Computational and Modeling Strategies for Cell Motility

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1 Introduction

A predictive simulation of the dynamics of a living cell remains a fundamental modeling and computational challenge. The challenge does not even make sense unless one specifies the level of detail and the phenomena of interest, whether the focus is on near-equilibrium or strongly nonequilibrium behavior, and on localized, subcellular, or global cell behavior. Therefore, choices have to be made clear at the outset, ranging from distinguishing between prokaryotic and eukaryotic cells, specificity within each of these types, whether the cell is “normal,” whether one wants to model mitosis, blebs, migration, division, deformation due to confined flow as with red blood cells, and the level of microscopic detail for any of these processes.
The review article by Hoffman and Crocker [51] is both an excellent overview of cell mechanics and an inspiration for our approach. One might be interested, for example, in duplicating the intricate experimental details reported in [45]: “actin polymerization periodically builds a mechanical link, the lamellipodium, connecting myosin motors with the initiation of adhesion sites, suggesting that the major functions driving motility are coordinated by a biomechanical process,” or to duplicate experimental evidence of traveling waves in cells recovering from actin depolymerization [37, 44]. Modeling studies of lamellipodial structure, protrusion, and retraction behavior range from early mechanistic models [88] to more recent deterministic [102, 117] and stochastic [54] approaches with significant biochemical and structural detail. Recent microscopic–macroscopic models and algorithms for cell blebbing have been developed by Young and Mitran [121], which update cytoskeletal microstructure via statistical sampling techniques together with fluid variables. Alternatively, whole cell compartment models (without spatial details) of oscillations in spreading cells have been proposed [37, 96, 114] which show positive and negative feedback mechanisms between kinetics and mechanics, and which are sufficient to describe a modality of sustained cell oscillations. The generalization of such a nonlinear limit cycle mechanism to include 3D spatial substructures consistent with cell mechanics, and biochemical kinetics and diffusion, charts a path that our group has elected. Detailed microscopic features are resolved through effective or collective properties of each substructure, which are dynamically updated by chemical species and processes. This choice is guided by a series of developments in the biophysics community on cell structure and rheology (cf. New Journal of Physics, Vol. 9, 2007), together with recent progress on the biochemical feedback mechanisms associated with cell morphological oscillations [37, 61] as well as other dynamic cell modes.

Our approach is likewise guided by multiphase (implying differentiated substructures) modeling and computational tools developed for analogous applications such as biofilms [71, 113, 124, 126] and complex fluid mixtures (polymer dispersed nematic rods [39, 69], liquid crystal drops in viscous fluids [38, 120]). We integrate these approaches to propose a multiphase cell model with an energy-based phase field formulation, which we then simulate to illustrate qualitative phenomena that are possible with such a model. We conclude the chapter with a summary of experimental information and model advances that will be necessary to make the model biologically relevant and applicable to experiments. Our goal is a modeling and numerical framework which captures sufficient biological structure acceptable to cell biologists, which relies upon experimental data to parametrize the model equations for the structure, and which can reproduce single cell dynamic morphology behavior including blebbing, migration, contractile waves, oscillations, membrane-cortex rupture, and division. An early two-phase model of cell motion is developed by Alt and Dembo [2].

We model the cell as a composite of multiple phases or substructures, where each phase has its own material properties and constitutive relations that must be experimentally determined (cf. [82]). In the phase field formalism, the boundary between adjacent phases is diffuse rather than sharp; a phase field variable is
introduced to model the thin transition layer, and an energy functional prescribes
the momentum and energy exchange in the diffuse interface domain rather than
traditional sharp interface elements such as surface tension and normal stress jumps.
The cell phases include a bilayer membrane, a nucleus, and the cytoplasm which
contains various protein filaments, other organelles, and aqueous cytosol [14].
Permeating the cytosol is a network of protein filaments of varying size and rigidity
called the cytoskeleton [43, 81, 99]. The cytoskeleton not only provides the cell with
mechanical integrity, but also provides a pathway for chemical and mechanical
transport. Eukaryotic cells contain three main types of cytoskeletal filaments:
actin filaments (microfilaments), intermediate filaments, and microtubules [43, 81].
Cytoskeletal elements interact extensively with cellular membranes and extracellular
materials through functional and regulatory molecules or molecule complexes
to affect cell motion [6, 64, 92, 93]. A distinguished phase, the cortical layer, lies
between the bilayer membrane and the interior cytosol, and plays a prominent role
in our model. Activation and deactivation in the cortical layer, triggered by specific
protein families, are fundamental to our model. The phase field formulation allows
for dramatic changes in each substructure, such as rupture of the bilayer membrane
or cortical layer, separation of the membrane from the cortical layer by influx of
cytosol, or even cell division. A long-term goal is to have sufficient biophysical and
biochemical resolution to describe any cell morphological dynamic process.

A motile cell can crawl or migrate, especially on a supportable substrate, by
protruding its front and retracting its rear [26, 52, 53, 63, 90, 94, 106, 107]. Cell
motility is a result of orchestrated dynamical reconstruction and destruction of
cytoskeletal structure coupled with cell membrane deformation. This reconstruction
process is triggered by cell–substrate interactions through extracellular signalling
and intracellular responses. The process of cell protrusion, the prelude of cell
motion, is based on the polymerization of G-actin into F-actin filaments and
force redistribution along other filament bundles like microtubules [92]. Actin
polymerization is a directional or more precisely a polar phenomenon. During this
process, the ATP (Adenosine-5’-triphosphate) bound G-actin is added to the barbed
end of the existing F-actin filament, then ATP hydrolyzes into ADP; subsequently,
the ADP bound actin drops off at the pointed end to depolymerize [14]. The
local actin polymerization/depolymerization dynamics are regulated by the local
concentration of functioning proteins, in particular, ATP-bound G-actin, ADP-
bound G-actin, various accessory proteins, and binding subunits such as WASP
proteins, Arp2/3 complexes, ADF/cofilin, profilin, thymosin β4, α–actinin, etc.
[93]. The accessory proteins and binding subunits can inhibit or promote the
polymerization/depolymerization process and thereby regulate the cell motility. In
our model, we cannot retain full biochemical resolution and dynamics initially
comparable to biochemical network models (cf. [1] and references therein), so
simplifying choices will be made focusing on the key activation and deactivation
species that are implicated in experiments.

In the case of cell migration on a substrate, the dynamic assembly and disassembly of focal adhesions plays a central role [13, 30, 94]. Focal adhesions are
specific types of large macromolecular assemblies through which both mechanical
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and regulatory signals are transmitted. They serve as the mechanical linkages to the extracellular matrix (ECM) and as a biochemical signaling hub to concentrate and direct various signaling proteins at sites of integrin binding and clustering. On the other hand, surface or substrate topography has long been recognized to strongly influence cell adhesion, shape, and motion. Patterning and aligning scaffolds at the micro- and nano-scale with topographical features (indentations or grooves) as well as ligand organization have been reported to influence cell responses, such as adhesion, shape deformation (oriented cell elongation), migration, and growth [24]. The phenomenon of surface topography influencing cell migration is known as “contact cue guidance” [57, 76].

The underpinning issue in the contact cue guidance of motile cells is cell motility via cell–substrate interaction. Theoretical and computational modeling of cell motility continues to evolve in a variety of directions and for diverse purposes. However, given the complexity in cell motility, a whole cell model is still in an immature stage. Significant advances are more focused, such as on local cytoskeletal and actin dynamics [11,47,83,87], chemotaxis [86], membrane shape conformation [31], and simple cell models with idealized microstructural details of the cytoplasm [2, 27, 28, 65, 103, 104, 118]. In studying how actin filaments interact with the membrane locally, there have been a host of interesting local cytoskeletal dynamical models developed [3,6,15,47,83].

In addition to the local dynamical models for cytoskeletal and membrane dynamics, models have been developed to study cell migration on substrates. One model was devised to study effects of adhesion and mechanics on cell migration incorporating cytoskeletal force generation, cell polarization, and dynamic adhesion for persistent cell movement [28]. In this model, a coarse-grained viscoelastic model was used to describe mechanics of the cell body. Stephanou et al. [103] proposed a whole cell model for the dynamics of large membrane deformations of isolated fibroblasts, in which the cell protrusion was treated as the consequence of the coupling between F-actin polymerization and contractibility of the cortical actomyosin network. A model for the contractility of the cytoskeleton including the effect of stress fiber formation and disassociation in cell motion was developed by Deshpande et al. to investigate the role of stress fibers in the reorganization of the cytoskeleton [27]. Models treating the cytoplasm as active gels were proposed to study cell movement and drug delivery by Wolgemuth et al. [118]. Two-phase fluid models have also been used to study cell motion, in which the motion of the membrane and the local forces due to actin polymerization and membrane proteins are coupled through conservation laws and boundary conditions [2]. The coupling of biochemistry and mechanics in cell adhesion was recently studied by a new model for inhomogeneous stress fiber contraction [11]. A computational cell model for migration coupling the growth of focal adhesions with oscillatory cell protrusion is developed to show more numerical detail in the migration process [104]. A new continuum modeling approach to study viscoelastic cytoskeletal networks is proposed to model the cytoplasm as a bulk viscoelastic material [65]. Each of these models, and others below, represents a step toward a multipurpose whole cell dynamics model.
Active polar gel models have emerged as a new and exciting topic in soft matter and complex fluids [4,9,68,74]. In an active material system, energy is continuously supplied by internal as well as external sources to drive the movement of the material system. In a living cell, cross-linking proteins bind two or more self-assembled filaments (e.g., F-actin or F-actin and microtubules) to form a dynamical gel, in which motor proteins bind to filaments and hydrolyze nucleotide ATP. This process coupled to a corresponding conformational change of the binding protein turns stored energy into mechanical work, thereby leading to relative motion between bound filaments [75]. Self-propelled gliding motion of certain bacterial species is another example of such an active material system, where molecular motors drive the cellular motion in a matrix of another material [9]. Both continuum mechanical models and kinetic theories have been proposed for active complex fluid systems [4, 9, 23, 66, 68, 74, 95]. The mathematical framework incorporates the source of “active forcing” into an otherwise passive material system. The models are based on free energy considerations, both equilibrium and nonequilibrium, where one can keep track of dissipative and conservative principles, and the challenge for biological fidelity is to construct relevant energy potentials and chemical–mechanical activation functions. These potentials require detailed viscous and elastic properties of the fundamental cell components or phases, for which experimental techniques are now advanced enough to make progress. The energy formulation is likewise compatible with mathematical modeling, numerical algorithms, and simulation tools that have been developed for the hydrodynamics of multiphase complex fluids in evolving spatial domains. The simultaneous modeling of reaction and diffusion of biochemical species is self-consistent with the energetic formulation. These advances lay the groundwork for our approach.

