

A Hybrid Continuum-Discrete Model for Modeling Single Cell Signaling and Motility - Magdalena Stolarska

Cell movement is an essential process at various stages in the life cycle of most organisms: Early development of multicellular organisms involves individual and collective cell movement. Leukocytes must migrate toward sites of infection as part of the immune response. In cancer directed movement is involved in invasion and metastasis. Movement entails signal processing and force generation within cells and mechanical interactions with their surroundings. Understanding how these processes are controlled in space and time to produce cell-level movement is important in understanding the functions of living organisms, and one means of understanding these processes is through the use of mathematical models.

A basic difficulty in modeling cell motility is the coupling between large-deformation mechanical processes and chemical kinetics. Of the few current models that address the coupling of these processes in a multi-dimensional framework, most employ a continuum approach [46,57]. The goal of the study described here is to develop a novel approach to computational modeling of cell motility where the reaction kinetics is handled in a continuum framework, and the mechanics is handled discretely.

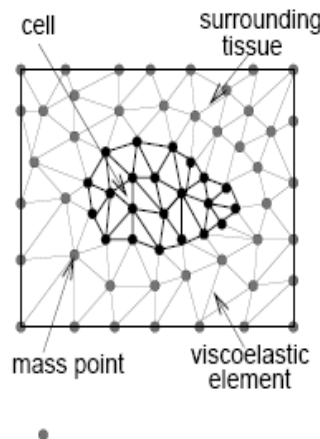


Figure 1: Finite element mesh and discrete mass point / viscoelastic element system for a cell moving through surrounding tissue.

The main idea of this hybrid continuum-discrete approach is that the reaction kinetics that control the directionality of cell movement are modeled by a system of reaction-diffusion equations and are solved in a continuum framework using the finite element method. Experimentally verified interactions of component chemical species serve as a basis of the reaction-diffusion model (for reviews see [14,8,42,34]). In addition, Jennifer Cruise, a faculty member in the biology department at the University of St. Thomas, has agreed to serve as a faculty advisor for this application (see attached letter of support).

As is illustrated in Figure 1, the underlying finite element mesh may be used to define a discrete series of mass points which are connected by viscoelastic elements (as most cells have been shown to exhibit viscoelastic material properties [21]). These mass points make up both the cell and the surrounding tissue. The motion of the discrete points is governed by a set of coupled ordinary equations (Newton's Law) of the form

$$m\ddot{x}_j = F_{\text{active}} + \sum_i^{N_{ve}} F_i,$$

where x_j is the position of mass point j , N_{ve} is the number of viscoelastic elements connected to mass point j , F_i is the force exerted on the mass point by a viscoelastic element, and F_{active} , which is only non-zero at point masses making up the cell, is an 'active force' that a cell generates internally in order to propel itself in a particular direction. It is through F_{active} that the reaction kinetics are coupled to the mechanics. The information needed to define F_{active} is provided by the solution of the reaction kinetics equations. Discrete modeling of the mechanical response of the cell is likely to provide an adequate framework. At the same time it also bypasses the need for using a complicated theory of nonlinear continuum mechanics. As a result, the research involving the hybrid model described here can be conducted by undergraduate students.

Discrete approaches to modeling motion of biological tissues in multiple dimensions have been used by Dallon and Othmer [15] and Bottino *et al.* [10]. In Dallon and Othmer, each individual cell is treated as a discrete, deformable ellipsoid the collection of which models the motion of the *Dictyostelium discoideum* slug, a multicellular organism. In Bottino *et al.*, a single cell is treated as a collection of mass points connected by elastic elements. However, in this case, reaction kinetics are not fully considered and only linear elasticity is used. Furthermore, Bottino *et al.* assume that the cell is crawling on a flat substrate while we consider a two-dimensional slice of a cell crawling through a three-dimensional material, as illustrated in Figure 1.

A group of students will work on this project in the following stages:

Study of reaction-diffusion processes and their application to biological systems.

Computer implementation of a simple system of reaction-diffusion equations using the finite element method. All calculations in this project can be done on a software package such as Mathematica.

Development of a discrete method to describe the mechanical response of the cell and its movement through the surrounding tissue.

Coupling of the continuum reaction-diffusion system with the discrete system.

Performing of studies using the resulting computational tool. One particular study of interest is the interaction of two or more cells with each other and the surround tissue.

The students that enter the proposed computational methods course and take on the proposed project should have a background that includes a knowledge of multivariable calculus, basic linear algebra and ordinary differential equations, and basic programming. While partial differential equations, namely diffusion-type equations, are involved in the project, I have found that students with a knowledge of multivariable calculus have been able to understand diffusion equations without difficulty.