# Letter of Transmittal

October 1, 2003

Faculty Search Committee
Department of Physics
Indiana University
Bloomington, IN 47405-7105

Dear Sir/Madam:

I wish to apply for the tenure track assistant professor position in the area of Mathematical Biology and Computational Biophysics as advertised on the web-site of the Department of Physics. Enclosed is a copy of my curriculum vitae, along with a list of references.

I have recently been working as a postdoctoral associate on continuum and discrete models of cell motility, under the guidance of Professor Hans G. Othmer at the University of Minnesota. I have a broad background in theoretical and computational science; my research interests are in the areas of mathematical biology, biophysics and computational solid state physics. I have also had considerable experience teaching undergraduates in both physics and mathematics.

I am currently working on extending the model of a fibroblast motility on two spacial dimensions. This model can be used to study cell motility issues related to embryonic development, immunity response to infection, wound healing, new blood vessel formation and cancer spreading. Further details are given in my curriculum vitae.

I am very committed to pursuing a career in academia, and look forward to hearing from you regarding my application. If you wish to discuss my educational and research background in further detail, please call me at (217) 352-2269.

Thank you for your time and consideration.

Sincerely,

Maria E. Gracheva M. Gracheva

gracheva@math.umn.edu
(217)352-2269

# Research Plan

Dr. Maria E. Gracheva

## 1 Cell motility model

Cell motility is extremely important for many aspects of life. It is involved in embryonic development, the immune system's response to infection, wound healing, new blood vessel formation and the spreading of cancer.

A fish cell (keratocyte) is an epidermal cell that shows motility. Intracellular calcium transients and waves have been identified in these cells that seem to regulate the cell ability to contract by using the actin-myosin cytoskeleton. Calcium is required for the production of actomyosin-based contractile forces, the regulation of the structure and dynamics of the actin cytoskeleton, and the formation and disassembly of cell adhesions. Calcium transients can also be induced in keratocytes by the stretching of elastic substrata with microneedles. Recent experiments show that calcium transients in locomoting keratocyte cells begin as stochastic sparks initiated via stretch activated calcium channels and then form calcium waves that propagate throughout the cell. There are several detachment mechanisms that depend on calcium. These include an increased actomyosin-based contractile force to pull up the rear cell edge; the disassembly of cell-substratum adhesions by calcium-dependent phosphatases; and proteases acting independently or in combination with increased cytoskeletal tension.

I plan to develop a stochastic model of calcium sparks and/or wave regulation of the motility of a keratocyte. The cell mechanics will be based on either a continuum or a discrete model. I will adopt one of the many models available to simulate calcium oscillations, in order to simulate the calcium activated calcium release through stretch activated calcium channels. Either a standard Monte-Carlo or the Gillespie Monte-Carlo approach will be used to take into account the stochastic effects of the calcium dynamics in keratocyte cells. All the model elements will be coupled together in an appropriate fashion.

A collaboration with an experimental group is essential for this project.

## 2 Cell signaling networks

An important aspect of cell biology involves cell signaling, which includes *intracellular* protein signaling cascades/networks, as well as *intercellular* cell communication via messengers such as calcium. I plan to concentrate on studying the regulation of the cell adhesion via integrin receptor signaling. Integrin receptors are located in a cell plasma membrane and connect a cell with the extracellular matrix. They serve both as points of mechanical connections and signaling conductors. The information about the extracellular environment is transmitted to a cell through these receptors. The

regulation of the internal cell function that defines a cell behavior via this interaction is the most interesting aspect of the problem. Some examples are the cell speed and the cell directional regulation via extracellular diffusable factors or substrate bound chemicals. The signalling map of proteins that connects the integrins with the cell elements is a subject of intense experimental study. The goal of this research will be to understand through modeling how cells coordinate the signals that are mediated by the intergin receptors to produce a specific response. I will use ODE/PDE and structural network analysis in this modeling project.

# 3 Actin dendritic model

Actin is a major protein component of the cell cytoskeleton. Monomeric actin polymerizes (assembles) into long actin filaments. These filaments are interconnected to form an actin filament network or actin filament bundles that give a cell its mechanical properties. Other cytoskeleton components include intermediate filaments and microtubules. Actin filaments have two polar ends. The actin filament mostly assembles at the plus (barbed) end, and mostly disassembles at the minus (pointed) end. The plus end also undergoes a dynamical instability that consists of periods of linear growth interrupted by occasional catastrophes (spontaneous disassembly).

The network of actin filaments is mostly polymerized at the cell front and depolymerized at the cell rear with the help of many accessory proteins such as profilin (promotes actin assembly at barbed ends), cofilin (actin-severing protein, adds actin depolymerization), ADF (actin depolymerizing factor) and capping proteins (cap barbed ends to control polymerization). In the network the daughter filaments are connected at $\sim 70^0$ to the mother branch. This connection is facilitated by the Arp2/3 protein complex that promotes branching. The dendritic model of actin network formation by branching will be useful in understanding how the cell actin cytoskeleton evolves, and what role accessory proteins play in controlling the overall cytoskeleton formation. We will use either molecular dynamics or Monte-Carlo techniques to study this problem. This project will be conducted in collaboration with The Moscow State University.