Given the collective advances in membrane and cytoskeletal modeling, cell–substrate coupling, and biochemical kinetics, it is now feasible to develop a whole cell model for migration on substrates. This global cell–substrate model will enable us to investigate cell motility, dynamics of signaling proteins, cytoskeleton–substrate coupling, and contact cue guidance of motile cells. The model predictions will provide qualitative comparisons with cell experiments in the first proof-of-principle stage, and potentially guide future experiments on detailed mechanisms associated with motility. As properties of each substructure become more quantified, the model will be able to make predictions to guide cell motility experiments. Given the complex nature of cell migration on topographically designed substrates, we must adopt a theoretical and computational platform that is applicable to a variety of dynamical modalities. Among the competing mathematical models for multiphase soft matter phenomena, the field phase approach is sufficiently versatile to handle the complexity of this challenge, and to sequentially incorporate additional biological complexity. We take up this topic next.

Phase field models have been used successfully to study a variety of interfacial phenomena like equilibrium shapes of vesicle membranes [31–36,110,125], dynamics of two-phase vesicles [41,42], blends of polymeric liquids [40, 108, 111, 112], multiphase flows [18, 38, 55, 56, 72, 73, 77, 115, 116, 119, 120, 122–124], dendritic
growth in solidification, microstructure evolution [50, 62, 80], grain growth [19], 193
crack propagation [20], morphological pattern formation in thin films and on 194
surfaces [70, 97], self-assembly dynamics of two-phase monolayer on an elastic 195
substrate [78], a wide variety of diffusive and diffusionless solid-state phase 196
transitions [20, 21, 109], dislocation modeling in microstructure, electromigration, 197
and multiscale modeling [105]. Phase field methods can also describe multiphase 198
materials [41, 42, 115]. Recently, phase field models are applied to study liquid 199
crystal drop deformation in another fluid and liquid films by our group and other 200
groups [38, 55, 72, 77, 115, 116, 119, 120, 122–124]. We will now apply the 201
phase field modeling formalism, treating the substructures of the cell as well as 202
its surrounding environment as distinct complex fluids, including an ambient fluid 203
or solid substrate or another cell(s). Distinct phases are differentiated by phase 204
variables. As a result, the entire material system can be modeled effectively as a 205
multiphase complex fluid in contact with a substrate [31]; the cell membrane is 206
modeled naturally as a phase boundary between the cortical layer and the ambient 207
fluid or substrate. Additional phase variables can be introduced to account for the 208
various complex fluid components (cortical layer, cytosol, nucleus) confined inside 209
the cell membrane; these phase variables can serve as volume fractions for each 210
of the cytoplasm components. The phase field formulation allows the dynamical 211
model developed for each phase of the mixture to be integrated to form the global 212
cell model.

We review an incremental set of models for active fluids of self-propelled 214
microconstituents and active gels, respectively. We will then propose a whole cell 215
model as a framework for proof-of-principle simulations and future development.

2 Models for Active Filaments

In a seminal paper by Simha and Ramaswamy [100], an active stress mechanism for 218
diverse model systems including bacteria, molecular motors, F-actin treadmilling 219
polymerization, and depolymerization mechanisms is formulated. Two fundamental 220
mechanisms are distinguished that lead to macroscopic motion, both of which are 221
tied to the existence of a pair of permanent force dipoles of the moving object. One 222
corresponds to contractile motion, called a puller mechanism by analogy with a 223
breast stroke of a swimmer, and the other is due to a tensile motion on the object, 224
called a pusher by analogy with the kick of a swimmer [46, 95, 100]. The fluid flow 225
field around the moving object in these two different situations exhibits distinct flow 226
patterns, both of which propel at the particle scale. The stress associated with this 227
motion is called the active stress. Since this is the essential part of the theories for 228
active filament material systems, we will give a brief overview of the derivation.

An ensemble of moving objects, including rod macromolecules, bacteria, F-actin 230
filaments, etc., are considered. An object has its center of mass located at \( \mathbf{r}_i \) and two 231
permanent force dipoles localized at \( \mathbf{r}_i + h\mathbf{n}_i \) and \( \mathbf{r}_i - b'\mathbf{n}_i \), respectively, where
n_i is a unit vector associated with the displacement direction of the i\textsuperscript{th} object. If b = b', the object is called apolar; otherwise, polar. The collective force exerted by the ensemble at location r is given by

\[ f^{(a)} = f \sum_i n_i \left[ \delta \left( r - r_i(t) - b n_i(t) \right) - \delta \left( r - r_i(t) + b' n_i(t) \right) \right], \]  

where \( f \) is the magnitude of the force dipole. We expand the \( \delta \)-function formally, and the force can be rewritten as:

\[ f^{(a)} = (b + b') f \nabla \cdot \left( \sum_i n_i n_i \delta(r - r_i) \right) - \frac{(b + b')(b - b')}{2} f \nabla \nabla : \left( \sum_i n_i n_i \delta(r - r_i) \right) + \cdots. \]  

From this force formula, the active stress tensor is deduced,

\[ \tau^{(a)} = (b + b') f \sum_i n_i n_i \delta(r - r_i) - \frac{(b + b')(b - b')}{2} f \nabla \cdot \left( \sum_i n_i n_i \delta(r - r_i) \right) + \cdots. \]  

At leading order, the active stress tensor is given by

\[ \tau^{(a)} = \alpha \sum_i n_i n_i \delta(r - r_i), \]  

where \( \alpha = (b + b') f \). Positive values correspond to pullers and negative values correspond to pushers.

In the case of ATP-driven polymerization and depolymerization, the active stress is given in the same form, where \( \alpha \) is proportional to the energy difference of the chemical potentials of ATP and the product molecules ADP and Pi. This latter expression defines the active stress at leading order in all active filament models discussed below.

### 2.1 Active Polar Filament Model

We consider a suspension of active polar filaments in a viscous solvent. The active polar filament model of Muhuri et al. [85] uses the concentration of the active polar suspensions c and the polarity vector of the filament particle p, in which a background fluid velocity v is introduced. The governing system of equations in
this model is summarized below. In this model, the polarity vector is assumed to represent the velocity of the active particle; the background velocity is assumed solenoidal, and inertia is neglected. Without external forces, the governing system of equations consists of:

\[
\begin{align*}
\nabla \cdot \mathbf{v} &= 0, \\
\nabla \cdot \mathbf{\sigma} &= 0, \quad \mathbf{\sigma} = \mathbf{\sigma}^a + \mathbf{\sigma}^r + \mathbf{\sigma}^d, \\
\mathbf{\sigma}^d &= \eta \left( \nabla \mathbf{v} + \nabla (\mathbf{v}^T) \right), \\
\mathbf{\sigma}^r &= -\frac{\lambda}{2} (\mathbf{p}h + h\mathbf{p}) + \Pi \mathbf{I}, \\
\mathbf{\sigma}^a &= Wc(x,t) \left( \mathbf{p}\mathbf{p} - \parallel \mathbf{p} \parallel^2 \frac{I}{3} \right), \\
\frac{\partial \mathbf{p}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{p} - \frac{1}{2} (\nabla \times \mathbf{v}) \times \mathbf{p} + \left[ \lambda_1 (\mathbf{p} \cdot \nabla) \mathbf{p} + \lambda_2 (\nabla \cdot \mathbf{p}) \mathbf{p} + \lambda_3 \nabla \parallel \mathbf{p} \parallel^2 \right] &= \frac{\lambda}{2} \left( \nabla \mathbf{v} + \nabla (\mathbf{v}^T) \right) \cdot \mathbf{p} - \zeta \nabla c + \Gamma \mathbf{h}, \\
\frac{\partial c}{\partial t} + \nabla \cdot (c(\mathbf{v} + \mathbf{p})) &= 0.
\end{align*}
\]

where \(\lambda_{1,2,3}, \lambda, \Pi, W, \zeta, \Gamma\) are model parameters. The sign of \(W\) determines the nature of the elementary force dipoles. Here, \(h\) is the molecular field for the polar vector \(\mathbf{p}\) and is given by

\[
h = c \left[ \alpha \mathbf{p} - \beta \parallel \mathbf{p} \parallel^2 \mathbf{p} + K \nabla^2 \mathbf{p} \right],
\]

where \(\alpha\) and \(\beta\) are model parameters, and \(K\) is the analog of the Frank elastic constant of the Ericksen–Leslie theory for liquid crystals in the one-constant approximation [25]. The stress tensors \(\sigma^d, \sigma^r, \sigma^a\) are the dissipative, reversible (or reactive) and active stress, respectively. The reversible stress is due to the response to the polar order gradient. The terms containing \(\lambda_{1,2,3}\) and \(\zeta\) are the symmetry-allowed polar contribution to the nematodynamics of \(\mathbf{p}\). The corresponding free energy for the system is identified as

\[
F = \int \frac{c}{2} \left[ -\alpha \parallel \mathbf{p} \parallel^2 + \beta \parallel \mathbf{p} \parallel^4 + K \parallel \nabla \mathbf{p} \parallel^2 \right] \, dx.
\]

The molecular field is defined by \(h = -\frac{\delta F}{\delta \mathbf{p}}\). The moving polar particle velocity and the background fluid flow velocity are fully coupled. With this model, Muhuri et al. studied shear-induced isotropic to nematic phase transition of active filament suspensions as a model of reorientation of endothelial cells. This model neglects the impact of energy changes to migration of polar filaments.
An analogous theory using the same set of hydrodynamical variables was developed by Giomi et al. [46] which involves more sophisticated coupling between the concentration, background fluid flow, and the polarity vector of the polar particles. It extends the previous theory to account for the energetic influence to filament migration. The governing system of equations is summarized below. In this model, inertial effects are retained and attention was paid to the variational structure of the governing system of equations. For instance, the missing asymmetric contribution to reactive stress in the previous model is supplemented.

