Modern Modeling of Single-Cell Migration: From Membrane Tension and Galvanotaxis to Machine Learning

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Cell migration phenomenon has inspired and benefited from computational modeling for decades. Here, we review recent applications of traditional bottom-up modeling to three aspects of cell migration: the role of membrane tension (MT) in organizing directional cell motility, the role of the electric field (EF) as the directional cue for migration, and the mechanics of three-dimensional migration. We then discuss nascent applications of machine learning (ML) to cell migration and galvanotaxis. We focus on the migratory mechanisms of the single cell and highlight the feedback between theory and experiment.

Cells migrate individually and in cohesive groups in many physiological processes, including wound healing, metastasis, immune response, and embryogenesis (SenGupta et al. 2021). A useful way to break down the phenomenon of cell migration is to think of it as the interaction of three dynamic processes—cell motility, polarization, and directional sensing (Shi et al. 2013). Namely, a cell must generate motility (protrusions and retractions around its periphery), and then it must polarize the protrusions to the front and retractions to the rear, and finally, it has to orient the rear–front axis in response to an external cue.

Several decades of using microscopy on single cells migrating in vitro on flat hard surfaces brought a detailed mechanistic understanding of each of these three processes (Blanchoin et al. 2014). In recent years, the focus has started to shift to multicellular migration (Shi et al. 2025) but studying individual migrating cells is not over. Even understanding of 2D cell migration is full of holes, and quantitative research on cells crawling through 3D tissues and the extracellular matrix (ECM) is still in its infancy (Yamada and Sixt 2019).

There are many excellent and comprehensive reviews of the cell biology of the migration phenomenon, for example (Blanchoin et al. 2014; Rappel and Edelstein-Keshet 2017; Van Helvert et al. 2018; SenGupta et al. 2021), which explain the interlinked action of actomyosin network mechanics and signaling pathways needed for motility, polarity, and directional sensing to self-organize and synergize. Even the number of reviews on the modeling of cell migration is great, we refer the reader to a few of them (Danuser et al. 2013; Buttenschön and

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Edelstein-Keshet 2020; DiNapoli et al. 2020). Due to the amount of attention paid to cell migration, choosing what else needs to be said is not an easy task. In this review, we decided to focus on three modern modeling problems, each related to the respective fundamental process of migration—mechanics of motility, migratory polarity, and direction sensing. We review several modeling frameworks applied to simulate single cells crawling through the 3D ECM, modeling the role of membrane tension (MT) as a global inhibitor in cell polarity maintenance, and nascent modeling of cells using electric fields (EFs) to navigate wounds. Lastly, we address initial efforts to change the modeling paradigm and embrace machine learning (ML) to predict traction forces (TFs) and learn migratory trajectories.

Two notes to mention are, in general, there are two modes of cell migration. One is called mesenchymal migration, in which a growing actin network generates protrusion, firm adhesion of the protrusion to the substrate, and actomyosin contraction to pull up the rear. Another is amoeboid motility (Callan-Jones 2022), in which cytoplasmic pressure is harnessed to generate a protrusion, and then actomyosin contraction causes a retrograde flow of an actin cortex, the friction of which against the ECM propels the cell. Here, we mostly discuss the mesenchymal migration. Second, even after narrowing the scope, we cannot discuss and cite a great number of relevant papers, for which we apologize.

MEMBRANE TENSION IN CELL MOTILITY

The well-understood mode of cell migration is 2D mesenchymal motility. However, one of its important aspects, the role of MT in maintaining motile cell polarity, has only recently become quantitatively elucidated. The number of publications on this topic is not too great, and several reviews of cell biological (Blanchoin et al. 2014; Van Helvert et al. 2018) and biophysical (Keren 2011; Diz-Muñoz et al. 2013; Sens and Plastino 2015; Sitarska and Diz-Muñoz 2020) aspects of this topic provide a very helpful guide to the MT role. Here, we focus on the plasma membrane and refer to it as "the membrane."

