

LIMITS AND CONTROL OF STOCHASTIC REACTION NETWORKS

organized by
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Workshop Summary

Introduction

During the workshop different aspects of stochastic reaction networks have been discussed. During the week, presentations have been given in accordance with the workshop goals: Linard Hoessly discussed the connection between structural properties of the reaction graph and the stationary distribution of the model, and Jinsu Kim discussed the convergence rate to stationarity, further investigated in a dedicated work group. Furthermore, Ankit Gupta introduced the concepts of control theory in biochemistry, gave examples and proposed the open problem of finding a small set of reactions that added to an existing model force the existence of oscillations. The problem was addressed in a dedicated work group. Ankit Gupta also discussed the concept of Absolute Concentration Robustness (ACR) as described in the seminal paper by Feinberg and Shinar (2010), and he related this definition to existing concepts of control theory. A work group on ACR originated. Hye-Won Kang presented the framework of multiscale models, described the existing results and introduced the still unexplored case of discreteness-induced switches. This topic was further investigated in the work group on the Togashi-Kaneko model. Chiara Franceschini introduced the concepts of duality and showed some recent examples in the setting of stochastic reaction networks. A work group on the topic was created. Lea Popovic and Wasiur KhudaBukhsh introduced measure-valued stochastic processes in relation to reaction networks: Lea Popovic considered measures describing the spatial location of the reacting molecules, while Wasiur KhudaBukhsh considered delayed reactions and measures on the time line describing the original time of reaction occurrences. Lea Popovic and Wasiur KhudaBukhsh further discussed the topic in the afternoon, but no new research direction emerged. Finally, Artur Stephan and Michiel Renger discussed connections between stochastic reaction network theory and thermodynamics. A dedicated work group was formed. More details on the work done in groups are given below.

Togashi-Kaneko model

Group members: Enrico Bibbona, Felipe Campos, Hye-Won Kang, Jonathan Mattingly, Lea Popovic, Grzegorz Rempala, Paola Siri, Ruth Williams, Carsten Wiuf, Chaojie Yuan, Wasiur Khudabukhsh.

The group worked on the so-called Togashi-Kaneko (TK) stochastic model of autocatalytic chemical reactions. The model is well studied in the chemical physics literature due to its peculiar dynamics in some regions of parameter space, namely the switching between the patterns of scarcity and abundance of specific reactants. Since it is known that the traditional deterministic ODE approximants cannot reproduce such patterns, the group has investigated whether the switching behavior of the TK model may be recovered when

using some more sophisticated approximations. The two approaches considered were based on (a) the multiscale reduction method and (b) stochastic differential equations respectful of the TK-model boundary conditions. The group has identified some promising initial results that appear to indicate that the new approximations proposed may be indeed useful not just for the TK model but also for a wider class of stochastic biochemical models with similar oscillatory behavior.

Duality

Group members: Andrea Agazzi, Chiara Franceschini, Luisa Andreis, Jonathan Mattingly, Daniele Cappelletti, Artur Stephan.

The group discussed whether it is possible to extend the algebraic approach to Markov duality theory, which relies on representations of non commutative algebras, to chemical reaction networks. We also talked about possible applications of such duality relations. So far, we were able to produce several specific examples. More specifically, the dual models are either stochastic reaction networks themselves, or interacting particle models. A special behaviour is shown by complex balanced networks. As a future plan, we would like to keep studying the examples found and prove more general results.

Convergence

Group members: Jinsu Kim, Chuang Xu, Chaojie Yuan, Louis Fan.

The presentation on mixing time given by Jinsu Kim motivated the discussion on the convergence rate of the stochastic models. Discussion on this topic continued throughout the week. We first reviewed the use of Poincaré inequality in proving exponential ergodicity. In particular we focused on (1) understanding and relaxing the technical structural assumptions that are required to obtain exponential ergodicity, and (2) investigating a model proposed in Jinsu Kim's talk with a slower mixing rate, whose mixing time may be large when starting on the boundary. Both topics would be helpful in providing different perspectives on generalizing sufficient conditions for exponential ergodicity, as presented in Jinsu Kim's talk.

Then we briefly looked at the problem of establishing convergence rates for general models. In particular, we explored structural/kinetic conditions under which the associated stochastic models have longer mixing time that are independent of the initial conditions. Several examples were constructed along this line of research, which were expected to exhibit longer mixing time and share similar dynamics as in the model Jinsu proposed in his talk. However as far as we know, dynamical properties of these stochastic reaction networks, including positive recurrence and/or existence of stationary distribution, were widely open at the moment. Hence new approaches in establishing positive recurrence for such models are currently being investigated, which would be widely applicable, including an alternative proof of positive recurrence for Togashi-Kaneko models, which were discussed extensively throughout the Workshop.

Absolute Concentration Robustness

Group members: Anne Shiu, Badal Joshi, Nidhi Kaihnsa, Ankit Gupta, Daniele Cappelletti, Tung Nguyen, Allison Fisher.

The group discussed a wide range of topics related to ACR, including examples of small motifs for ACR, network operations that preserve/destroy ACR property, possible definition for stochastic ACR and its relation with deterministic counterpart, and prevalence of ACR among random reaction networks.

During the discussion, we formulated several concrete questions and conjectures. We discussed some possible ideas or approaches that we can use to answer these questions. We also discussed some additional assumptions that may be applied to reduce the complexity of some of the questions, so that we could have a reasonable starting point. For the next stage, we have a plan to start working on some of the questions we posed during the workshops, with Anne Shiu, Nidhi Kaihnsa and Tung Nguyen meeting in person, and with Badal Joshi possibly joining through online means.

Controllers for robust oscillations

Group members: Jinsu Kim, Badal Joshi, Ankit Gupta.

Suppose there is an arbitrary biomolecular reaction network (with possibly unknown parameters) with some predefined output species X. We consider the problem of inducing robust oscillations in the dynamics of X by interfacing the network with a controller module which is itself a biomolecular reaction network. The goal of this project is to find such a controller module and prove that for a large class of networks, it can successfully induce oscillations with frequency and/or amplitude depending only on the controller module parameters. Hence perturbations in the parameters of the controlled network are rejected, and the oscillatory properties of the output species are maintained.

We identified a candidate controller involving two species and numerically studied the behavior of the system near a Hopf bifurcation. We identified intrinsic system parameters and control parameters and showed that a Hopf bifurcation involves a combination of both. Next stage plan: Jinsu Kim, Badal Joshi and Ankit Gupta have already scheduled bi-weekly meetings to continue discussing the project. We first plan to conduct an extensive simulation study with our candidate controller to determine how oscillation amplitudes and frequency depend on its reaction rate constants. We shall then study how oscillatory properties change if this oscillator is interfaced with different types of biomolecular reaction networks. We are in the process of creating a Matlab code to implement a massive simulation framework and test how each parameter contributes to the system behavior to get insights about controlling oscillation.

Thermodynamics

Group members: Luisa Andreis, Andrea Agazzi, Daniele Cappelletti, Allison Fisher, Chiara Franceschini, Linard David Hoessly, Badal Joshi, Jinsu Kim, Jonathan Mattingly, Robert Patterson, Lea Popovic, Michiel Renger, Anne J. Shiu, Artur Stephan, Carsten Wiuf

The group discussed the connection between thermodynamics and complex balancing. In particular, a conjecture was discussed that relates bijectively the use of relative entropy as a quasipotential for the small noise dynamics and the complex balancing property of the underlying reaction network.