\[
\begin{align*}
\rho \left( \frac{\partial}{\partial t} + \mathbf{v} \cdot \nabla \right) \mathbf{v} &= \nabla \cdot \sigma , \\
\nabla \cdot \mathbf{v} &= 0 , \\
\sigma &= \sigma^d + \sigma^r + \sigma^a + \sigma^b , \\
\sigma^d &= 2\eta \mathbf{D} , \\
\sigma^r &= -\pi I - \frac{\lambda}{2} (\mathbf{h} \mathbf{p} + \mathbf{h} \mathbf{p}^T) + \frac{1}{2} (\mathbf{h} \mathbf{p} - \mathbf{h} \mathbf{p}) , \\
\sigma^a &= \frac{\alpha c^2}{T} (\mathbf{p} \mathbf{p} + \mathbf{I}) , \\
\sigma^b &= \frac{\beta c^2}{T} (\nabla \mathbf{p} + \nabla (\mathbf{p}^T) + \nabla \cdot \mathbf{p} ) , \\
\frac{\partial \mathbf{c}}{\partial t} + \nabla \cdot [ \mathbf{c} (\mathbf{v} + c \beta_1 \mathbf{p}) + \Gamma' \mathbf{h} + \Gamma'' \mathbf{f} ] &= 0 , \\
\left( \frac{\partial}{\partial t} + (\mathbf{v} + c \beta_2 \mathbf{p}) \cdot \nabla \right) \mathbf{p} + \mathbf{\Omega} \cdot \mathbf{p} &= \lambda T r (\nabla \mathbf{v}) \mathbf{p} + \Gamma \mathbf{h} + \Gamma' \mathbf{f}, \tag{8}
\end{align*}
\]

where \( \mathbf{h} \) is the molecular field given by \( \mathbf{h} = -\frac{\delta F}{\delta \mathbf{p}} \), \( \mathbf{f} = -\nabla \frac{\delta F}{\delta \mathbf{c}} \) is the molecular flux of the active rods, \( \mathbf{D} = \frac{\nabla \mathbf{v} + \nabla (\mathbf{v}^T)}{2} \) is the rate of strain tensor, \( \mathbf{\Omega} = \frac{1}{2} (\nabla \mathbf{v} - \nabla (\mathbf{v}^T)) \) is the vorticity tensor, \( \sigma^b \) is a dissipative stress (an analogue of \( \sigma^d \)), and all the unspecified parameters depend on both passive and active contributions [46]. This model adds additional fluxes to the transport of the concentration \( \mathbf{c} \) due to the energetic activity of both polar velocity field \( \mathbf{p} \) and the concentration fluctuations of \( \mathbf{c} \). The convective effect of the polar velocity \( \mathbf{p} \) is added to the transport of both \( \mathbf{c} \) and \( \mathbf{p} \) as well. An additional

\[
\begin{align*}
F &= \int \left[ \frac{C}{2} \left( \frac{\delta \mathbf{c}}{c_0} \right)^2 + \frac{a_2}{2} \| \mathbf{p} \|^2 + \frac{a_4}{4} \| \mathbf{p} \|^4 + \frac{K_1}{2} (\nabla \cdot \mathbf{p} )^2 + \frac{K_3}{2} (\| \nabla \times \mathbf{p} \|)^2 \\
&\quad + B_1 \frac{\delta \mathbf{c}}{c_0} \nabla \cdot \mathbf{p} + B_2 \| \mathbf{p} \|^2 \nabla \cdot \mathbf{p} + \frac{B_3}{c_0} \| \mathbf{p} \|^2 \mathbf{p} \cdot \nabla \mathbf{c} \right] d\mathbf{x}, \tag{9}
\end{align*}
\]

where \( \delta \mathbf{c} = \mathbf{c} - c_0 \), \( c_0 \) is a baseline concentration, \( C \) is the compression modulus, and \( K_{1,3} \) are the splay and bend elastic constants; the other coefficients depend on both passive and active contributions [46]. This model adds additional fluxes to the transport of the concentration \( \mathbf{c} \) due to the energetic activity of both polar velocity field \( \mathbf{p} \) and the concentration fluctuations of \( \mathbf{c} \). The convective effect of the polar velocity \( \mathbf{p} \) is added to the transport of both \( \mathbf{c} \) and \( \mathbf{p} \) as well. An additional
“viscous” stress $\sigma^b$ is added analogous to the viscous stress $\sigma^d$. The free energy contains additional coupling terms between the polar velocity and the concentration gradient.

This model is used to study sheared active polar fluids. An extremely rich variety of phenomena are identified including an effective reduction or increase in the apparent viscosity, depending on the nature of the active stresses and flow alignment property of the particles, nonmonotone stress-strain-rate relationship, and yield stress for large active forcing [46]. In the limit of strongly polarized states where the magnitude of $\mathbf{p}$ is locked, this formulation can be recast in terms of a unit vector $\mathbf{u} = \frac{\mathbf{p}}{||\mathbf{p}||}$. The details can be found in [46].

### 2.2 Active Apolar Filament Models

When the polarity on the moving objects is weak, instead of the polarity vector, a second order nematic tensor can be employed to describe both the nematic order as well as the active stress. For apolar filament fluids, a coarse-grained model can be derived with only the nematic order tensor [16,49]. We summarize the version used by Cates et al. [16] in this section. Let $\mathbf{Q}$ be a traceless second order tensor denoting the nematic order in the active filament fluid. The governing system of equations consist of the following equations.

\[
\nabla \cdot \mathbf{v} = 0, \\
\rho \left( \frac{\partial}{\partial t} + \mathbf{v} \cdot \nabla \right) \mathbf{v} = \nabla \cdot (\sigma), \\
\mathbf{H} = -\frac{\delta F}{\delta \mathbf{Q}} + \frac{1}{3} Tr \left( \frac{\delta F}{\delta \mathbf{Q}} \right) \mathbf{I}, \\
\sigma = -P_0 \mathbf{I} + 2\eta \mathbf{D} + 2\xi \left( \mathbf{Q} + \frac{1}{3} \mathbf{I} \right) \mathbf{Q} : \mathbf{H} - \xi \mathbf{Q} \left( \mathbf{Q} + \frac{1}{3} \mathbf{I} \right) \mathbf{Q} - \xi \left( \mathbf{Q} + \frac{1}{3} \mathbf{I} \right) \mathbf{H}
\]

\[
\nabla \cdot \frac{\delta F}{\delta \nabla \mathbf{Q}} + \mathbf{Q} \cdot \mathbf{H} - \mathbf{H} \cdot \mathbf{Q} - \zeta \mathbf{Q}, \\
\left( \frac{\partial}{\partial t} + \mathbf{v} \cdot \nabla \right) \mathbf{Q} - \Omega \cdot \mathbf{Q} + \mathbf{Q} \cdot \Omega - [\mathbf{D} \cdot \mathbf{Q} + \mathbf{Q} \cdot \mathbf{D}] = \Gamma \mathbf{H}, \tag{10}
\]

where $c$ is the concentration of the apolar active rod assumed constant in this model, $\xi$ is the friction coefficient, $P_0$ is the hydrostatic pressure, $\zeta$ is the activity parameter with $\zeta > 0$ corresponding to extensile and $\zeta < 0$ contractile motion. The free energy density of the material system is given by a simplified Landau-deGennes functional

\[
F = k_B T c \left[ \left( 1 - \frac{N}{3} \right) \frac{\mathbf{Q} : \mathbf{Q}}{2} - \frac{N}{3} \mathbf{Q}^3 + \frac{N}{4} (\mathbf{Q} : \mathbf{Q})^2 + \frac{K}{2} \left( \nabla \mathbf{Q} : \nabla \mathbf{Q} \right)^2 \right]. \tag{11}
\]
where $k_B$ is the Boltzmann constant, $T$ is the absolute temperature, $N$ measures the strength of the bulk part of the potential, and $K$ is the one-constant Frank elastic coefficient. This model was used to study sheared active gels close to the isotropic–nematic transition. This model was later extended to add an active term in the nematodynamic equation for $Q$ and simulated with lattice Boltzmann numerical methods [79].

### 2.3 Kinetic Models for Active Fluids

In an effort to unify the polar and apolar models for active fluids, Liverpool, Marchetti and collaborators developed a framework for active filament fluids using a polymer kinetic theory formulation [75]. Here, we briefly describe the 2-D formulation of the theory and its coarse-graining procedures to yield the moment equations. Let $c$ be the number density of rigid active rods. The Smoluchowski equation is given by

$$\frac{\partial c}{\partial t} + \nabla \cdot \mathbf{J} + \mathbf{R} \cdot \mathbf{J}^R = 0,$$

$$\mathbf{J} = \mathbf{v}_c - D \nabla c - \frac{1}{k_B T} \mathbf{D} \cdot \mathbf{c} \nabla V_{\text{ex}} + \mathbf{J}^a,$$

$$\mathbf{J}^R = c \mathbf{\omega} - D_r \left[ \mathbf{R} c - \frac{c}{k_B T} \mathbf{R} V_{\text{ex}} \right] + \mathbf{J}^a_r,$$  

(12)

where $\mathbf{J}$ is the translational flux, $\mathbf{J}^R$ is the rotational flux, $D = D \mathbf{u} + D_\perp (\mathbf{I} - \mathbf{u} \mathbf{u})$ is the translational diffusivity, $\mathbf{u}$ is the unit vector in the direction of the molecular velocity, $D_r$ is the rotational diffusivity, $\mathbf{\omega}$ is the angular velocity, $\mathbf{R} = \mathbf{u} \times \frac{\partial}{\partial \mathbf{u}}$ is the rotational gradient operator, the active translational and rotational fluxes are defined by

$$\mathbf{J}^a = cb^2m \int \int v_a(u, s_1, u_2, s_2)c(r + \xi, u_2, t)du_2d\xi,$$

$$\mathbf{J}^a_r = cb^2m \int \int \mathbf{\omega}_a(u, s_1, u_2, s_2)c(r + \xi, u_2, t)du_2d\xi.$$  

(13)

$v_a$ and $\omega_a$ are the translational and rotational velocities, respectively. The excluded volume potential is given by the Onsager potential

$$V_{\text{ex}} = k_B T \int \int \| \mathbf{u} \times u_2 \| c(x + \mathbf{s}, u_2, t)dsdu_2,$$  

(14)
$b$ is a parameter and $m$ is the mass of the rod. The active velocities are given by

$$v_a = \frac{1}{2} v_r + V_m,$$

$$v_r = \frac{\tilde{\beta}}{2} (u_2 - u) + \frac{\tilde{\alpha}}{2l} \xi,$$

$$V_m = A (u + u_2) + B (u_2 - u),$$

$$\omega_a = 2 \left[ \gamma_P + \gamma_{NP}(u \cdot u_2) \right] (u \times u_2),$$

(15)

where $\gamma_P$ and $\gamma_{NP}$ are the rotational rates, $\tilde{\alpha} = \alpha (1 + u \cdot u_2)$, $\tilde{\beta} = \beta (1 + u \cdot u_2)$, $A = -(\beta - \alpha (s_1 - s_2)/2)/12$, and $B = \alpha (s_1 - s_2)/24$ for long thin rods [4]. $\alpha$ and $\beta$ are model parameters. All four parameters can be related to the stiffness of the crosslinkers and to the rate $u(s)$ at which a motor cluster attached at position $s$ steps along a filament toward the polar end [75]. The concentration has a generalized Fourier expansion

$$c(x, u, t) = \frac{c(x, t)}{2\pi} \left[ 1 + 2p \cdot u + 4Q : uu + \cdots \right],$$

(16)

where the zeroth, first, and second moments are defined by:

$$c(x, t) = \int c(x, u, t) du,$$

$$cp(x, t) = \int uc(x, u, t) du,$$

$$cQ(x, t) = \int \left( uu - \frac{\|uu\|^2}{2}\right) c(x, u, t) du.$$

(17)

The force due to the stress for the system is given by

$$\nabla \cdot \sigma = \int \int c(x - \xi, u, t) \left[ \delta(\xi - su) \mathcal{F}^h(s) \right] d\xi du,$$

(18)

where $\mathcal{F}^h(s)$ is the hydrodynamic force per unit length exerted by the suspension at position $s$ along the rod. The force can be approximated by the first two terms in the Taylor expansion

$$\nabla \cdot \sigma = \int c(x, u, t) F^h du - \int \left( \frac{s}{L} \right)^2 \left( \frac{u \nabla}{L} \right) c_{\tau^h} du.$$  

(19)
Computational and Modeling Strategies for Cell Motility

We denote \( \tilde{\sigma} = \sigma - T r(\sigma) \frac{1}{3} \).

\[
\tilde{\sigma} = \tilde{\sigma}^a + \sigma^d,
\]

\[
\tilde{\sigma}^a = 2k_B T_a c \left[ \left( 1 - \frac{c}{c_f N} \right) Q - \frac{c}{c_f N} \left( pp - \frac{||p||^2}{2} I \right) \right] + C_1 c \left( \frac{4}{3} Q + pp - \frac{||p||^2}{2} I \right),
\]

\[
+ C_2 c \left[ \nabla p - \frac{V}{2} I - \frac{1}{4} (\nabla p - \nabla p^T) \right],
\]

\[
\tilde{\sigma}^d = C_3 \left[ \frac{1}{2} \left( D - \frac{1}{2} T r(D) \right) + \frac{1}{3} (Q T r(D) - D_3 \cdot Q) + \frac{2}{3} (D \cdot Q + Q \cdot D) \right],
\]

where \( C_1, C_2, C_3 \) are model parameters [75].