About 15 years ago, early models explained how motile cells could use the peculiar physics of the lipid membrane to serve as a global mechanical inhibitor: the membrane is a nonstretchable 2D fluid (Keren 2011), so if the membrane is tensed locally, the elevated MT spreads globally throughout the cell surface on a subsecond scale (Kozlov and Mogilner 2007). The main source of this local MT is pushed by the growing branched actin network on the inside of the membrane (Lieber et al. 2013). Nowhere does this simplistic concept work better than in one of the fastest cell types—fish epidermal keratocyte—in which the large motile appendage, lamellipodium, is a wide and flat actin network polymerizing against the unfolded and unconnected to the actin membrane. According to the simplest model of the lamellipodium (Ofer et al. 2011), actin, pushing from the inside, generates the globally spread MT (Fig. 1). This MT crushes the actin network weakened by gradual disassembly at the cell rear (Pontes et al. 2017) and stops actin at the sides from protruding, so that the actin network treadmills, polymerizing at the front, retracting at the rear, and disassembling throughout the lamellipodium. This model explains how this steady motility can be maintained even without the contractile action of myosin (Ofer et al. 2011). In the laboratory coordinate system, the actomyosin network is essentially immobile due to firm adhesions throughout the lamellipodium, away from the cell edges. Thus, in the moving cell, myosin is essentially swept to the rear, where its contractile action helps to crush the network allowing MT to retract the rear (Kozlov and Mogilner 2007; Gauthier et al. 2011) in sync with the protruding front. According to both experiments and models, high MT also helps compress and realign the actin network, enhancing the contractile action at the rear (Gauthier et al. 2011; Lomakin et al. 2015). Another model, based on experiments with motile nematode sperm cells, which use a network of fibers made of major sperm protein instead of actin, posited another function of MT—to compress the sides of the motile cell thereby aligning

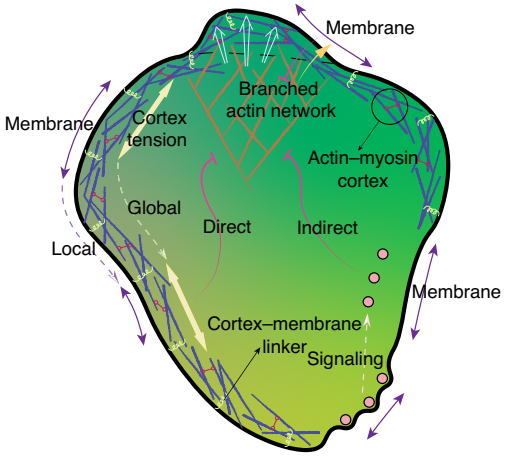

Figure 1. Membrane tension assists cell polarization at the onset of motility. Local growth of branched actin network pushes on the inside of the cell leading edge stretching membrane and generates tension. In-plane tension spreads locally in the plasma membrane, while tension propagates globally in the actin–myosin cortex. The membrane and cortex are interlinked, which, together with their complex mechanical properties and the nature of local mechanical action of the pushing force at the leading edge, fine-tunes the speed and range of the tension spread from the leading edge. The tension directly stalls actin protrusions at the cell sides and rear, thereby enabling actin–myosin contraction there. In addition, the tension could stretch out the membrane folds, releasing signaling molecules and triggering indirect regulatory pathways that selectively inhibit actin dynamics.

the growing fibers along the rear–front axis focusing the protrusion at the cell front (Batchelder et al. 2011).

As the cell crawls, the membrane envelope around the cell must be propelled forward. One respective mechanism is exocytosis at the leading edge (Gauthier et al. 2011) accompanied by endocytosis throughout the cell, together with forward motor–driven translocation of membrane vesicles in the cell (Bretscher 1984). A recent mathematical model of the cell moving in a 3D ECM integrated experimental data (Hetmanski et al. 2019) points out that MT is lower at the cell rear triggering endocytosis there. These endocytic vesicles recruit molecules activating myosin, so myosin retracts the cell rear lowering MT and creating the positive feedback loop. However, in the absence of endocytosis/exocytosis, the membrane can simply flow forward in its own plane in the motile cell. This flow is driven by the slight tension gradient: MT is elevated by the actin pushing at the front and is lower at the rear (Fogelson and Mogilner 2014; Schweitzer et al. 2014).

