The 4th International Workshop on Stochasticity in Biochemical Reaction Networks

November 17, 2013

Introduction

The fundamental calculations of life occur within tiny cells and sub-cellular compartments in which the total number of molecules of any species is particularly small. In this regime, the number and timing of critical chemical reactions may vary substantially between cells due merely to the intrinsic stochastic fluctuations of the system. How are complex cellular computations, required for normal growth, signaling, and development, reliably executed amidst such variability? Is this variability exploited by evolution to enable unique collective cell behaviors? What experimental tools and mathematical approaches can we use to gain insight into the way stochastic noise arises, is propagated, is filtered, or is exploited? To address these questions, the 4th International Workshop on Stochasticity in Biochemical Reaction Networks was convened in Banff in September 2013.

Workshop Participation

Stochastic effects in biochemical reactions have attracted the interest of researchers from a broad range of fields. These include mathematicians and physicists interested in the properties of stochastic systems with certain constraints derived from experimental data, biologists wishing to understand the implications of these effects for cell behavior and animal development, computer scientists working on efficient algorithms to simulate rare stochastic events, and engineers interested in designing and building devices from biological components. These diverse research programs and academic backgrounds provide a wealth of skills and techniques, mathematical, computational and experimental, which can aid our understanding of biochemical stochasticity. However, substantial cultural and linguistic barriers separate these disciplines, and consequently few journals, conferences or workshops exist to facilitate the exchange of ideas between these groups despite their overlapping aims. This leads to both duplication of efforts and a lack of information flow about what tools and assumptions are the most accurate.

The workshop aimed to bring together an international group of researchers from across these broad disciplines. Participants had PhDs in mathematics, physics, chemical engineering, and molecular biology, and worked in an equally broad range of academic departments (and one in industry). Additionally, we sought to attract a number of participants who have worked closely at the boundaries of some of the involved disciplines for several years, and who have become adept at facilitating communication across these lines. All presentations were structured in a discussion-based format, allowing participants to stop the speaker to explain discipline-specific terminology, assumptions, or ideas. Every single presentation elicited both clarification questions and discussion of fundamental concepts, with several themes from these discussions being carried on through multiple presentations. Most participants were young researchers with highly interdisciplinary training, including 11 pre-tenure faculty, 7 post-docs and 2 graduate students in addition to 7 senior faculty. While most participants came from the US, 7 traveled from Europe, 1 came from the Middle East and 1 from Canada. All presenters have contributed substantially to the field of biochemical networks through either theoretical or experimental approaches, with the majority having contributed in both areas.

Scientific Progress

Results presented at the workshop indicated substantial scientific progress in several clear directions. One was a renewed focus not just on noise arising intrinsically from the random nature of chemical reactions and molecular binding events, but also on noise sources extrinsic to cells' reaction machinery. Experimental work coupled with simple stochastic models from several researchers highlighted conditions where variations in cell size (Arjun Raj [12, 13, 21]), changes during the cell cycle (Narendra Maheshri [29]), and other sources of extrinsic noise have a dominant effect on population diversity. The degree of the effect of extrinsic noise depends strongly on gene expression level and on the time scale on which extrinsically fluctuating parameters change (Michael Assaf [2, 5]). Improved experimental techniques for measuring these time scales through imaging live cells (Ido Golding [24, 25], Jie Xiao [6]) offered additional means to uncoupling intrinsic and extrinsic noise, and provided a deeper picture into the memory mechanisms which reflect gene state (Jie Xiao [6], Daniel Zenklusen [3, 10, 28]). One specific example of how measurements of extrinsic variation are changing perceptions in the field includes the surprising correlation between cell size and total expression levels of a gene reported by Arjun Raj at the workshop. This suggested the existence of a global mechanism for controlling the concentration (rather than transcription rate) even for non-autoregulatory genes. This finding opens new territory for theoretical models that can propose potential mechanisms by which such global control can be accomplished, and experimental work to test and compare such models.