This together with the continuity equation for the average velocity \( v \) and the momentum balance equation in the form of Stokes equation constitute the governing system of equations for the kinetic theory.

\[
\nabla \cdot v = 0,
\]

\[
\nabla \cdot (\sigma + 2\eta D - P_0 I) = 0,
\]

where \( \eta \) is the viscosity of the solvent and \( P_0 \) is the hydrostatic pressure.

Shelley and Santillian studied dilute active rod particle fluids using a kinetic theory in which only convective transport is accounted for [95];

\[
J = v c + v_0 u c, \quad J^R = c \omega.
\]

In their model, the active stress tensor is given by

\[
\tilde{\sigma}^a = \xi Q.
\]

Next, we present one of the latest versions of the kinetic theory in which the active flux due to rod–rod binary collisions is carefully considered. Baskaran and Marchetti derived a Smoluchowski equation for self-propelled hard rods in 2-D [10].

\[
\frac{\partial c}{\partial t} + \nabla \cdot J + R \cdot J^R = 0,
\]

\[
J = c v + v_0 u c - D^{SP} \cdot \nabla c - \frac{1}{k_B T} D \cdot c \nabla V_{ex} - \frac{D_{||} m v_0^2}{2k_B T} I^{SP},
\]

\[
J^R = c \omega - D_t \left[ R c + \frac{c}{k_B T} R V_{ex} \right] - \frac{D_{r} m v_0^2}{2k_B T} I^{SP},
\]

where \( J \) is the translational flux and \( J^R \) is the rotational flux,

\[
D^{SP} = D_{\perp} I + (D_{||} + D_{S} - D_{\perp}) uu
\]
is the translational diffusivity, $D_S = \frac{v_0^2}{\zeta}$, $v_0$ is the speed of the moving rod, $D_{||}$ and $D_{\perp}$ are the diffusivity in the parallel and perpendicular direction of the rod, $m$ is the mass of the rod, and the additional fluxes due to collisions are given below.

$$\mathbf{I}_{SP} = \int \int \sin^2(\theta_1 - \theta_2) \left[ \Theta (\sin(\theta_1 - \theta_2)) - \Theta (-\sin(\theta_1 - \theta_2)) \right] \times \left[ u_1^+ c \left( x_1 + s u_1 - \frac{l}{2} u_2, u_2, t \right) + u_2^+ c \left( x_1 + s u_2 - \frac{l}{2} u_1, u_2, t \right) \right] d\mathbf{s} d\mathbf{u}_2,$$

$$\mathbf{I}_{\perp} = z \int \int \sin^2(\theta_1 - \theta_2) \left[ \Theta (\sin(\theta_1 - \theta_2)) - \Theta (-\sin(\theta_1 - \theta_2)) \right] \times \left[ s c \left( x_1 + s u_1 - \frac{l}{2} u_2, u_2, t \right) + \frac{l}{2} \cos(\theta_1 - \theta_2) \right. $$

$$\left. \times c \left( x_1 + s u_2 - \frac{l}{2} u_1, u_2, t \right) \right] d\mathbf{s} d\mathbf{u}_2. \quad (26)$$

where $z = \mathbf{u} \times \mathbf{u}_2$, $\theta_1$ and $\theta$ are the initial angles of $\mathbf{u}$ and $\mathbf{u}_2$, respectively, before collision. $\Theta(x)$ is the Heaviside function.

Taking the zeroth moment, the first moment, and the second moment of the Smoluchowski equation, the transport equation for the rod density, polarity vector, and the nematic order tensor can be derived [10].

These models are developed for dilute to semidilute suspensions of active filaments and rods in viscous solvents. Inside a cell, the cytoplasm is comprised of various cytoskeletal filaments, microtubules, and intermediate filaments immersed in the cytosol. The resulting network structures and buffer solution behave like a gel. We briefly review new models for active biogels next.

3 Models for Active Gels

In active gels, networks of active filaments can form either temporarily or on a longer timescale. The solvent permeation into the network must be accounted for in the gel. We next describe several relevant models for active gels briefly.

3.1 Isotropic Active Gel Model

Banerjee and Marchetti proposed a phenomenological model for isotropic active gels based on a continuum model for physical gels [7]. The governing system of equations are summarized. We denote by $\mathbf{u}$ the position vector of the network, $\mathbf{v}$ the velocity of the solvent fluid, $c_b$ the concentration of bound motor proteins, $c_u$ the
concentration of the unbound motors, $\rho$ the mass density of the gel network, and $\rho_f$ the density of the fluid. The model is based on the two-component formulation of multiphase fluids, in which network is treated as a viscoelastic material while the solvent is modeled as a viscous fluid. The momentum conservation for each phase is enforced and the mixture is assumed incompressible i.e., the combined velocity is assumed solenoidal. The interaction between the solvent and the network is through a friction term in the momentum balance equations for both materials.

$$\rho \frac{\partial^2 u}{\partial t^2} = -\Gamma (\dot{u} - v) + \nabla \cdot \sigma,$$

$$\sigma = \sigma^e + \sigma^d + \sigma^a,$$

$$\sigma^e = \mu (\nabla u + (\nabla u)^T) + \lambda Tr(\nabla u)I,$$

$$\sigma^d = \eta_s (\nabla \dot{u} + (\nabla \dot{u})^T) + \left( \eta_b - \frac{2\eta_s}{3} \right) Tr(\nabla \dot{u})I,$$

$$\sigma^a = \zeta (\rho, c_b) \Delta \mu I,$$

$$\rho_c \dot{v} = \nabla \cdot (-P I + 2\eta D) + \Gamma (\dot{u} - v),$$

$$\frac{\partial c_b}{\partial t} + \nabla(c_b u) = -k_u c_b + k_b u_c,$$

$$\frac{\partial c_a}{\partial t} = D \nabla^2 c_a + k_a c_b - k_b c_u,$$

$$\nabla \cdot \left( (1 - \phi_p) v + \phi_p \dot{u} \right) = 0. \quad (27)$$

where $P$ is the hydrodynamic pressure for the solvent, $\eta$ the fluid viscosity, $\lambda$ and $\mu$ the Lame coefficients of the gel network, $\eta_b$ and $\eta_s$ are the bulk and shear viscosity arising from internal friction in the gel, $\Delta \mu$ is the change in chemical potential due to hydrolysis of ATP, $\zeta$ is a parameter with units of the number density describing the stress per unit change in chemical potential due to the action of crosslinkers, $k_b$ is the bounding rate of the motor molecules, $k_u$ is the unbinding rate, $D$ is the diffusion coefficient for the unbound motor, and $\phi_p$ is the volume fraction of the active gel network. A transport equation for $\phi_p$ is needed to complete the system. In their model, the volume fraction is assumed small, $\phi_p \ll 1$, so the incompressibility condition reduces to $\nabla \cdot v = 0$.

The active contribution to the stress is an active pressure on the gel network proportional to $\Delta \mu$. The gel network is modeled as a viscoelastic material subject to an active stress due to ATP activities on the motors bound to the filament. This model leads to spontaneous oscillations at intermediate activity and contractile instability of the network at large activity [7].
3.2 Active Polar Gel Model

In a series of papers, Joanny, Prost, Kruse, Julicher et al. [59, 60, 66, 67, 96] studied active gels pertinent to cytoskeletal dynamics. We discuss one of their generic models below. We denote the domain occupied by the gel by $\Omega$, the number density of monomers in the gel by $\rho$, an average velocity transporting the gel by $\mathbf{v}$. The transport equation for $\rho$ is given by

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\mathbf{v} \rho) = -k_d \delta(S) \rho + k_p \delta(S), \quad (28)$$

where $k_p$ is the rate of polymerization and $h_d$ is the rate of depolymerization at the gel surface defined by the level surface $\{x|S = 0\}$. The polymerization and depolymerization in this model are assumed to only take place at the gel surface. Let $\rho^a$ be the number density of diffusing free monomers and the diffusive flux $j^a$ of free monomers. The transport equation for $\rho^a$ is

$$\frac{\partial \rho^a}{\partial t} + \nabla \cdot j^a = k_d \delta(S) \rho - k_p \delta(S). \quad (29)$$

Note that the total number of monomers is conserved

$$\frac{\partial}{\partial t} (\rho + \rho^a) + \nabla \cdot (\rho \mathbf{v} + j^a) = 0. \quad (30)$$

Active processes are mediated by molecular motors. Let $c^{(b)}$ be the concentration of bound motors and $c^{(m)}$ the concentration of the free diffusing motors. The conservation equations for the motors are given by

$$\frac{\partial c^{(m)}}{\partial t} + \nabla \cdot j^{(m)} = k_{pff} c^{(b)} - k_{on} \left(c^{(m)}\right)^n, \quad (31)$$

$$\frac{\partial c^{(b)}}{\partial t} + \nabla \cdot (\mathbf{v} c^{(b)}) + \nabla \cdot j^{(b)} = -k_{pff} c^{(b)} + k_{on} \left(c^{(m)}\right)^n,$$

where $k_{on}$ and $k_{off}$ denote the attachment and detachment rate, respectively, and $j^{(b)}$ and $j^{(m)}$ are the flux of free motors and the bounded ones relative to the gel motion. In the timescales considered in their model, the momentum balance is replaced by a force balance equation

$$\nabla \cdot \left(\sigma^{\text{total}} - \Pi\right) + \mathbf{f}^{\text{ext}} = 0, \quad (32)$$

where $\mathbf{I}$ is the identity matrix, $\mathbf{f}^{\text{ext}}$ is the external force, $\sigma^{\text{total}}$ denotes the total stress tensor, and $\Pi$ is the pressure.
Let \( \mathbf{p} \) be the polarity vector describing the polar direction of the monomer. The time rate change of the system free energy is given by

\[
\dot{F} = - \int \text{d}x \left[ \sigma_{\text{total}} \cdot \nabla \mathbf{v} + \mathbf{h} \cdot \mathbf{P} + \Delta \mu r - c^{(b)} \mu^{(b)} - c^{(m)} \mu^{(m)} - \dot{\rho} \mu - \rho^a \mu^a \right],
\]