The first systematic investigation of the MT's polarizing effect was conducted in a seminal study on neutrophils (Houk et al. 2012). The authors (Houk et al. 2012), after establishing the global inhibitory effect of MT on protrusions away from the leading edge of these cells of the immune system, asked whether this effect is not the direct and immediate mechanical effect, as in the keratocyte models, but rather an indirect action of signaling molecules, activated by the leading edge protrusions, diffusing to the cell rear and triggering a reaction that inhibits the protrusions there. Elegant experiments with bilobed cell shapes with a long and narrow corridor between one protruding and one passive lobe and simulations of two plausible reaction–diffusion models on these shapes demonstrated that such indirect mechanisms would be much slower than observed, leaving the rapidly and globally spreading MT (Fig. 1) as the only factor explaining the measurements (Houk et al. 2012).

It turned out that not only direct mechanical tension but also additional mechanosensory feedback, indirectly linking MT with actin assembly, stalls the side and rear protrusions (Diz-Muñoz et al. 2016). Specifically, elevated MT acts globally through signaling molecules to limit actin nucleation (Fig. 1). How exactly these signaling molecules are affected by MT is not yet known, but a very recent study (Quiroga et al. 2023) hints at the following possibility: at low MT, the membrane bends and folds creating local evaginations, to which curvature-sensing proteins can bind and potentially deactivate the actin inhibitors. High MT stretches out the membrane causing unbinding of the curvature-sensing proteins reactivating the actin inhibitors (Fig. 1). Mathematical modeling suggests roles for both direct (mechanical) and indirect (mechanochemical) feedbacks in organizing cell polarity and motility (Diz-Muñoz et al. 2016): the

indirect feedback leads to competition between multiple protrusions, essential for nimble path finding, while the direct feedback spatially restricts the protrusion to the single wide leading edge for persistent movement.

The early successes of the MT modeling were thrown into doubt by the more recent study (Shi et al. 2018), which demonstrated a relatively slow (minutes rather than seconds) and not global MT propagation around the source of MT tension. However, the latest study (De Belly et al. 2023), employing both modeling and experiment, offers an elegant and convincing explanation for the controversy. This study draws attention to the fact that in most cell types (keratocyte is but a rare exception), the membrane is underlined by the thin shell of the actomyosin cortex, linked to the membrane by multiple proteins (Fig. 1). De Belly et al. (2023) found that a global MT propagation occurs either after an optogenetic activation of local cortex contraction (not directly affecting the membrane) or during micropipette aspiration experiments that exert a tugging force on the cell envelope locally and directly affecting both membrane and cortex. In contrast, pulling a membrane tether (not directly affecting the cortex) did not lead to global MT propagation (Fig. 1). These results are explained by a mathematical model (De Belly et al. 2023), which treats the membrane as an elastic contour, the cortex as a viscous, and contractile contour and links between them as elastic links. We find it difficult to explain the results of this model's simulations intuitively, but they show that in certain parameter ranges, the model accounts for all three experimental results.

An alternative recent model (Barnoy et al. 2023; Dharan et al. 2025) looks at the same problem from a different angle. This model posits that the membrane is subdivided into submicron compartments by a network of transmembrane protein "picket-fences." These fences are hydrodynamic barriers for the in-plane membrane flow. According to the model, the propagation speed of MT perturbations on the cell surface is set by the intracellular pressure and hydrodynamic permeability of the fences and can vary by several orders of magnitude, so that MT spreads globally and fast at high cytoplasmic pressures and only locally and slowly at low cytoplasmic pressures.

Three recent modeling studies make additional predictions for the MT role. All these models simulate motile cells as free boundary bodies, so the boundary contours (cell edges) in 2D protrude and retract locally according to some dynamic rules. The first of these models (Chen et al. 2023) considers adhesion linkers that turn over and diffuse along the cell periphery, detaching at a force-dependent rate, while the local force is set by MT. The local protrusion/retraction rates are then set by the local linkers' density and MT. This model predicts an instability of a randomly perturbed, nonpolar cell shape, and that different MT levels can result in diverse motility modes, including gliding, zigzagging, rotating, and chaotic movements.

The second, most detailed model couples MT, actin, and myosin dynamics with the action of Rac/Rho molecules regulating actin and myosin (Tao et al. 2020). Simulations of this model predict that there is an optimal tension for rapid migration: the low tension allows multiple protrusions in random directions without persistent motile progress and the high-tension stalls protrusion everywhere. The latter conclusion is also reached by the third model (Winkler et al. 2016) in which the "phase field," which determines dynamic cell shape and area, is coupled to the evolving "polarization field" variable, describing the average local orientation of actin filaments inside the cell and to MT that effectively attenuates actin dynamics.

