Analysis of Dynamics and Predictability in Stochastic Reaction Networks

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Summary

Understanding systems such as gene transcription, cell signaling, and surface catalytic reactions is critical in the areas of bioenergy, biomedicine, and fuel cells. Computational models can be powerful tools to gain deeper insight into these systems and to enable an engineering approach to improved performance. Due to inherent variability, these systems are best described by stochastic reaction networks. While many methods are available to simulate such networks, there is a lack of tools for analyzing their dynamical behavior and uncertainty. This project develops methods to analyze the dynamics and predictability of stochastic reaction networks. These methods will enable a detailed understanding of these systems in terms of their functionality, robustness under experimental data uncertainty and inherent variability, and their core components that may be targets for engineered performance improvement.

Models for molecular level phenomena are generally inferred from noisy data sets that cover a sparse subset of the molecular species in the system. Combined with the inherent variability in reactions between small numbers of molecules, this leads to stochastic reaction networks with large uncertainties in the reaction rates as well as the model structure itself. This project develops methods for the analysis of such reaction networks. More specifically, this year, we made progress towards predictability and reduced order models.

Building on our methodology for sensitivity analysis in stochastic reaction networks [1], we are developing an approach for predictability studies. The main difference between these two analyses is that while sensitivity analysis looks at small parameter perturbations, predictability studies need to quantify the effect of actual, and often large, uncertainties in the model parameters. If the uncertainties in the parameters span across critical values, discontinuous changes in the system behavior can occur (e.g. transition to bistable behavior).

For a rigorous convergence study of the sensitivity analysis and to handle discontinuous system responses for predictability studies, an appropriate spectral basis set is needed. Instead of expansions in terms of Hermite polynomials of Gaussian random variables, which were used in the sensitivity analysis, we applied expansions in terms of Legendre polynomials of uniformly distributed random variables. The compact support of these functions facilitates convergence analysis. Also, the Legendre-Uniform (LU) basis sets can be used as building blocks for multiwavelet representations that are very effective in representing discontinuous functions.

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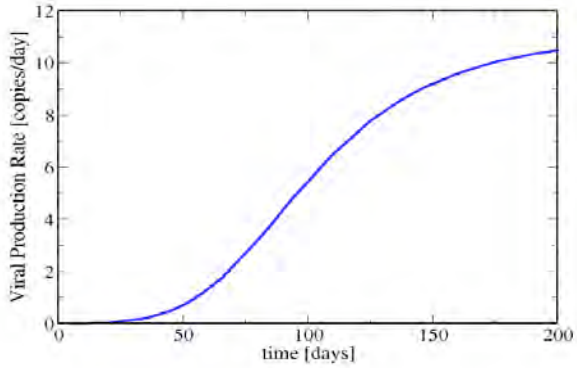

Fig. 1: Viral production rate for a model non-lytic virus up to 200 days post infection; averaged over 50000 realizations.

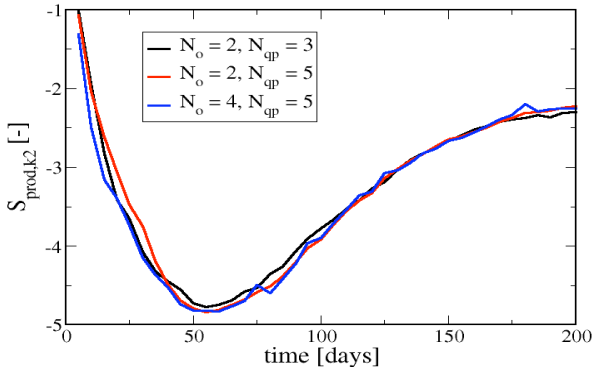

Fig. 2: Sensitivity of the production rate w.r.t. the decay rate of viral templates. Both 2nd and 4th order expansions, with 3 or 5 quadrature points, agree within the sampling noise level.

We performed a rigorous study of the performance of the LU representations for sensitivity analysis as a function of sampling noise, number of quadrature points, and spectral order. Consider, e.g. a viral kinetics model [2], with its average viral production rate shown in Fig. 1. Fig. 2 shows results with the new LU basis functions for the sensitivity of this production rate w.r.t. the template decay rate. Both 2nd and 4th order expansions, with 3 or 5 quadrature points, gave the same results within the level of sampling noise, indicating convergence.

For discontinuous response functions in predictability studies, we are enhancing our LU basis sets with an adaptive multiwavelet scheme [3], which is currently being added to our general-purpose uncertainty quantification (UQ) toolkit. This toolkit, to be released as open source, will facilitate the application of our spectral methods to a variety of problems in the user community.

For reduced order modeling, we are continuing to develop our Karhunen-Loève based approach to represent a system as a sum of eigenmodes, multiplied with associated random variables. We are studying the transformation of these random variables into a set of independent standard random variables, using e.g. the Nataf and Rosenblatt transformations, which will be added to the UQ toolkit.

Our analysis tools will enable a detailed understanding of the operation and dominant mechanisms in stochastic reaction networks. As such systems often form the controlling processes for cell metabolic and signaling networks, such an understanding is critical to improve the effectiveness of processes in biomedical and bioenergy applications.

References:

[1] Kim, D., Debusschere, B., and Najm, H., Biophysical J., 92(2):379-393, 2007.
[2] Srivastava, R. *et al.*, J. Theoretical Biology, 218:309-321, 2002.
[3] Le Maître, O., Najm, H. *et al.*, SIAM J. Sci. Comput. 29(2):864-889, 2007.

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