where \( \mathbf{h} \) is the molecular field, \( \mathbf{P} = \frac{\partial}{\partial \mathbf{p}} \mathbf{p} + \mathbf{v} \cdot \nabla \mathbf{p} + \Omega \cdot \mathbf{p} \) is the corotational derivative of \( \mathbf{p} \), \( \Delta \mu \) is the chemical force conjugate to the ATP production rate \( r \) which determines the number of ATP molecules hydrolyzed per unit time and unit volume. The dot denotes time derivative, \( \rho^a, \mu^a, \mu^{(b)}, \mu^{(m)} \) are the chemical potentials corresponding to \( \rho, c^a, c^{(b)}, c^{(m)} \), respectively. The total stress is given by

\[
\sigma_{\text{total}} = \sigma + \frac{1}{2} (\mathbf{ph} - \mathbf{hp}),
\]

where \( \sigma \) is the symmetric part of the stress. The symmetric stress tensor \( \sigma \), \( \mathbf{P} \), and the ATP consumption rate \( r \) can be decomposed into reactive part and dissipative part, respectively,

\[
\sigma = \sigma^r + \sigma^d,
\]

\[
\mathbf{P} = \mathbf{P}^r + \mathbf{P}^d,
\]

\[
r = r^r + r^d,
\]

where the superscripts \( r \) denote the reactive response and \( d \) the dissipative response. The constitutive equations for the dissipative response are given by

\[
\left( 1 - \tau^2 \frac{D^2}{Dt^2} \right) \sigma^d = 2\eta D - \tau \frac{D}{Dt} \left( \frac{\nu_1}{2} (\mathbf{ph} + \mathbf{hp}) + \tilde{v}_1 (\mathbf{p} \cdot \mathbf{h}) \mathbf{I} \right),
\]

\[
\left( 1 - \tau^2 \frac{D^2}{Dt^2} \right) \mathbf{P}^d = \left( 1 - \tau^2 \frac{D^2}{Dt^2} \right) \left( \frac{\mathbf{h}}{\gamma_1} + \lambda_1 \mathbf{p} \Delta \mu \right)
+ \tau \frac{D}{Dt} (\nu_1 \nabla \mathbf{v} \cdot \mathbf{p} + \tilde{v}_1 T_r (\nabla \mathbf{v}) \mathbf{p}),
\]

\[
r^d = \Lambda \Delta \mu + \lambda_1 \mathbf{p} \cdot \mathbf{h} + \lambda \mathbf{p} \cdot \nabla \mu^{(b)}.
\]

where \( \nu_1, \tilde{v}_1, \Lambda, \lambda_1 \lambda \) are model parameters and \( \tau \) is the relaxation time. The fluxes for the monomers and motor molecules, which do not have reactive parts, are given by

\[
\mathbf{j}^{(a)} = -D^{(a)} \nabla \rho^{(a)} + \lambda^{(a)} \Delta \mu \mathbf{p},
\]

\[
\mathbf{j}^{(m)} = -D^{(m)} \nabla c^{(m)} + \lambda^{(m)} \Delta \mu \mathbf{p},
\]

\[
\mathbf{j}^{(b)} = -D^{(b)} \nabla c^{(b)} + \lambda^{(b)} \Delta \mu \mathbf{p}.
\]
where $D^{(i)}$ are the diffusion coefficients, $\lambda^{(i)}$ are coupling parameters.

The reactive fluxes, the polarity vector, and the ATP consumption rate, are given next.

$$
\sigma^r = -\tau \left( \frac{D\sigma^d}{Dt} + A \right) - \zeta \Delta \mu \mathbf{pp} - \bar{\zeta} \Delta \mu \mathbf{I} - \zeta' \Delta \mu \|\mathbf{p}\|^2 \mathbf{I} + \frac{v_1}{2} (\mathbf{ph} + \mathbf{hp}) + \bar{v}_1 \mathbf{p} \cdot \mathbf{hl},
$$

$$
\left( 1 - \tau^2 \frac{D^2}{Dt^2} \right) \mathbf{P}^r = -v_1 \nabla \mathbf{v} \cdot \mathbf{p} - \bar{v}_1 Tr(\nabla \mathbf{v}) \mathbf{p},
$$

$$
r^r = \zeta \mathbf{pp} : \nabla \mathbf{v} + \bar{\zeta} Tr(\nabla \mathbf{v}) + \zeta' \|\mathbf{p}\|^2 Tr(\nabla \mathbf{v}), \tag{38}
$$

where $\zeta, \bar{\zeta}, \zeta'$, $v_1$, $\bar{v}_1$ are model parameters and

$$
\mathbf{A} = v_2 \left( \nabla \cdot \sigma^d + \sigma^d \cdot \nabla \mathbf{v} \right) + v_3 Tr(\nabla \mathbf{v}) \sigma^d + v_4 Tr(\nabla \mathbf{v}) Tr(\sigma^d) \mathbf{I} + v_5 Tr(\sigma^d) \nabla \mathbf{v} + v_6 \nabla \mathbf{v} : \sigma^d \mathbf{I}, \tag{39}
$$

where $v_i$ are the model parameters analogous to the eight-constant Oldroyd model.

Combining the reactive and dissipative parts, the total stress, polarity vector, and the ATP consumption rate are finally given by

$$
2\eta \mathbf{D} = \left( 1 + \tau \frac{D}{Dt} \right) \left( \sigma + \zeta \Delta \mu \mathbf{pp} + \zeta' \Delta \mu \|\mathbf{p}\|^2 \mathbf{I} + \bar{\zeta} \Delta \mu \mathbf{I} + \tau \mathbf{A} \right)
$$

$$
- \frac{v_1}{2} (\mathbf{ph} + \mathbf{hp} - \bar{v}_1 (\mathbf{p} \cdot \mathbf{h}) \mathbf{I}),
$$

$$
\left( 1 - \tau^2 \frac{D^2}{Dt^2} \right) \mathbf{P} = \left( 1 - \tau^2 \frac{D^2}{Dt^2} \right) \left( \frac{\mathbf{h}}{\gamma_1} + \lambda_1 \mathbf{p} \Delta \mu \right)
$$

$$
- \left( 1 - \tau \frac{D}{Dt} \right) \left( v_1 \nabla \mathbf{v} \cdot \mathbf{p} + \bar{v}_1 Tr(\nabla \mathbf{v}) \mathbf{p} \right),
$$

$$
r = \Lambda \Delta \mu + \lambda_1 \mathbf{p} \cdot \mathbf{h} + \lambda \mathbf{p} \cdot \nabla \mu^{(b)} + \zeta \mathbf{pp} : \nabla \mathbf{v} + \bar{\zeta} Tr(\nabla \mathbf{v}) + \zeta' \|\mathbf{p}\|^2 Tr(\nabla \mathbf{v}). \tag{40}
$$

By restricting $\mathbf{p}$ to be a unit vector and using a free energy for polar liquid crystals

$$
F = \int \left[ \frac{K_1}{2} (\nabla \cdot \mathbf{p})^2 + \frac{K_3}{2} \|\mathbf{p} \cdot \nabla \mathbf{p}\|^2 + k \nabla \mathbf{p} - \frac{h}{2} \|\mathbf{p}\|^2 \right] \, dx. \tag{41}
$$

Kruse et al. studied point defects in two dimensions [67]. This model was later extended to a multicomponent active fluid model by Joanny et al. [58].
3.3 Three-Component Active Fluid Model

In this multicomponent model, the active fluid is assumed to consist of three effective components [58]. Let \( n_0 \) denote the number density of the monomeric subunits in a polar network, \( n_1 \) the number density of the free monomeric subunits, and \( n_2 \) the number density of the solvent molecules. The effect of ATP hydrolysis is considered in the model. The conservation equations for the three densities are given by

\[
\frac{\partial n_0}{\partial t} + \nabla \cdot \mathbf{J}_0 = S, \\
\frac{\partial n_1}{\partial t} + \nabla \cdot \mathbf{J}_1 = -S, \\
\frac{\partial n_2}{\partial t} + \nabla \cdot \mathbf{J}_2 = 0, \tag{42}
\]

where the source term \( S \) represents the polymerization and depolymerization which leads to the exchange of monomers between the gel and the solvent, the flux constitutive equations are

\[
\mathbf{J}_0 = n_0 \mathbf{v} + \frac{\mathbf{j}_0}{m_0}, \\
\mathbf{J}_1 = n_1 \mathbf{v} + \frac{\mathbf{j}_1}{m_1}, \\
\mathbf{J}_2 = n_2 \mathbf{v} - \frac{\mathbf{j}_0}{m_2} - \frac{\mathbf{j}_1}{m_2}. \tag{43}
\]

\( m_{0,1,2} \) are the molecular masses of monomers in the gel, free monomers in the solution, and the solvent molecules, respectively. The mass density of the material system is given by \( \rho = m_0 n_0 + m_1 n_1 + m_2 n_2 \). These equations warrant the conservation of mass

\[
\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0 \tag{44}
\]

because \( m_0 = m_1 \). If the monomeric subunits on the polymer network (\( m_0 \)) differs from those free ones (\( m_1 \)), the mass conservation may not be upheld in the model. In this case, the transport equation for \( n_i \) must be modified.

The conservation of linear momentum is given by

\[
\frac{\partial}{\partial t} (\rho \mathbf{v}) + \nabla \cdot (\rho \mathbf{v} \mathbf{v}) = \nabla \cdot \mathbf{\sigma}, \tag{45}
\]
where $\sigma$ is the total stress of the system and external forces are absent. We denote the free energy density by $f$ and the free energy by $F$, i.e., $F = \int f \, dx$. The time rate of change of the free energy is given by

$$\frac{dF}{dt} = \int \left[ \partial_i \left( \frac{\rho}{2} \| \mathbf{v} \|^2 \right) + \sum_{i=0}^{2} \mu_i \partial_i n_i - \mathbf{h} \cdot \partial_r \mathbf{p} - r \Delta \mu \right] \, dx, \quad (46)$$

where $\mu_i = \frac{\delta F}{\delta n_i}, i = 0, 1, 2$ are the chemical potentials for the three effective components, respectively, $\mathbf{h} = -\frac{\delta E}{\delta \mathbf{p}}$ is the molecular field, $r$ is the rate at which ATP molecules are hydrolyzed, and $\Delta \mu = \mu_{\text{ATP}} - \mu_{\text{ADP}} - \mu_p$ is the difference in chemical potentials of ATP and the product molecules ADP and $P_i$, respectively. Using the generalized Gibbs–Duhem relation for a multicomponent polar fluid

$$\nabla \cdot \sigma^c = -\sum_{i=0}^{2} n_i \nabla \mu_i - \nabla \mathbf{p} \cdot \mathbf{h}, \quad (47)$$

where $\sigma^c$ represents the Ericksen stress, the free energy rate of change is rewritten into