QUANTITATIVE UNDERSTANDING OF GALVANOTAXIS

Motile and polarized cells orient their rear–front axis in response to multiple external signals. Many such "taxis" behaviors were studied; the most researched of these is chemotaxis (Shi et al. 2013), a response to spatial chemical gradients, but other biased migration (i.e., topotaxis [response to ECM density gradients] and durotaxis [response to gradients in ECM stiffness]) also received attention (SenGupta et al. 2021). Here, we focus on galvanotaxis—the directional re-

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sponse of migrating cells to an EF (Chang and Minc 2014). Physiological EFs, generated by inhomogeneous transepithelial ion flows, are ubiquitous in wounds and developing embryos (Chang and Minc 2014). Normally, the cathode (negative EF terminal) is in the wound, and several types of migrating cells move to the cathode closing and repairing the wound in the healing process (Zhao 2009). Importantly, several experiments established that EF overrides other directional signals, such as chemotaxis (Zhao 2009; Sun et al. 2019). Mathematical modeling of cells navigating chemotactic gradient and EF simultaneously was reported in Vanegas-Acosta et al. (2012). However, very little modeling of galvanotaxis was done, and here we review these modeling efforts.

Galvanotaxis uses the same intracellular signaling pathways that guide motile cytoskeletal machinery as chemotaxis (Zhao et al. 2006), and the latter was extensively studied, both experimentally and theoretically (Shi et al. 2013). Thus, the main question about galvanotaxis is what the EF sensors are upstream of the intracellular signaling pathways. As the cell cytoplasm is an electric conductor, the low-frequency physiological EF does not penetrate the cell (Taghian et al. 2015), and the EF sensors must be on the cell surface. Four biologically relevant EF-sensing mechanisms are (Fig. 2; Allen et al. 2013) (1) EF-sensitive ion channels can be differently affected on the cathodal and anodal (negative and positive EF terminals, respectively) cell sides. This mechanism is known to orient the growth of bacteria and yeast cells (Chang and Minc 2014). There is also an interesting mathematical model showing that if, for example, ion channels on the cell front/rear are opened/closed, respectively, then ion influx creates a high osmotic pressure near the leading edge, which can generate a local water influx inflating the cell front and effectively driving the cell movement (Fig. 2; Li et al. 2015). However, for epithelial migrating cells, this mechanism was ruled out experimentally (Allen et al. 2013). (2) The cell surface has a net charge (McLaughlin and Poo 1981), so a small Coulomb force acts on the whole cell in EF, tugging the cell to either cathode or anode. A mathematical model demonstrated that such force can significantly bias the swimming of some cell types (Ogawa et al. 2006), yet again, for epithelial migrating cells this mechanism is highly unlikely (Allen et al. 2013). (3) Extracellular fluid is an electrolyte, and EF generates the so-called electro-osmotic flow: mobile counterions near the cell surface are pulled by EF to either the cathode or anode and the ions drag the extracellular fluid with them. The resulting force from this flow is too small to affect the cell directly (Allen et al. 2013), but this flow can drag mobile membrane proteins with charged residues outside the cell to