Another theme arising repeatedly in the workshop was the emphasis on us-

ing experimental data to reject models and mechanisms rather than arguing that a particular model is both a complete and an accurate description of the system (Johan Paulsson, Jeff Moffitt, Narendra Maheshri). Both Johan Paulsson [11,22] and Jeff Moffitt [17–19] illustrated mathematical approaches to deal with complex systems in which only a subset of the interactions are known. In many cases the architecture of the known interactions still places fundamental constraints on the statistical properties of the whole system, and these statistical properties can be used to rule out alternative simple models. One specific example was being able to place a lower bound on the number of kinetic transitions in an enzymatic pathway, without being able to directly observe each transition (Jeff Moffit [17]). Intrinsic variation itself may be another tool to zero in on the fundamental architecture of a regulatory network. Steven Altschuler presented an approach where intrinsic variation in the properties of single cells allows chemical interactions to be inferred based on correlation analysis of covariates [9, 26]. The engineers at the workshop presented a complementary approach to handling incomplete knowledge of a system. For example, if the purpose of having a model is to manipulate a system's behavior in a particular way (Elisa Frano, Hyun Youk, Georg Seelig, Mustafa Khammash [16]), then feedback control systems may provide an effective way to do so, despite incomplete knowledge and the unavoidable presence of noise (Mustafa Khammash). Together, these approaches clearly demonstrated that not only does the structure of a network determine its noise properties (Christoff Zimmer, Michal Komorowski [8,14,27]), but that the stochastic properties can be used to narrow down its structure.

Increased exploration into multicellular systems (Stanislav Shvartsman [15], Pankaj Mehta, Elizabeth Read [23], Hyun Youk) and into the spatial structure of stochastic networks at the molecular scale (Jane Kondev [4,7], Steve Abel), the sub-cellular scale (Pieter Rien ten Wolde [20], Steve Abel [1]), and the cell and tissue scale (Bastian Drees, Stanislav Shvartsman) also received considerable attention. These efforts are introducing new tools to observe dynamic aspects of spatial patterning (Stansilav Shvartsman) as well a variety of improved and refined mathematical techniques for understanding the role of space at different levels of biochemical signaling (Jane Kondev, Steve Abel, Pankaj Mehta, Pieter Rien ten Wolde, Bastian Drees). A key theme was that spatial heterogeneity at the molecular level can change the function of reaction networks or increase a cell's computational power (Steve Abel, Pieter Rien ten Wolde).

Outcome of Meeting

The workshop had a variety of direct benefits to the participants, from exposing members to new ideas and approaches to forming new professional connections and collaborations. We believe that through the impact of these opportunities for the participants, the broader community as a whole will benefit by the future work of these individuals. Many of these new collaborations and projects would not have been likely without the unique interdiscplinary and collaborative

environment provided by this workshop.

The impact of the meeting on the future research agenda and careers of the participants is perhaps best seen in the anonymous feedback from the participants themselves.

- The intimate setting and interactive format connected and energized participants during and after the workshop:

  > "I thought that it was a very vibrant, young workshop full of postdocs and young faculty. This added a really good vibe and energy to some fascinating science."

  > "The small number of participants allowed for one-on-one meetings (got to know people)."

  > "The workshop facilitated interactions that would be difficult to have during a typical conference. I left the workshop feeling energized and particularly excited to work on problems I discussed with others during the workshop. I hope to maintain contact with several of the scientists I met during the meeting."

- It also facilitated connections across disciplinary boundaries, and among people who would not have otherwise interacted:

  > "Great mix of speakers, small group, very interactive."

  > "[I enjoyed] the mix between experimentalists and theorists and the discussions on how experiment affects theory and vice versa."

  > "I would not have had the chance to meet most of the participants in such an intimate setting had it not been for this workshop."

  > "A forum for discussing blindspots in the field."

- For some the workshop led directly to new collaborations:

  > "The workshop introduced me to new people and work in the field, and allowed me to reconnect with others. I am already using a paper by one of the participants in a trial problem with a potential graduate student who wants to work in my group."

  > "I think the informal atmosphere will inevitably end up in a future collaboration though the workshop was a little too short to settle on something concrete."

  > "Detailed sharing of methodology and results is usually initiated by a thorough Q&A when one presents work. This workshop allowed for that and provided time for discussion, in a way that other conferences do not. We will be trying a few different techniques (both experimental and computational) based on speaking to others at the conference."

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