$$\frac{dF}{dt} = \int \left[ -\sigma^s : \nabla \mathbf{v} + \sum_{i=0}^{1} \tilde{j}_i \cdot \nabla \tilde{\mu}_i + (\mu_0 - \mu_1) S - \mathbf{P} \cdot \mathbf{h} - r \Delta \mu \right] \, dx, \quad (48)$$

where $\sigma^s$ is the symmetric part of the stress less the Ericksen stress as well as the anisotropic stress, $\tilde{\mu}_i = \frac{\mu_i}{m_i} - \frac{\mu_2}{m_2}$, $\mathbf{P} = \frac{\partial}{\partial \mathbf{p}} \mathbf{p} + \mathbf{v} \cdot \nabla \mathbf{p} + \Omega \cdot \mathbf{p}$ is the convected corotational derivative of $\mathbf{p}$, $\Omega$ is the vorticity tensor,

$$\sigma^c = \sigma - \sigma^a - \sigma^{c,s},$$

$$\sigma^a = \frac{1}{2} (\mathbf{ph} - \mathbf{hp}),$$

$$\sigma^{c,s} = \text{sym} \left[ \left( f - \sum_{i=0}^{2} \mu_i n_i \right) \mathbf{I} - \frac{\partial f}{\partial \nabla \mathbf{p}} \cdot \nabla \mathbf{p} \right], \quad (49)$$

where $\text{sym}$ denotes the symmetric part of the stress. We can identify the generalized force fields $(\nabla \mathbf{v}, -\nabla \tilde{\mu}_i, \mathbf{h}, \Delta \mu)$. The corresponding conjugate fluxes are $(\sigma^a, \tilde{j}_i, \mathbf{P}, r)$, assuming the fluxes are functions of the forces, and expanded to linear order. The force fields are distinguished in that some forces change signs when time is reversed like $\nabla \mathbf{v}$ while others do not. The stress component obeying time reversal is dissipative and the others are reactive. With this, we propose the following phenomenological dissipative fluxes.
\[
\sigma^{s,d} = 2\eta \left( \nabla v - \frac{Tr(\nabla v)}{3} \mathbf{I} \right) + \bar{\eta} Tr(\nabla v) \mathbf{I},
\]
\[
\mathbf{j}^d_i = -\sum_{j=0}^{1} \gamma_{ij} \nabla \bar{\mu}_j + \bar{\lambda}_i \mathbf{h} + \kappa_i \mathbf{p} \Delta \mu,
\]
\[
\mathbf{p}^d = +\bar{\lambda}_i \nabla \bar{\mu}_i + \frac{h}{\gamma_1} - \lambda_1 \Delta \mu \mathbf{p},
\]
\[
r^d = -\sum_{i=0}^{1} \kappa_i \mathbf{p} \cdot \nabla \bar{\mu}_i + \lambda_1 \mathbf{p} \cdot \mathbf{h} + \Lambda \Delta \mu,
\]
where \((\gamma_{ij})\) is nonnegative definite, \(\Lambda, \gamma_1\) are nonnegative. The reactive terms are proposed as follows:

\[
\sigma^{s,r} = -\sum_{i=0}^{1} \frac{\epsilon_j}{2} (\mathbf{p} \nabla \bar{\mu}_j + \nabla \bar{\mu}_j \mathbf{p}) - \sum_{j=0}^{1} \tilde{\epsilon}_j \mathbf{p} \cdot \nabla \bar{\mu}_j \mathbf{I} + \frac{\nu_1}{2} (\mathbf{p} \mathbf{h} + \mathbf{h} \mathbf{p})
\]
\[
+ \bar{\nu}_1 \mathbf{p} \cdot \mathbf{h} \mathbf{I} - \zeta_1 \mathbf{p} \mathbf{p} \Delta \mu - \zeta_2 \Delta \mu \mathbf{I} - \zeta_3 \|\mathbf{p}\|^2 \Delta \mu \mathbf{I},
\]
\[
\mathbf{j}^r_i = -\epsilon_i \nabla v \cdot \mathbf{p} - \bar{\epsilon}_i Tr(\nabla v) \mathbf{p},
\]
\[
\mathbf{p}^r = -\nu_1 \nabla v \cdot \mathbf{p} - \bar{\nu}_1 Tr(\nabla v) \mathbf{p},
\]
\[
r^r = \zeta_1 \mathbf{p} \mathbf{p} : \nabla v + \zeta_2 Tr(\nabla v) + \zeta_3 \|\mathbf{p}\|^2 Tr(\nabla v),
\]
where \(\zeta_{1,2,3}\) are the coefficients for the active terms. By applying the Onsager reciprocal principle and verifying the long and short time asymptotic behavior, the constitutive equation can be extended to account for viscoelastic behavior and chirality.

\[
\sigma^{s,r} = -\tau \left[ \frac{D}{Dt} \sigma^{s,d} + A \right] - \sum_{i=0}^{1} \frac{\epsilon_j}{2} (\mathbf{p} \nabla \bar{\mu}_j + \nabla \bar{\mu}_j \mathbf{p}) - \sum_{j=0}^{1} \tilde{\epsilon}_j \mathbf{p} \cdot \nabla \bar{\mu}_j \mathbf{I}
\]
\[
+ \frac{\nu_1}{2} (\mathbf{p} \mathbf{h} + \mathbf{h} \mathbf{p}) + \bar{\nu}_1 \mathbf{p} \cdot \mathbf{h} \mathbf{I} - \zeta_1 \mathbf{p} \mathbf{p} \Delta \mu - \zeta_2 \Delta \mu \mathbf{I} - \zeta_3 \|\mathbf{p}\|^2 \Delta \mu \mathbf{I}
\]
\[
+ \frac{\Pi_1}{2} (\mathbf{p} \times \mathbf{h} + \mathbf{h} \times \mathbf{p}) + \sum_{j=0}^{1} \frac{\Pi_2}{2} (\mathbf{p} \times \nabla \bar{\mu}_j \mathbf{p} + \mathbf{p} \times \nabla \bar{\mu}_j),
\]
\[
\mathbf{j}^r_i = -\epsilon_i \nabla v \cdot \mathbf{p} - \bar{\epsilon}_i Tr(\nabla v) \mathbf{p} - \Pi_2 \nabla v \cdot \mathbf{p} \times \mathbf{p},
\]
\[
\frac{D}{Dt} \mathbf{p}^r = \tau \frac{D}{Dt} \frac{\mathbf{h}}{\gamma_1} - \nu_1 \nabla v \cdot \mathbf{p} - \bar{\nu}_1 Tr(\nabla v) \mathbf{p} - \Pi_1 \nabla v \cdot \mathbf{p} \times \mathbf{p},
\]
\[
r^r = \zeta_1 \mathbf{p} \mathbf{p} : \nabla v + \zeta_2 Tr(\nabla v) + \zeta_3 \|\mathbf{p}\|^2 Tr(\nabla v),
\]
where \( \Pi_1, \Pi_2 \) denote the coefficients for the chiral terms. The dissipative parts are given by

\[
\left(1 - \tau^2 \frac{D^2}{Dt^2}\right) \sigma^{s.d} = 2\eta \left( \nabla \mathbf{v} - \frac{T r(\nabla \mathbf{v})}{3} \right) + \tilde{\eta} T r(\nabla \mathbf{v}) \mathbf{I},
\]

\[
\mathbf{j}_i^d = -\sum_{j=0}^{1} \gamma_{ij} \nabla \tilde{\mu}_j + \tilde{\lambda}_i \mathbf{h} + \kappa_i \mathbf{p} \Delta \mu + \Pi_i \mathbf{p} \times \mathbf{h}.
\]

\[
\mathbf{p}^d = +\tilde{\lambda}_i \nabla \tilde{\mu}_i + \frac{\mathbf{h}}{\gamma_1} - \lambda_1 \Delta \mu \mathbf{p} - \sum_{j=0}^{1} \Pi_j \mathbf{p} \times \nabla \tilde{\mu}_j,
\]

\[
r^d = -\sum_{i=0}^{1} \kappa_i \mathbf{p} \cdot \nabla \tilde{\mu}_i + \lambda_1 \mathbf{p} \cdot \mathbf{h} + \Lambda \Delta \mu, \quad (53)
\]

where \( \Pi_i \) denotes coefficients for the chiral terms. The reactive and dissipative parts can be combined to yield the constitutive equations for the active gel system. The details are available in [58].

4 A Phase Field Model for a Cell Surrounded by Solvent

We take a simplistic view of the cell structure recognizing the cell membrane as an elastic closed surface, the nucleus/core as a relatively hard, closed 3-D object inside the membrane, the remaining cytoplasm/cytoskeleton as a mixture of ATP bound and ADP bound G-actin, actin filament networks (or polymer-networks), and a third phase material called solvent which includes all other accessory proteins, organelles, and other unaccounted for material in the cytoplasm. In the simplified formulation, we assume the G-actin is available for polymerization at the barbed end and depolymerization at the pointed end [14]. This assumption will be refined later in the following.

We use a single-phase field variable or labeling function \( \phi(x,t) \) to denote the material inside or outside the cell. Since the core is always disjoint from the outside of the cell membrane, we simply use \( \phi = -1 \) to denote or label the material outside the cell membrane and the one inside the core at the same time; whereas the material in the cytoplasmic region is denoted by \( \phi = 1 \). We treat all materials in the cytoplasm as multiphase complex fluids or complex fluid mixtures. The interfacial free energy at the interfaces associated with the phase field variable \( \phi \) is given by

\[
f_{mb} = \frac{k_B T \kappa_b}{2} \int_S \left[ \left( \tau_0 + (C_1 + C_2 - C_0)^2 + \kappa_G C_1 C_2 \right) dS + \kappa_d (\Delta S - \Delta S_0)^2 \right].
\]

(54)
where $f_{mb}$ is the Helfrich elastic membrane energy, $\epsilon$ is the transitional parameter that scales with the width of the interfacial region, $k_B$ is the Boltzmann constant and $T$ the absolute temperature, $t_0$ is a constant that is the analog of surface tension of the membrane, $k_b$ is the bending rigidity and $k_G$ is the Gaussian bending rigidity, respectively, $C_1$ and $C_2$ are the principle curvatures, respectively, $d$ is a constant for the nonlocal bending resistance also related to the area compression modulus of the membrane surface, and $S$ denotes the membrane surface. For single-layered membranes, $k_d = 0$, whereas it maybe nonzero for bilayers. We notice that the Gaussian bending elastic energy integrates to a constant when the cell membrane does not undergo any topological changes. For simplicity, we will treat it as a constant in this book chapter.