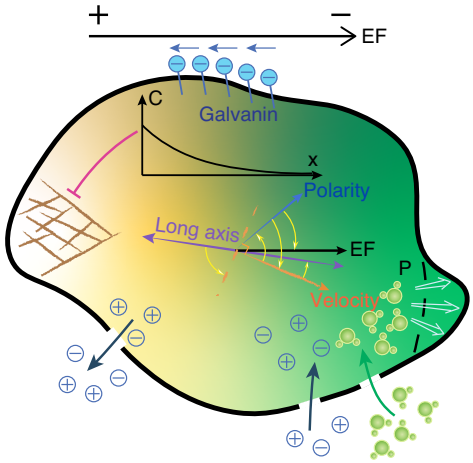

Figure 2. Electric field (EF) orients migrating cells. An electric field drives negatively charged mobile membrane proteins (Galvanin) to the anodal (positive terminal) side of the cell, generating a concentration (C) gradient of this protein and inhibiting protrusion at that side thereby enabling the cell to polarize toward the cathode (negative terminal). Another potential orientation mechanism is based on the differential opening/closing of voltage-sensitive membrane ion channels at the anodal/cathodal cell sides, respectively, leading to the respective outflow/inflow of ions. The resulting high ion concentration at the cathodal cell side creates local osmotic pressure and influx of water through aquaporin channels. Combined local pressure (P) generates protrusion toward the cathode. Hypothesized feedback in a model of cell orientation in an electric field are shown in the center: cell polarity vector aligns with the cathodal direction and turns to the velocity vector; in turn, velocity rotates to the polarity vector and pivots to the cell long axis. Lastly, the cell's long axis adjusts perpendicularly to the velocity.

one of the cell sides (McLaughlin and Poo 1981). (4) EF applies Coulomb force to the mobile membrane proteins with charged residues outside the cell causing the so-called electrophoresis of these proteins and their accumulation to one of the cell sides (Fig. 2; McLaughlin and Poo 1981; Allen et al. 2013). Biophysical experiments reported in Allen et al. (2013) demonstrated indirectly that the accumulation of charged mobile membrane proteins to one of the cell sides is the most likely EF-sensing mechanism.

Recently, a seminal study (Belliveau et al. 2024) appeared reporting experimental proof that a highly negatively charged mobile membrane protein Galvanin is biased to the anodal side of the migrating cell. As soon as a threshold accumulation of Galvanin at the anodal side is reached, the net protrusion at that side is stalled (Fig. 2), and the cell starts biased migration to the opposite, cathodal side. Galvanin is likely either a direct part of the signaling relay affecting actomyosin dynamics downstream or is a binding partner to a key intracellular signaling molecule.

Simple galvanotaxis-related mathematical models have addressed related redistribution of the charged mobile membrane proteins in EF. The earliest of such models showed that electro-osmotic flow can counteract the Coulomb force and, depending on cell surface charges, can move the charged mobile proteins to either the cathodal or anodal side of the cell (McLaughlin and Poo 1981). A detailed model of electro-osmotic flow was considered in Sarkar et al. (2019). Allen et al. (2013) analyzed the drift-diffusion model for the charged protein moving along the membrane and derived formulas for steady protein concentration gradient in EF and the time scale for gradient development (Fig. 2; Allen et al. 2013).

Another mathematical model, supported by microscopy data (Lin et al. 2017), demonstrated that in addition to individual charged proteins, highly charged glycolipid redistribution in EF can be an alternative candidate as the primary EF sensor. This study showed that rather than individual glycolipids, charged lipid rafts polarized to the cathode in EF, while in the randomly migrating cells without EF, no preferential raft distribution was found. In EF, the rafts merged and increased in size while approaching the cathode, which decreased the raft mobility and stabilized their cathodal bias. Several signaling molecules were shown to colocalize with the rafts to the cathode, while their distributions were not spatially biased in the absence of EF.

Three quantitative models were applied to learn the principles of galvanotaxis from analyses of cell trajectories in EF. The earliest of these theories (Gruler and Nuccitelli 2000) modeled the orientation of the velocity vector of the motile cell undergoing a biased random walk in an angular space, so deterministic turning of this vector to the cathodal direction is juxtaposed with random velocity turns while the cell speed is independent of EF signal (Gruler and Nuccitelli 2000). Another recent model (Prescott et al. 2021) considered three additional (to the velocity bias [Gruler and Nuccitelli 2000]) possible ways by which the EF could bias the random cell turns: polarity bias of the cell, an increase of cell speed in the cathodal direction, and speed alignment with EF. The authors (Prescott et al. 2021) used experimental training data sets—cell trajectories with and without EF and a Bayesian approach to parameter inference—to compare all four possible ways of migration. They concluded that only the polarity bias effect of the EF explains the data. Finally, an ML model was applied, for the first time (Sargent et al. 2022), to forecast the direction of cell migration in EF. The ML network was trained to predict cell direction one time-step ahead, given measured cell directions at previous time points and using several hypothetical models, such as (1) velocity vector does not change in time, and (2) velocity vector is a linear function of velocity vectors of previous two time steps, etc. The model trained by the data of certain EF strengths makes successful predictions for migration in other EF strengths and in time-varying EFs.

