BIRS Focused Research Group Report: Dynamics of biopolymers across multiple scales

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1 Overview

The main objective of our Focused Research Group (FRG) was for our pre-established team of collaborators to meet in person for intensive work on extending our current project and completing a manuscript currently in progress. This FRG was originally scheduled to occur in July, 2020, but was postponed to 2022 due to the pandemic. Broadly, we aimed to extend and refine our current working models and devise concrete measurements to holistically capture actin network formation, connecting from a stochastic model describing microscale phenomena at the molecular actin level, to a continuum model describing macroscale behavior at the cellular level. Our group was formed in June 2019 at the Collaborative Workshop for Women in Mathematical Biology, held through the Institute for Pure and Applied Mathematics at the University of California, Los Angeles (IPAM UCLA). This week-long workshop brought together female-identifying mathematicians of varying career levels and backgrounds with the goal of examining an unfamiliar topic from a multifaceted, new perspective. Following this workshop, our group continued to collaborate by meeting remotely each week and we have been highly productive, resulting in one published paper, one paper in preparation for submission, and ideas for at least two more papers. At the time of our initial application in January, 2020, our group consisted of six members in five distinct geographic regions (California, Florida, Ohio, Oklahoma, and New York) at various stages of our academic careers: one graduate student, two postdoctoral researchers, one tenure-track assistant professor, and two associate professors with tenure. At the 2022 FRG meeting, there had been changes in both geography and career stage: we hail from five distinct regions (Ohio, Oklahoma, New York, Boston, and Ottawa) and at various career stages (one postdoctoral researcher, three tenure-track assistant professors, and two full professors). While we have successfully continued our remote collaboration, the 2019 UCLA IPAM workshop revealed how well we function as a collective group and how rapidly we can progress in our research project when gathered in person. The FRG program offered by BIRS

was an exceptional opportunity for us to work intensively, in person, on the proposed project. Our time at BIRS was used to catalyze our current research into one complete paper draft, to make substantial progress on the objectives listed below, and to develop a concrete plan for our continuing research.

2 Objectives and Scientific Progress Made

Objective 1: Develop a spatially- and resource-constrained environment. Our current model, as outlined in our earlier book chapter (Copos et al. 2021 [1]), adopts a simplified approach to actin dynamics in that it assumes an unlimited amount of space and resources for the formation of the actin network. While this setup enabled us to create our initial modeling platform, it could be made more biologically relevant by including the presence of barriers such as the cell membrane. Additionally, the availability of actin monomers necessary for network growth is constrained in both amount and location within a cellular environment, both of which could potentially influence microscopic network dynamics and macroscopic end states. We have recently introduced a spatially constrained environment in which resource availability and dynamics primarily occur at the leading edge of the growing actin network. Our initial results suggest these constraints can produce complex spatial patterns.

Progress toward Objective 1: Some of our time at BIRS was spent collectively analyzing these complex spatial patterns, yielding insights into regulatory mechanisms inside cells.

Objective 2: Expand sensitivity analysis focus and techniques. Copos et al. 2021 [1] connected our stochastic model to our continuum model using a relation between the mean displacement of the actin network and the diffusion coefficient in the continuum model. We then explored the influence of key parameters on this relationship, highlighting different measures by which we should evaluate the network growth and change, such as the spatial spread, density, and fractal dimension of the network, in addition to the distances between actin tips and branches. These measurements will become of particular interest when the environment and resources of the network are constrained. Using more advanced sensitivity techniques, such as the extended Fourier Amplitude Sensitivity Test (eFAST) and Latin Hypercube Sampling (LHS), we will create a more complete picture of the actin network dynamics across both scales. Synthesizing the results of this analysis will be far more efficient and comprehensive when done in person.

Progress toward Objective 2: In the years following our initial FRG submission, our goals temporarily shifted away from sensitivity analysis and toward Machine Learning (see comment below Objective 4). However, we still spent some time at BIRS evaluating the effect of certain parameters (in particular, the capping probability) on resulting actin network architectures as well as the efficacy of a variety of classification techniques. Some techniques, such as shape PCA, provided inconclusive information, while others, such as symmetry quantification using Transformation Information, allowed us to identify groupings of actin network structures with common features. We found that different Machine Learning (ML) techniques have widely varying success in identifying underlying mechanisms that result in a particular network structure. This led us to not only recognize new properties and limitations of ML techniques but also the range of actin network characteristics that can be generated by a straightforward stochastic simulation framework.