Note that $\int_\Omega \frac{1+\phi}{2} \text{d}x = V_c$ is the volume of the cytoplasm region. To conserve the volume of this region, we can simply enforce $V(\phi) = \int_\Omega \phi \text{d}x = V(\phi(t = t_0))$ at some specified time $t_0$. In addition, the surface area of the membrane can be approximated by the formula

$$A(\phi) = k_a \int_\Omega \left( \|\nabla \phi\|^2 + \frac{(\phi^2 - 1)^2}{2\epsilon^2} \right) \text{d}x, \quad (55)$$

where $k_a$ is a scaling parameter. In the case of $k_d = 0$, the free energy can be represented by the phase field variable $\phi$ [31–34, 36]

$$f_{mb} = \frac{k_B T k_b}{k_a \epsilon} \int_\Omega \left[ \tau_0 \left( \frac{\epsilon}{2} \|\nabla \phi\|^2 + \frac{1}{4\epsilon} (1 - \phi^2)^2 \right) + \epsilon \left( \Delta \phi - \frac{1}{\epsilon^2} (\phi^2 - 1) \left( \phi + \sqrt{2}C_0 \epsilon \right) \right)^2 \right] \text{d}x. \quad (56)$$

If $k_d \neq 0$, we can similarly formulate the last term of (54).

For a weakly compressible and extensible membrane, we modify the elastic energy as following:

$$f_{mb} = \frac{k_B T k_b}{k_a \epsilon} \int_\Omega \left[ \tau_0 \left( \frac{\epsilon}{2} \|\nabla \phi\|^2 + \frac{1}{4\epsilon} (1 - \phi^2)^2 \right) + \epsilon \left( \Delta \phi - \frac{1}{\epsilon^2} (\phi^2 - 1) \left( \phi + \sqrt{2}C_0 \epsilon \right) \right)^2 \right] \text{d}x + M_1 (A(\phi) - A(\phi(t_0)))^2 + M_2 (V(\phi) - V(\phi(t_0)))^2, \quad (57)$$

where $M_1$ and $M_2$ are penalizing constants. In this formulation, we penalize the volume and surface area difference to limit the variation of the two conserved quantities as in Du et al. [31–34, 36]. We can drop the surface tension term since we are penalizing it in the energy potential already.
\[ f_{mb} = \frac{k_B T \kappa_b}{k_a \varepsilon} \int_\Omega \left[ \epsilon \left( \Delta \phi - \frac{1}{\epsilon^2} (\phi^2 - 1) \left( \phi + \sqrt{2} C_0 \varepsilon \right) \right)^2 \right] \, dx \]
\[ \quad + M_1 (A(\phi) - A(\phi(t_0)))^2 + M_2 (V(\phi) - V(\phi(t_0)))^2. \] (58)

This will be the free energy density used in our cell model.

We denote \( v \) as the velocity of the mixture, and \( p \) the hydrostatic pressure. We denote by \( \rho_1 \) the mass density of the fluid outside the membrane and inside the core and by \( \rho_2 \) the mass density of the mixture in the cytoplasm. We assume the material is incompressible in both domains, i.e., \( \rho_1 \) and \( \rho_2 \) are constants. The density of the mixture is defined as

\[ \rho = \frac{\rho_1}{2} (1 - \phi) + \frac{\rho_2}{2} (1 + \phi). \] (59)

From mass conservation, we have

\[ \nabla \cdot v = - \frac{\rho_2 - \rho_1}{\rho_1 + \rho_2} \frac{d\phi}{dt}. \] (60)

This is true when

\[ \frac{d\phi}{dt} + \phi \nabla \cdot v = - \frac{1}{\lambda} \mu. \] (61)

Here, \( \frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + v \cdot \nabla \phi \) is the material derivative and \( \mu \) is the chemical potential of the material system.

If we use

\[ \frac{d\phi}{dt} = - \frac{1}{\lambda} \mu \] (62)

to transport \( \phi \), the continuity equation should be

\[ \nabla \cdot v = - \frac{\rho_2 - \rho_1}{\rho} \frac{d\phi}{dt}. \] (63)

The balance of linear momentum is governed by

\[ \rho \frac{dv}{dt} = \nabla \cdot (-p I + \tau) + F_e, \]
\[ \tau = \tau_1 + \tau_2, \] (64)

where \( \tau_1 \) is the stress tensor for the fluid outside the membrane and inside the core, \( \tau_2 \) is the stress tensor inside the cytoplasmic region, and \( F_e \) is the external force exerted on the complex fluid.
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Constitutive equations:

We assume the ambient fluid material surrounding the cell is viscous, whose extra stress is given by the viscous stress law:

$$\tau_1 = (1 - \phi) \eta_1 \mathbf{D},$$  \hspace{1cm} (65)

where $\mathbf{D} = \frac{1}{2} [\nabla \mathbf{v} + (\nabla \mathbf{v})^T]$ is the rate-of-strain tensor for the mixture. The viscosities outside the cell and inside the core are distinct.

The extra stress for the cytoplasm is a volume-fraction weighted stress:

$$\tau_2 = (1 + \phi) \eta_s \mathbf{D} + \tau_p,$$  \hspace{1cm} (66)

where $\eta_s$ is the zero shear rate viscosity and $\tau_p$ is the viscoelastic stress [40].

The total free energy for the complex fluid mixture system is given by

$$f = f_{mb} + f_n,$$  \hspace{1cm} (67)

where $f_n$ is the free energy associated to the active cytoplasmic material:

$$f_n = f_n(\phi, \mathbf{Q}, \nabla \mathbf{Q}),$$  \hspace{1cm} (68)

where $\mathbf{Q}$ is the orientation tensor in cytoplasm with $tr(\mathbf{Q}) = 0$. It is zero outside the cell. We denote the chemical potential with respect to $\phi$ by

$$\mu = \frac{\delta f}{\delta \phi}.\hspace{1cm} (69)$$

The time evolution of the membrane interface is governed by the Allen–Cahn equation

$$\frac{d\phi}{dt} = -\frac{1}{\lambda_1} \mu,$$  \hspace{1cm} (70)

where $\lambda_1$ is a relaxation parameter. The Cahn–Hilliard dynamics can also be used if we assume the volume conservation without additional constraint:

$$\frac{d\phi}{dt} = \nabla \cdot (\lambda_1 \nabla \mu),$$  \hspace{1cm} (71)

where $\lambda_1$ is the mobility parameter which has different physical units than the analogous parameter in the Allen–Cahn dynamics. In this latter case, the term $V(\phi) - V(\phi_0)$ is identically zero in the energy potential and can be dropped from the surface energy expression.
The transport equation for the orientation tensor $Q$ is proposed as following

$$
\frac{dQ}{dt} + W \cdot Q - Q \cdot W - a[D \cdot Q + Q \cdot D] = + \frac{a(1 + \phi)D}{3} - 2aD : (Q + (1 + \phi)I/6)(Q + (1 + \phi)I/6) + \Gamma H + \lambda_2 Q.
$$

(72)

where $\lambda_2$ is an active parameter, $W$ is the vorticity tensor, $D$ is the rate of strain tensor, $H = -\frac{\partial f}{\partial Q} - tr(\frac{\partial f}{\partial Q})(1 + \phi)I/6$ is the so-called molecular field and $f_n$ is the free energy density associated with the orientational dynamics given by

$$
f_n = A_0 \left(\frac{1 + \phi}{2}\right)^r \left[\frac{1}{2} (1 - N/3) Q : Q - \frac{N}{3} tr(Q^3) + \frac{N}{4} (Q : Q)^2\right] + \frac{(1 + \phi)^r K}{2r+1} (\nabla Q : \nabla Q) + f_{\text{anch}}.
$$

(73)

where $r = 1$ is a positive integer, $N$ is the dimensionless concentration, $K$ is an elastic constant, and $f_{\text{anch}}$ is the anchoring potential [12].

**Elastic stress**

The elastic stress is calculated by the virtual work principle [29]. Consider a virtual deformation given by $E = \nabla \delta v \delta t$. The corresponding change in the free energy is given by

$$
\delta f = \mu \frac{\partial \phi}{\partial t} \delta t - H : \frac{\partial Q}{\partial t} \delta t.
$$

(74)

The variation of $\phi, Q$ are given, respectively, by

$$
\delta \phi = \frac{\partial \phi}{\partial t} = - \nabla (\phi \delta v) \delta t,
$$

$$
\delta Q = \left[ - \nabla \cdot (\nabla Q) + W \cdot Q - Q \cdot W + a[D \cdot Q + Q \cdot D] + \frac{a(1 + \phi)}{3} D - 2aD : (Q + (1 + \phi)I/6)(Q + (1 + \phi)I/6) \right] \delta t.
$$

(75)

So, the elastic stress is calculated as

$$
F_e = -\phi \nabla (\mu) + \nabla (H_{ij}) Q_{ij},
$$

$$
\tau_p = -(H \cdot Q - Q \cdot H) - a(H \cdot (Q + (1 + \phi)I/6) + (Q + (1 + \phi)I/6) \cdot H) + 2a(Q + (1 + \phi)I/6) : H(Q + (1 + \phi)I/6) - \zeta Q.
$$

(76)
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where $\zeta < 0$ (respectively, $\zeta > 0$) represents a contractile (respectively, extensile) filament.

$$\mu = \frac{\delta f_n}{\delta \phi} + \frac{\delta f_{mb}}{\delta \phi}$$

$$= \frac{\delta f_n}{\delta \phi} - 4M_1 (A(\phi) - A(\phi_0)) \kappa_a \left( \nabla^2 \phi + \frac{2}{\varepsilon^2} \phi (1 - \phi^2) \right) + M_2 (V(\phi) - V(\phi_0)) + \frac{2 \phi (\phi^2 - 1)}{\varepsilon^2} + k_e \epsilon \left[ \nabla^2 \left( \nabla^2 \phi - \frac{1}{\varepsilon^2} (\phi^2 - 1) \left( \phi + \sqrt{2} C_0 \epsilon \right) \right) \right]$$

$$- \frac{2}{\varepsilon^2} \left( \nabla^2 \phi - \frac{1}{\varepsilon^2} (\phi^2 - 1) \left( \phi + \sqrt{2} C_0 \epsilon \right) \right) \phi \left( 3 \phi^2 + 2 \sqrt{2} C_0 \epsilon \phi - 1 \right)$$

$$H = -\frac{A_0 (1 + \phi)^{\gamma}}{2r^2} \left[ (1 - N/3) Q - N Q^2 + N Q : Q \left( Q + \frac{(1 + \phi) I}{6} \right) \right]$$

$$+ \frac{K}{2r} \nabla \cdot (((1 + \phi)^\gamma \nabla Q) - \frac{\delta f_{anch}}{\delta Q}. \right) \right) (77)$$

### 4.1 Approximate Model

We impose a solenoidal velocity field

$$\nabla \cdot v = 0. \quad (78)$$

Then, the model can be simplified further.

$$\frac{d\phi}{dt} = \frac{1}{\lambda_1} \mu,$$

$$\rho \frac{dv}{dt} = \nabla \cdot (-p I + \tau) + F_c,$$

$$\rho = \frac{(1 - \phi)}{2} \rho_1 + \frac{(1 + \phi)}{2} \rho_2,$$

$$\tau = \tau_1 + \tau_2, \tau_1 = (1 - \phi) \eta_1 D, \tau_2 = (1 + \phi) \eta_2 D + \tau_p.$$
\[ \tau_p = - (\mathbf{H} \cdot \mathbf{Q} - \mathbf{Q} \cdot \mathbf{H}) - a (\mathbf{H} \cdot (\mathbf{Q} + (1 + \phi) I/6) + (\mathbf{Q} + (1 + \phi) I/6) \cdot \mathbf{H}) \]
\[ + 2a (\mathbf{Q} + (1 + \phi) I/6) : \mathbf{H}(\mathbf{Q} + (1 + \phi) I/6) - \zeta \mathbf{Q}, \]
\[ \frac{d\mathbf{Q}}{dt} + \mathbf{W} \cdot \mathbf{Q} - \mathbf{Q} \cdot \mathbf{W} - a [\mathbf{D} \cdot \mathbf{Q} + \mathbf{Q} \cdot \mathbf{D}] = \frac{a(1 + \phi)}{3} \mathbf{D} \]
\[ -2a \mathbf{D} : (\mathbf{Q} + (1 + \phi) I/6)(\mathbf{Q} + (1 + \phi) I/6) + \Gamma \mathbf{H} + \lambda_2 \mathbf{Q}, \]
\[ \zeta = \zeta_0 (1 + \phi), \lambda_2 = \lambda_2^0 (1 + \phi), \Gamma = \Gamma_0 (1 + \phi). \tag{79} \]

where \( \zeta_0 \) and \( \lambda_2^0 \) are parameters which depend on regulatory proteins such as the Rho family of GTPases for the active gel. As a proof-of-principle illustration for this article, we assume these activation parameters are prescribed functions of space and time.

