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BRIDGING MECHANICAL STIMULATION OF CELLULAR AND MOLECULAR STRUCTURE THROUGH LATTICE BASED COMPUTATIONAL SIMULATIONS

Kathleen Puskar[1], Leonard Apeltsin[2], Shlomo Ta'asan[3], Russell Schwartz[2], Philip R. LeDuc[1]
[1]Department of Mechanical Engineering, [2]Biological and Computer Science, and [3]Mathematical Science, Carnegie Mellon University, 5000 Forbes Avenue, Pittsburgh, Pennsylvania 15213

ABSTRACT

Understanding the connection between mechanics and cell structure requires a critical exploration of molecular structure. One of these molecular bridges is known to be the cytoskeleton, which is involved with intracellular organization and mechanotransduction. In order to examine the structure in cells, we have developed a computational simulation that is able to probe the self-assembly of actin filaments through a lattice based Monte Carlo method. We have modeled the polymerization of these filaments based upon the interactions of globular actin through a probabilistic scheme with both inert and active proteins. The results show similar response to classic ordinary differential equations at low molecular concentrations, but a bi-phasic divergence at realistic concentrations for living mammalian cells. Further, these inert monomers have a limiting effect based upon their relative density ratios, which alter the polymerization process. Finally, by introducing localized mobility parameters, we are able to set up molecular gradients that are found in non-homogeneous protein distributions *in vitro*. This method and results have potential applications in cell and molecular biology as well as self assembly in inorganic systems.

INTRODUCTION

Actin is the most abundant protein in many eucaryotic cells. It exists in both monomer and filamentous forms, where single actin proteins form linear polymers through the addition or subtraction of monomers. It plays a key structural role in functions such as motility, shape, and division [1-3]. To probe these biologically vital processes, understanding the spatiotemporal assembly of actin is requisite.

Classical modeling methods of molecular assembly assume that biochemical reactions emerge in a large, uniformly distributed, and uncrowded environment, where reactants can diffuse and combine without interference [4-6]. The models are parameterized with constants that characterize the kinetic binding and unbinding rates of the reactants. These rate constants are typically obtained experimentally *in vitro* at low actin concentrations of 1-2 mg/mL, closely matching those conditions assumed by the models. However, total molecular concentrations *in vivo* can be 50-400 mg/mL [7, 8]. These models may not sufficiently represent processes that occur in cells or sub-cellular compartments; Small or irregularly shaped compartments, densely packed molecules or minimal numbers of individual subunits, and sharp local concentration gradients, all create variations from the ideal situation assumed by classical models.

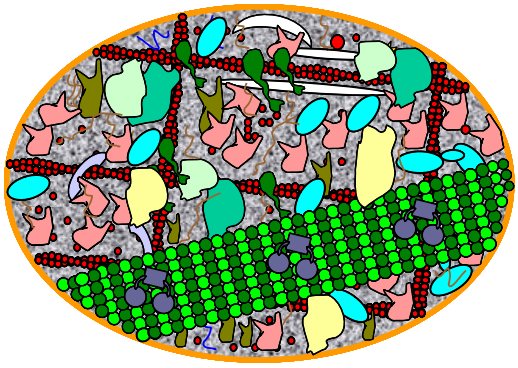

Figure 1: Drawing of a crowded molecular environment.

We have developed a Lattice Based Biological Monte Carlo model (LaBB) to examine these spatial effects on cellular biochemistry. Our intention is to compare this space-aware simulation method to a space-free model using classical ordinary differential equations (ODEs) in order to determine under what conditions spatial factors noticeably influence molecular behavior in cellular biochemistry. Here, we present a simplified model of the one-dimensional constrained assembly of actin filaments from globular actin. Inert particles and directed motility gradients are then introduced to investigate these influences on filament formation.

METHODS

All monomers are initially placed randomly on a rectangular lattice under periodic boundary conditions and

assigned one of four orientations. At every time step all unbounded monomers are given the opportunity to move and change orientation. There is a probability assigned for moving into each of the neighboring sites, remaining at the same lattice position and binding with adjacent monomers; occupied neighboring sites increase the probability for remaining in the same position.

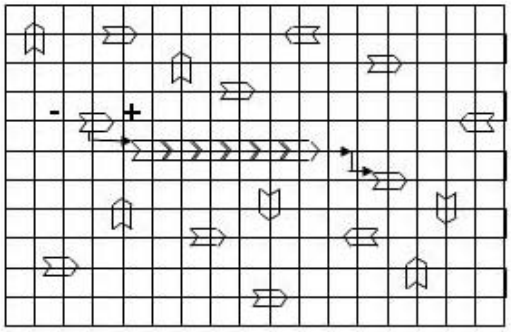

Figure 2: LaBB scheme for actin polymerization and depolymerization on a square lattice.

For the ODE model, we utilize a time-dependent reaction for polymerization and depolymerization of actin lacking spatial variance. To match rate constants between the spatial and nonspatial models, numerical approximations for k_+ and k_- are derived from the ODE model and the constants are calculated using data extracted from the LaBB model.

RESULTS AND DISCUSSION

Simulations performed with the LaBB and ODE models reveal analogous filament development and length distributions when the rates for the non-spatial models correlate to low-concentration regions in the spatial model. This is seen in Figure 3 for pure actin concentrations of 83 μM, or ~4 mg/mL.

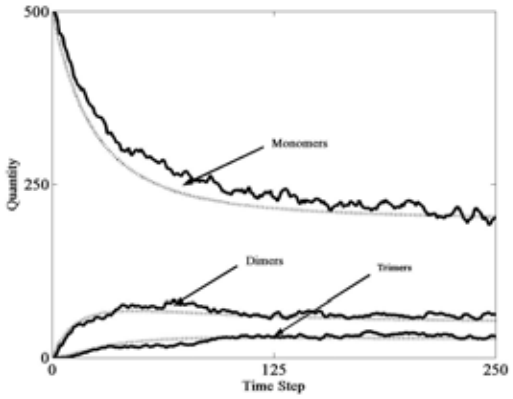

Figure 3: Actin dynamics for a concentration of 83 μM. LaBB model (solid lines) results for a 100 x 100 grid and 500 monomers. The ODE model (dotted lines) results for 500 monomers and kinetic rate constants of 65 ml·mg^{-1}·s^{-1} and 2s^{-1}.

Simulations were performed using pure actin and actin with inert particles, for a wide range of concentrations. Since concentration effects are not accounted for in the ODE model and inert particles are non -reactive, the binding rate is constant over the entire range of concentrations for the ODE model; the value is initially derived from the LaBB model for low monomer concentrations of 16.6 μM (<1mg/mL). At low levels the binding rates extracted from the LaBB model are virtually independent of concentration. But as the concentration is increased the models begin diverge for pure monomers above 166 μM, and for combined monomer-inert particles above 500 μM.

The LaBB and ODE models converge in low concentration domains typical of the *in vitro* conditions under which these binding parameters would be obtained. However, it deviates significantly from a constant value in the presence of high concentrations of either reactants or inert molecules that are not accounted for in a space-free ODE model. This may be relevant when modeling certain processes where actin filament formation plays a key role.

One such process occurs during cell motility when monomer concentrations with a significantly higher density are observed at the leading edge of the cell. We model this with LaBB by altering the probabilities for protein motion to be directionally favorable towards a lattice boundary. At pseudo steady-state filament distribution is then seen to be a gradient with high concentrations of the actin filaments in this region.

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