Objective 3: Explore alternative continuum models that more closely match the stochastic model. Both Fisher's equation and Skellam's equation are continuum models frequently used to describe actin dynamics. However, in our previous work, we observed that their fit to the stochastic model was not fully satisfactory. Now, we aim to identify a continuum model that more suitably matches our stochastic model. We have preliminary results showing that a reaction-diffusion equation with a Poisson-type reaction term results in a better match to the stochastic model output.

Progress toward Objective 3: We spent a bit of time at BIRS working collectively (capitalizing on the distinct expertise of all group members) to derive more appropriate partial differential equations from first principles. We now have several avenues we plan to continue to pursue, including: reaction-diffusion PDEs with saturated growth terms, PDEs based on biased or constrained random walks (rather than

unbiased), PDEs that can account for the branching of actin networks, and data-driven PDEs whose terms and coefficients are discovered by ML techniques based on experimental or synthetic data.

Objective 4: Improve the computational efficiency of the stochastic simulations. In our previous work, we found that simulating the stochastic model becomes quite challenging in terms of both run time and memory as the filamentous actin network becomes increasingly dense. This occurred at long simulation times and high probabilities of branching and polymerization, and prohibited us from exploring certain parameter regimes crucial in connecting our model to higher-order phenomena observed on a full cell level. We plan to improve various aspects of our stochastic model implementation, including parallelization.

Progress toward Objective 4: Prior to arrival at BIRS, we had synchronized our efforts and ensured uniformity of microscale stochastic code across all group members; we also wrote and tested a parallel version of the code which allows us to leverage high-performance computers to efficiently generate large amounts of data for the ML algorithms (see the next objective). At BIRS, we were able to confidently run new simulations as necessary, share results, and collectively talk through the implications of those results.

New Objective: In the few years following the submission of our proposal to BIRS, our goals have expanded due to the group's growing interests and expertise in ML. While we have made good progress towards Objectives 1, 3, and 4 in the proposal, what we decided to focus on in our next paper and during our stay at Banff is using ML techniques to uncover the dominant mechanisms underlying an actin network.

Progress towards the New Objective: Before arriving at Banff, we had developed the necessary software and written a draft of the paper. By meeting as a group in Banff, we were able to work intensively on the paper and finish the bulk of the project.

3   Outcome of the Meeting

Indeed, our FRG was highly productive from a scientific perspective. As a group, we examined, debated, and validated the ML techniques used to obtain the preliminary results. Since we are all beginners of ML, having these discussions in person was necessary and educational. They were also invigorating as we have diverse research expertise, and each of us offered unique perspectives and asked refreshing, thought-provoking questions. We realized that while our pre-Banff work used supervised ML algorithms only, unsupervised ML algorithms can be used in conjunction with supervised ML algorithms to produce better results. This is a brilliant realization and strengthens our paper.

Our FRG was also highly productive with respect to our manuscript writing. Before coming to Banff, despite having obtained promising results on multiple fronts, we were unsure about the theme, structure, and presentation of the next paper. It felt like we had many interesting pieces but did not know how they fit together to tell a coherent story. Utilizing the scenic meeting rooms at Banff and with the support of the extremely helpful staff of BIRS, we had many brainstorming sessions and breakout sessions to finalize the content and structure of our next paper. (It turns out the old-fashioned outlining on the blackboard, printing out our draft, and taping the relevant pages next to the outline are still highly effective.) This allowed us to form "working groups" that tackled different parts of the paper. Upon leaving Banff, we had a considerably improved draft that we anticipate will be submitted in the near future.

References

[1] C. Copos, B. Bannish, K. Gasior, R. Pinals, M. Rostami, A. Dawes, Connecting actin polymer dynamics across multiple scales, in: *R. Segal, B. Shtylla, S. Sindi (Eds.), Using Mathematics to Understand Biological Complexity*, Vol. 22, Springer, Cham, 2021, pp. 7–33. doi:10.1007/978-3-030-57129-0_2.