Luis Nieves-Rosado - Graduate Research Plan
Understanding the Role of the Cytoskeleton on Intracellular Particle Dynamics

Introduction – Intellectual Merit:

The dynamics of the cytoplasm, which includes the cell chromosome and other intracellular particles is relevant to many biological processes, including cell replication and genomic control. However, these systems exist out of equilibrium and show complex dynamic behavior, not easily explained by classic dynamic theory.

Recently, new fluorescent labeling techniques have allowed intracellular particles to be tracked as they move though the cell[1,2]. These experiments, done on *E. coli,* have shown that that these particles show sub-diffusive behavior. It seems that the cell environment confines the movement of these particles, and blocks them from fully exploring their surroundings.

Various theories have been proposed to explain this behavior.[3,4.] These depend mostly on studying polymer models for the chromosomes and treating the cytoplasm as a viscoelastic medium with a simple memory kernel. This continuum approach has shown some success in reproducing the sub-diffusive behavior of particles.

However, there is no need to introduce an artificial memory kernel, the cytoplasm can be modeled explicitly using colloidal models. Then, the particles are treated as colloids moving in a Newtonian medium (water). Then the constraints that induce the caging on these particles and lead to sub-diffusive behavior can be inserted explicitly.

There are two factors that could lead to this diffusive behavior. The first is the fact that the particles are confined in the cell. This confinement could lead to a reduced ability to explore certain parts of the cell. Additionally, the cell cytoskeleton would induce an additional major hindrance to their movement.

The existence of the bacterial cytoskeleton has only recently been recognized[5]. However, by now it is well understood that prokaryotes have analogues to most components of the eukaryotic cytoskeleton. These help give the cell it's structure, and connect different parts of the cell with each other. However, they are also major sources of hindrance in the movement of the cell particles.

It is appropriate to use a colloidal model of the cytoplasm, since many large biomolecules easily fall in the colloidal size regime. The hindered diffusive behavior is analogous to that seen in classic colloidal glassing[6], and could be explored using the same fundamental theory.

Goal:

We wish to develop a simple colloidal model to study particle dynamics within a cell, including the role of confinement and the cytoskeleton. This model will demonstrate that this confinement, along with the additional interference of the cell cytoskeleton leads to the sub-diffusive behavior shown in experiments.

To achieve this, we will first use existing polymer models to properly study the behavior of the bacterial cytoskeleton. Then Brownian Dynamics studies of a simple cell model would be realized, and the confined movement of the particles in the model cell would be studied. Finally, the role of hydrodynamics would be explored, using newly developed theory and computational methods.

Objective 1: Match Cytoskeleton Dynamics to Polymer Models:

The first step is to develop a good model for the cytoskeleton, which is a complex network of polymer chains that connect different parts of the cell. A convenient way to model the behavior

of these polymers is to use the shearable stretchable Worm Like Chain (ssWLC) model developed by the Spakowitz Group to study general semi-flexible polymers[7].

This general model allows one to study a wide range of polymers at many timescales. Using their methodology[7] to match the known chemical structure of the components of the bacterial cytoplasm[5], we can obtain a simple polymer model applicable for Brownian Dynamics, which we will use in the following simulations.

Objective 2: Study Particle Diffusion in Cellular Environment:

The cell can be modeled as a sphere, and the cytoplasm can be modeled as a colloidal solution inside this sphere. The sphere would have polymers, whose dynamics follow the ssWLC model in a network analogous to the bacterial cytoskeleton[5]. Then the dynamics of the colloidal solution would be explored using Brownian Dynamics, a classic simulation methodology in colloidal physics.

Various factors can affect the overall dynamics of the solution. The first is the concentration, which would be kept neat to cellular concentrations. Additionally, the exact structure of the cytoskeleton is likely to be very relevant. Various randomized structures would be used to study this effect. Finally, a single particle would be used as a probe, and its movement though the cell would be studied to determine if it shows sub-diffusive behavior.

Objective 3: Explore the Role of Hydrodynamics:

An important factor in the dynamics of a colloidal system is hydrodynamics. These can be included in the Brownian Dynamics simulation through the use of the Accelerated Stokesian Dynamic methodology[8]. This methodology includes the full effects of hydrodynamics.

A challenge is exploring the role of the confinement in the hydrodynamics. Fortunately, the relevant mobility functions have recently been published[9]. These would be used along the classic particle-particle mobility, which are well known[8], and can be extended to the polymer model[10]. Since these computations are likely to require significant computational power, they would be parallelized using newly developed methods[11].

Broader Impacts:

Understanding the dynamics of the intracellular environment could lead to increased understanding of genome expression. This in turn could lead to new understanding of many genetic diseases and their mechanism of action.

Every effort would be undertaken to undergraduate students in this project. Several parts, including the managing of simulations, can be easily performed by a student new to the field, and could serve as a great learning opportunity. This would be done through REU and other programs for underrepresented students.

All papers published from this project will be made available to the wider public using Open-Access publication models.

References:

1. Weber, S. C. et al. 2010. Physical Review Letters 104, 238102.
2. Kuwada, N. J. et al. 2013. Nucleic Acids Research 41 (15).
3. Lampo, T. J. et al 2015. Biophysical Journal. 108.
4. Tampo, T. J. et al 2016. Biophysical Journal 110.
5. Cabeen, M. T. et al. 2010. Annual Reviews of Genetics 44.
6. Parry, B. R. et al. 2014. Cell 156 (1-2)
7. Koslover, E. F. 2013. Soft Matter. 9, 7016
8. Banchio, A. J. et al. 2003. The Journal of Chemical Physics. 118 (10323)
9. Aponte-Rivera, C. et al. 2016. Physical Review Fluids 1 (2).
10. Nieves-Rosado, L. et al 2016. Unpublished Work
11. Bülow, F. et al. 2016. Computer Physics Communitcation. 204.