**Remark.** (i) What should the anchoring condition be at the membrane interface?

The anchoring potential density is given by

\[ f_{\text{anch}} = W_0 \left( 1 - \phi^2 \right) \left[ \alpha_1 \left( \mathbf{Q} + \frac{(1 + \phi) I}{6} \right) : (\nabla \phi \nabla \phi) \right. \]
\[ \left. + \alpha_2 \left( \| \nabla \phi \|^2 - \left( \mathbf{Q} + \frac{(1 + \phi) I}{6} \right) : (\nabla \phi \nabla \phi) \right) \right] \]
\[ = W_0 \left( 1 - \phi^2 \right) \left[ (\alpha_1 - \alpha_2) \left( \mathbf{Q} + \frac{(1 + \phi) I}{6} \right) : (\nabla \phi \nabla \phi) + \alpha_2 \| \nabla \phi \|^2 \right], \tag{80} \]

where \( \alpha_2 = 0 \) gives the tangential anchoring and \( \alpha_1 = 0 \) gives the normal anchoring. Then, the variations of the potential are given by

\[ \frac{\delta f_{\text{anch}}}{\delta \mathbf{Q}} = (\alpha_1 - \alpha_2) W_0 \left( 1 - \phi^2 \right) \left( \nabla \phi \nabla \phi - \frac{I}{3} \| \nabla \phi \|^2 \right), \]
\[ \frac{\delta f_{\text{anch}}}{\delta \phi} = -2\phi W_0 \left[ (\alpha_1 - \alpha_2) \left( \mathbf{Q} + \frac{(1 + \phi) I}{6} \right) : (\nabla \phi \nabla \phi) + \alpha_2 (\| \nabla \phi \|^2) \right] \]
\[ -2W_0 \left( 1 - \phi^2 \right) \left[ \alpha_2 \nabla^2 \phi + (\alpha_1 - \alpha_2) \nabla \cdot \left( \left( \mathbf{Q} + \frac{(1 + \phi) I}{6} \right) \cdot \nabla \phi \right) \right] \]
\[ + \frac{W_0(\alpha_1 - \alpha_2) \left( 1 - \phi^2 \right)}{6} \| \nabla \phi \|^2. \tag{81} \]

We need to update the \( \mathbf{H} \) and \( \mu \) using the above equations.

(ii) How do we deal with the core of the cell? If we don’t want to introduce additional variables and equations, we could use the same membrane equation at the cytoplasm-core interface. The viscosity at the core will have to be much higher than the viscosity in the fluid outside the cell. An alternative is to introduce a second phase variable \( \psi \) to deal with the interface between the cytoplasm and the core.
In the following, we apply the multiphase complex fluid cell model to an active cortical layer near the membrane. Everything outside the layer is treated as a viscous fluid for simplicity. Our goal is to investigate how this cytoskeletal-membrane coupled model responds to an imposed ATP-activated stress in the cortical layer.

5 Numerical Results and Discussion

The coupled flow and structure equations are solved using a spectral method in 2D built from analogous multiphase phase field codes [98, 120, 122]. The computed domain size is $[0, 1] \times [0, 1]$, which we emphasize encompasses the cell and ambient viscous fluid. The number of grid points in each direction for the reported simulations is 256. The parameters used are $k_a = 0.01, K = 0.01, M_1 = 0.1, M_2 = 1, k_BT = 1 - 9, \lambda_1 = 1, \lambda_2 = 0.001, a = 0.8, N = 6, \Gamma = 0.2, \xi_0 = 4, \eta_1 = 1, \eta_8 = 1, W_0 = 0.01, \epsilon = 0.02$.

5.1 Activation of a Local Domain in the Cortical Layer

In this simulation, we impose the active region on the left side of the cell within the cortical layer. The initial shape of the cell and active region are shown in Fig. 1. As time evolves, the activated region induces a protrusion in the membrane and cortical

![Fig. 1 Initial shape and activation domain are indicated by the contours](image-url)
Fig. 2 Snapshots of cell activation and subsequent movement at $t = 0.1, \cdots, 80$. The anchoring condition is not enforced at the membrane ($\alpha_1 = \alpha_2 = 0$). The cell migrates to the direction where the cortex layer is activated.

layer due to the activation of the nematic cortical layer. The cell deformation and translational motion are simulated with respect to variations in the energy associated with tangential anchoring conditions in the diffuse interface layer between the membrane and nematic cortical layer: without enforcing an anchoring condition, a weak anchoring condition, and then strong anchoring.

In order to conserve the cell volume, the entire cell undergoes a deformation represented by a passive retraction on the opposite side of the cell, leading to clear cell migration to the left. The activation domain pulls the cell in its direction. Several snapshots are shown in Figs. 2, 3, 4. Figures 5, 6, 7 contrast the cell membrane profile at select times in the interval $t = [0.1, 80]$ to show cell movement. Recall that we track the membrane by the zero level set of the phase variable.
Fig. 3 Snapshots of cell activation and subsequent movement at $t = 0.1, \ldots, 80$. Tangential anchoring energy is enforced in the diffuse interface between the membrane and cortical layer with $(\alpha_1 = 0.1, \alpha_2 = 0)$. The cell migrates to the direction where the cortex lay is activated.

We first simulate the cell movement under the influence of local activation of the nematic phase in the cortical layer without explicitly enforcing an anchoring boundary condition at the membrane (the diffuse interface). The activation affects both the membrane and the interface between the cortical layer and the interior cytoplasm/cytosol region. Both outward and inward protrusion of the cortical layer are shown in Fig. 2. We then repeat the simulation with the same set of model parameters while allowing for tangential anchoring energy at the membrane. The protrusion is reduced in magnitude. However, the inward invasion nearly disappears while the cell membrane bulges slightly on both sides of the prominent protrusion. This is depicted in Fig. 3 with a few selected snapshots. In the third numerical experiment, we impose the tangential anchoring condition at the membrane with
Fig. 4 Snapshots of cell activation and subsequent movement at $t = 0.1, \ldots, 80$. Tangential anchoring energy is enforced in the membrane-cortical layer diffuse interface ($\alpha_1 = 0.5, \alpha_2 = 0$). The cell migrates to the direction where the cortex lay is activated an enhanced anchoring energy. The resulting deformations of the membrane and cortical layer demonstrate an outward protrusion and a propagation of the cortical layer deformation reminiscent of a slice of a cortical ring contraction wave.

5.2 Active Regions Alternating on Opposing Sides of the Cell

We impose time-dependent activation to two regions located on opposite sides of the cortical layer within the cell membrane. This imposed activation scheme is motivated by the compartment model of [5,61] where there are positive and negative
feedback loops of protein species on either side of the cell. The region on the left is first activated for $t \in (0, 6)$. At $t = 6$, the active region on the left is turned off while an active region on the right is started until the end of the simulation at $t = 40$. The dynamical process is shown in Fig. 8. Due to longer activation at the right, the cell exhibits a protrusion on the right.

This formulation is now amenable to reaction–diffusion of protein species or other components whose concentrations provide the activation potential in the cortical layer. These features are necessary to explore the possible simulation within this framework of the cell oscillation modes identified in the Jacobson lab [61] and modeled by Allen and Elston [5]. To be biologically useful, many features in these illustrative simulations will need to be based on experimental data. For example, we have not attempted to use consistent cell membrane properties, cortical layer properties, cytosol viscoelastic properties, nor have we introduced a cell nucleus phase. The detailed biochemical species, and their reaction and diffusion rates as well as activation potentials, have to be integrated into the model, as well as constraints for proteins that are bound to the membrane and cortical layer. The addition of substrate boundary conditions instead of an ambient viscous fluid is relatively straightforward to put into the model, yet experimental data on the appropriate surface energies is needed.

Fig. 5 The profile of the cell conformation at $t = 80$ contrasted with the initial shape at $t = 0$
Fig. 6 The profile of the cell conformation at $t = 80$ contrasted with the initial shape at $t = 0.1$ for tangential membrane-cortical layer anchoring energy with $\alpha_1 = 0.1, \alpha_2 = 0$

6 Conclusion

We have surveyed recent theoretical and numerical developments that are relevant to modeling of cell motility. We have integrated many of these advances into a phase field model of the cell with multiple substructures (the ambient fluid, bilayer membrane, nematic cortical layer, and internal cytosol) with an activation potential in the cortical layer that resolves chemical–mechanical transduction. For this chapter, we have imposed the activation domains, amplitudes, and timescales, which in the future will be triggered by biochemical processes. The simulated phase field model exhibits plausible cell morphology dynamics, which are only a cartoon at this point. To make the model and simulations more biologically relevant, we plan to use experimental characterizations of the physical properties of the membrane, cortical layer, cytoplasm, and nucleus, and biochemical kinetics of reacting and diffusing G protein species which trigger activation and deactivation.

Acknowledgments Wang’s research is partly supported by National Science Foundation grants CMMI-0819051 and DMS-0908330. Yang’s research is supported in part by the army research office (ARO) W911NF-09-1-0389. Forest’s research is supported in part by grants NSF DMS-0908423 and DMS-0943851.
Fig. 7 The profile of the cell conformation at $t = 80$ compared with the shape at $t = 1$ for tangential anchoring in the membrane-cortical layer diffuse interface, where $\alpha_1 = 0.5, \alpha_2 = 0$.

Fig. 8 Activation in the cortical layer on opposing sides of the cell, from $t = 2 - 40$ in equal increments. The active part on the LHS is shut down at $t = 6$ and the RHS is activated for the next 34 time units. Tangential anchoring energy is enforced with $\alpha_1 = 0.1, \alpha_2 = 0$. 
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AQ4
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AUTHOR QUERIES

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