and provide access to the derivatives of two different types of macroscopic variables. These variables can be defined without identifying processes occurring on different time scales, which is the usual basis for definition of the macroscopic variables used in equation-free computation. The approach demonstrated here should enable diverse derivative-based methods of numerical analysis to be brought to bear on rule-based models.

RESULTS

We validate the equation-free method (and in extension our choice of macro-variables) by comparing simple projective integration to direct simulation in the context of the well studied Epidermal Growth Factor (EGF) Receptor signaling model. The results of projective integration using two different sets of macro variables, a coarser and a finer set of variables, are compared to results from pure simulation. We also detail how to further refine the macro-variable set in a principled manner so as to achieve greater accuracy. In the EGFR model, projective integration with the coarser macro-variables captured qualitatively many aspects of the true dynamics. Furthermore, projective integration with the finer macro-variables produced results that were in mostly indistinguishable from pure simulations; often the projective integration was significantly faster than simple simulation as well.

CONCLUSION

The equation free approach can be seen as an approximate method of model reduction. For systems that are much complex than the EGFR model, finding tractable reductions which are exactly preserve the dynamics of the system may be impossible. We propose to use Equation-Free methods to aid in the simulation of such systems and in further numerical analysis of these systems. We show that the Equation-Free method can faithfully reproduce the dynamics of the EGFR system while also being much more efficient than traditional simulation in many cases.

[1]Center for Nonlinear Studies, Los Alamos National Laboratory.
[2]Applied Mathematics and Plasma Physics Group, Los Alamos National Laboratory.
[3]Theoretical Biology and Biophysics Group, Los Alamos National Laboratory.