MARKOV MODELS FOR ACTIN POLYMER DYNAMICS AND CELL MEMBRANE PROTRUSION

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ABSTRACT

Actin is a helical polymerizing protein, which is vital to the eukaryotic cell. This protein forms the cytoskeleton of the cell and plays a key role in cell motility. Without the ability to move cells would not be able to perform critical cell processes such as wound healing, immune system response and embryonic development. This work focuses on the role of actin in membrane protrusion, which is the first in a series of steps leading to cell motility. We present three similar one-dimensional Markov models for actin polymerization, depolymerization and polymer capping. The membrane-polymer interaction is modeled as a Brownian Ratchet where the thermal fluctuations of the membrane create space for the actin filament to polymerize. Each Markov model presented tracks the positions of barbed and pointed ends of the polymer as well as the membrane position. The concentration and diffusion of both active ATP-bound and inactive ADP-bound monomers in the cytoplasm is also included in the models. The main goals of this work are as follows: (1) Determine the polymer length distribution and discern if the length remains approximately the same when the system has reached steady-state. This behavior is referred to as treadmilling. (2) Examine the polymer-membrane interaction and determine the protrusion velocity. (3) Understand the mechanism that delivers the monomer pool to the leading edge of polymer growth and determine if diffusion is a sufficient means for accomplishing this task.

The Two Variable Independent Model gives the simplest description of the system and is the most straightforward to implement numerically and gives rise to probabilistic distributions of barbed and pointed ends. However, knowing the distribution of the positions of ends does not give adequate information for determining the polymer length distribution. We present a model for calculating the polymer length distribution by maximizing the entropy or randomness in the system. This gives the least biased estimate for the distribution given the limited information known about the system.

The second model presented is the derivation of the Probability Master Equa-

tion. This model gives the most complete description of the polymer, monomer and membrane system. The thermal fluctuations of the membrane make tracking the monomer concentrations and diffusion difficult due to the variable boundary. The probability master equation determines what happens to the monomers that are directly adjacent to the membrane when the membrane makes a random jump inward toward the cell center. The result is the monomers are "pushed" inward such that only the concentrations of monomers in the immediate area by the membrane are affected. Numeric simulations of the probability master equation are not performed due to the high number of variables to track and the lengthy computation time that would be involved.

The results of the probability master equation are implemented in the final model presented, the Joint Probability with Conditional Concentration Model. Here we examine the joint probability of barbed end, pointed end and membrane positions as well as the concentration and diffusion of monomers conditional on the membrane position. With the joint probability distribution we directly compute the polymer length distribution and find no treadmilling behavior for varying initial monomer concentrations. Treadmilling is seen in the laboratory and is believed to drive the protrusion. The mean membrane position is tracked over time and used to calculate the protrusion velocity, which is useful is describing the motion of the cell membrane. We find the velocity is modeled with a strictly decreasing function that approaches zero asymptotically as $t \to \infty$. One possible explanation for the slowing velocity and lack of treadmilling is the diffusion is not a sufficient mechanism for supplying the leading edge with monomers.