

RESEARCH PROPOSAL

The Protein-Mediated Signaling Network for Cell Locomotion : a biophysical approach

Agung T. Sutomo
Faculty of Mathematics and Natural Science
University of Al-Azhar Indonesia
INDONESIA

1. Introduction

Cell locomotion plays a central role in many biological phenomena, as there are embryogenesis, inflammation, wound healing, and during the growth of axons [1]. Although the molecular components participating in the regulation of cell motility are known to a large extent, their cooperativity and their formation of a signaling network is poorly understood [2].

In general, it is assumed that the locomotion of biological cells is based on signal-mediated polymerization of their cytoskeletons. Recently, it has been shown [3,4] using computer simulations and theoretical considerations, that the persistency of the random motion and the chemotaxis of a cell is basically due to the autocatalytic polymerization kinetics of the cytoskeletal actin network. It has been demonstrated how substrate coupling and energy supply, under which the motion is performed, leads together with polymerization processes to a general concept of cell motility.

However, in all the considerations the biochemical network of cellular proteins (among others, Arp2/3, cofilin, gelsolin, profilin, capZ) which regulates the polymerization of the cytoskeleton has been not taken into account explicitly. This aspect can be very crucial since these proteins may change the rate constants of polymerization and may change the geometry of the cytoskeletal network which hence determine among others velocity and direction of cell locomotion [5-9].

2. Proposal

I want to study the influence of polymerization-regulating proteins on cell motility and cell locomotion. In particular, I want to address the question whether a dynamical network of interacting cellular proteins, including a feedback control cycle, similar as found for bacterial chemotaxis [10], can regulate efficiently the concentration of the polymerization-regulating proteins in space in time and hence control velocity and direction of cell locomotion.

The long range achievement of my study is to develop a self-consistent model for cell locomotion which can contribute from a biophysical point of view to our understanding of biological phenomena as are there are embryogenesis, inflammation, wound healing, and the growth of axons.

Scientific Methods :

Cellular models, ranging from the molecular to the coarse-grained description will be developed and studied using mathematical methods and computer simulations. Starting from previous studies [3,4], I will extend these investigations and include explicitly the concentrations, varying in space and time, of Arp2/3 and other regulatory proteins. Based on a certain set of regulatory proteins, a dynamical control cycle will be constructed, similar as in studies of bacterial chemotaxis [10-13].

Brownian dynamics and Monte Carlo simulations will be applied to the cellular model in order to investigate various properties as cell velocity, orientation of motion, cellular distributions of concentrations, etc.

Research Tools:

This research will use statistical mechanics as main method. Java and C++ programming will be used for data mining and simulation programs, respectively.

The simulations will be performed on workstations, for developing and testing the programs and analyzing the results, and on the supercomputer IBM Regatta at the Research Centre Juelich to conduct production runs of the programs.

2. Working Plan

First year:

1. Modeling a two-dimensional cell including the relevant proteins (G-actin, Arp2/3) and the cell membrane on a triangular lattice. Modeling of the polymerization processes for linear and branched actin networks. This follows similar lines as previously [3,4]. The new aspect is the triangular lattice which provides a more suitable model including fast performance on the computer and allowing (in later steps) the inclusions of explicit other proteins at certain concentrations.

2. This model will be simulated by Monte Carlo methods. In a first step we want to recover previous results in order to ensure the reliability of our model and simulation program. In a second step, we want to establish the appearance of a persistent random walk of a crawling cell in two dimensions when a chemotactic bias is absent. This study has not yet been performed, and it would be of great importance to investigate how the cellular velocity depends on polymerization kinetics and concentrations of proteins. Summary of this first year work in a publication.

Second year:

1. During this year, we plan to include an appropriate chemotactic protein network in our program. In a first step, we consider the same bacterial chemotactic protein network as reported previously [10-12], but here we will use our cell model on a triangular lattice. The new aspect of this study, as compared to the previous one, is the explicit space-time dependency of the concentrations of the various chemotactic proteins (Aspartate, Tar, CheY, CheB, CheR). We expect a significant effect on the response functions at various concentrations. One publication on this subject is planned.

2. Since this bacterial chemotactic network cannot be explicitly related to a simulation model of bacterial swimming, we replace this question by a subsequent study on the relation between chemotactic signaling network and cell migration. Here we consider again our polymerization-regulated cell model and assume, in addition, a chemotactic protein signaling network as proposed for cells [14,15]. The summary of the study is planned to be published.

Third year:

1. Writing the thesis.
2. Submitting the thesis in the second half of the third year.

5. Literature

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