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Superconvergent second order Cartesian method for solving free boundary problem for invadopodia formation

Olivier Gallinato, Clair Poignard *

Team MONC, INRIA Bordeaux-Sud-Ouest, Institut de Mathématiques de Bordeaux, CNRS UMR 5251 & Université de Bordeaux, 351 cours de la Libération, 33405 Talence Cedex, France

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ABSTRACT

In this paper, we present a superconvergent second order Cartesian method to solve a free boundary problem with two harmonic phases coupled through the moving interface. The model recently proposed by the authors and colleagues describes the formation of cell protrusions. The moving interface is described by a level set function and is advected at the velocity given by the gradient of the inner phase. The finite differences method proposed in this paper consists of a new stabilized ghost fluid method and second order discretizations for the Laplace operator with the boundary conditions (Dirichlet, Neumann or Robin conditions). Interestingly, the method to solve the harmonic subproblems is superconvergent on two levels, in the sense that the first and second order derivatives of the numerical solutions are obtained with the second order of accuracy, similarly to the solution itself. We exhibit numerical criteria on the data accuracy to get such properties and numerical simulations corroborate these criteria. In addition to these properties, we propose an appropriate extension of the velocity of the level-set to avoid any loss of consistency, and to obtain the second order of accuracy of the complete free boundary problem. Interestingly, we highlight the transmission of the superconvergent properties for the static subproblems and their preservation by the dynamical scheme. Our method is also well suited for quasistatic Hele–Shaw-like or Muskat-like problems.

1. Introduction

Early-stage carcinoma are mostly confined to the epithelium, which is separated from the underlying tissue by a basement membrane composed of dense fibers of extracellular matrix (ECM). In order to cross this tight barrier, metastatic cells use a complex internal machinery, named *invadopodia*, which lies on the actin polymerization and that leads to the formation of proteolytic, protrusive and very localized subcellular structures. *Invadopodia* are elongated shapes, which are formed during cell invasion and mesenchymal migration. This phenomenon is the crucial and initiating point in the metastasic process, which is the major cause of death from cancer. The authors and colleagues proposed recently a free boundary problem to model invadopodia and more generally for cell protrusion formation [16]. In this paper, we present a superconvergent second order method on Cartesian grid to solve this quite complex free boundary value problem. Our finite difference method is based on the derivation of appropriate superconvergent schemes: wide-stencils are proposed to reach specific superconvergence properties for the solutions of the Poisson problem. As a result, the global method leads to the

* Corresponding author.
E-mail addresses: olivier.gallinato@inria.fr (O. Gallinato), clair.poignard@inria.fr (C. Poignard).

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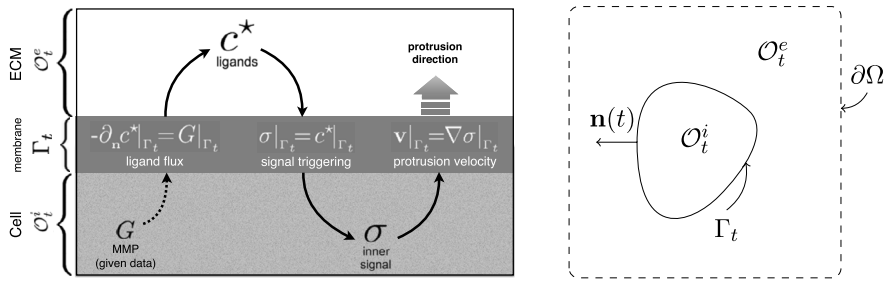

(a) Schematic diagram of the molecular interactions for invadopodia.

(b) Geometrical setting.

Fig. 1. Schematic diagram of the molecular interactions involved in our model and geometrical settings. The cell $\mathcal{O}_t^i$ is imbedded in the bath $\mathcal{O}_t^e$. The whole domain Ω does not depend on the time variable. It is defined by $\Omega = \mathcal{O}_t^e \cup \overline{\mathcal{O}_t^i}$.

second-order accuracy of the moving interface, its normal vector and even its curvature. The accuracy on the curvature will be of major interest in further study for the use of interface regularization techniques in order to model subsequent phenomena involved in cell migration, as myosin-dependent protrusion retraction, for instance.

The purpose of the study is to simulate accurately cell protrusion formation, however the domain of applications can be extended to free-boundary problems arising from physics or biology such as Hele–Shaw, Muskat or quasistatic two-phase Stefan like problems.

1.1. Free-boundary problem for invadopodium formation

The invadopodium process relies on a coupled dynamics between the outer and the inner of the cell. Let us present briefly the new model of the phenomenon detailed in [16]. Specific enzymes (MT1-MMPs) produced by the cell membrane degrade the extracellular matrix (ECM), producing ligands that diffuse and bind to membrane receptors. In response, cell generates a signal which diffuses inside the cell and, which leads to actin polymerization: rigid filaments are polymerized, oriented towards the location of the detected ligand. The force exerted by the filaments on the membrane generates a protrusion which grows at the velocity of the filament polymerization. The scheme of the process is given by Fig. 1(a), while the geometrical framework is detailed in Fig. 1(b). At any time t, the cell membrane is parameterized by the map $\gamma(t,.)$ defined on the torus $\mathbb{T} = \mathbb{R}/2\pi\mathbb{R}$:

$$\Gamma_t = \left\{\gamma(t,\theta), \quad \theta \in \mathbb{T}\right\}.$$

The cell cytoplasm $\mathcal{O}_t^i$ is the domain enclosed by Γ_t and the ECM is the outer domain

$$\mathcal{O}_t^e = \Omega \setminus \mathcal{O}_t^i.$$

Assume the flux of MT1-MMP enzymes $g(t,\cdot)$ be given at any time on the cell membrane. It generates a flux of the degraded matrix (called ligands and denoted by $c^\star$) on the cell boundary, and these ligands diffuse in the extracellular medium as described by equations (1a)–(1b). When bound to the cell membrane, the ligands generate a signal σ, which diffuses inside the cell, as accounted for in equations (1c)–(1d). The cell membrane motion is described by equation (1e).

Degradation of the ECM:

$$\Delta c^\star = 0, \quad x \in \mathcal{O}_t^e, \tag{1a}$$

$$c^\star|_{\partial\Omega} = 0, \quad -\partial_{\mathbf{n}} c^\star|_{\Gamma_t} = g|_{\Gamma_t}. \tag{1b}$$

Generation of the inner signal for actin polymerization:

$$\Delta\sigma = 0, \quad t \in [0,T], \quad x \in \mathcal{O}_t^i, \tag{1c}$$

$$\sigma|_{\Gamma_t} = c^\star|_{\Gamma_t}. \tag{1d}$$

Motion of the cell membrane:

$$\partial_t \gamma(t,\theta) = \nabla\sigma(\gamma(t,\theta)), \quad \theta \in \mathbb{T}, \quad \text{and} \quad \Gamma_t = \{\gamma(t,\theta), \theta \in \mathbb{T}\}. \tag{1e}$$

The interested reader will refer to [16] for further details about biological phenomena, and modeling hypotheses. The theoretical analysis of the free-boundary problem is also performed in this article. In particular, the well-posedness of the free-boundary problem in Sobolev spaces is precisely proven, provided strictly positive boundary data $g|_{\Gamma_t}$. The proof is based on the explicit characterization of Dirichlet-to-Neumann maps thanks to complex analysis tools. Then, appropriate