Lastly, a very recent model of galvanotaxis, which considered not only overall cell movements but also the cell dynamic shape, was proposed (Fig. 2; Nwogbaga and Camley 2023). In this model, the following processes are postulated: the cell is characterized by separate velocity and polarity vectors that turn randomly but also

toward each other; velocity tends to turn to the cell's long axis and to align to the polarity vector; the cell elongates perpendicularly to the velocity; and polarity tends to align with EF vector. Simulations of this model, fitted to experimental data on keratocyte galvanotaxis, predicted that stiff, slow cells react to EF slowly but follow EF reliably. When cells are exposed to EF that switch direction rapidly, cells follow the average EF directions, while if the field is switched more slowly, cells follow a "staircase" trajectory.

MECHANICS OF THREE-DIMENSIONAL MIGRATION

There are important physiological examples of 2D cell migration (Labuz et al. 2023), but frequently cells migrate through the ECM, a complex 3D porous structure dominated by collagen fibers (Caswell and Zech 2018). Understanding 3D motility mechanics is complicated by the remarkable plasticity of cells switching between amoeboid and mesenchymal motility in the ECM. For example, 3D cells generate a variety of protrusions; their nucleus, which is an afterthought in 2D, becomes a limiting mechanical factor; often, cells deploy metalloproteases to cleave ECM and enlarge pore diameters on their path (Wolf et al. 2013). Modeling of the 3D motility is also hindered by much scarcer 3D microscopy data: we have only a vague idea about the ultrastructure of the 3D actomyosin networks. One of the rare exceptions is an elegant experimental study (Wilson et al. 2013) illustrating how complex 3D motile designs can become. This study discovered that the leading edge of a cell confined in a channel generates two distinct F-actin networks: an adherent network that polymerizes perpendicular to the channel walls and a "free" network that grows from the free membrane at the cell front. The authors propose that inward growth of the adherent network prevents retrograde movement of the free network enabling polymerization of the latter to be converted to forward protrusion (Wilson et al. 2013).

Despite this complexity, computational modeling of 3D cell migration through the ECM is a vigorous subfield. Early simple models of 3D random walks (Parkhurst and Saltzman 1992) and of an unstructured cell and ECM with anisotropic TFs (Zaman et al. 2005) started this effort; reviews of such modeling can be found in Rangarajan and Zaman (2008). Here, we give a limited review of the recent evolution of detailed mechanistic models of 3D migrating cells that started to deal with specific cell and ECM geometries. These models can be grouped into five categories (Fig. 3). We briefly mention biological insights from these models (so far very modest) focusing instead on the modeling frameworks. Many other notable computational models of 3D cell migration (Schlüter et al. 2012; van Oers et al. 2014; Cao et al. 2015; Heck et al. 2020; Godeau et al. 2022; Merino-Casallo et al. 2022), to mention but a few, can be loosely classified into one of the five categories that we discuss below.

First, there is a conceptually simple motile structure of the motor-clutch mechanism (Campbell et al. 2021): a dynamic adhesion clutch with a force-dependent detachment rate connects ECM fibers with the protruding end of a treadmilling segment of an actin network. Inward, the disassembling end of the actin segment is pulled to the cell body by myosin motors that obey a force–velocity relation. Effectively 1D, the motor-clutch mechanism becomes an "arm" of a cell, pulling the cell body along an ECM fiber (Fig. 3). In the efficient "cell migration simulator" (Bangasser et al. 2017; Prahl et al. 2020), the model cell resembles a spider with one cell body pulled by several such motor-clutch arms on the spiderweb of the ECM (Fig. 3). Simulations of this model make expected predictions, for example, about an ECM stiffness optimum for rapid migration that can be shifted by altering the number of active molecular motors and clutches. Despite the simplicity of this model, it has recently brought insight into glioblastoma cell migration (Hou et al. 2024). The authors of this study first reduced the 11-dimensional parameter space of the cell migration simulator to three principal mechanical parameters: motor number (responsible for myosin activity), clutch number (describing adhesion strength), and actin polymerization rate. A comparison of simulations and experiments showed

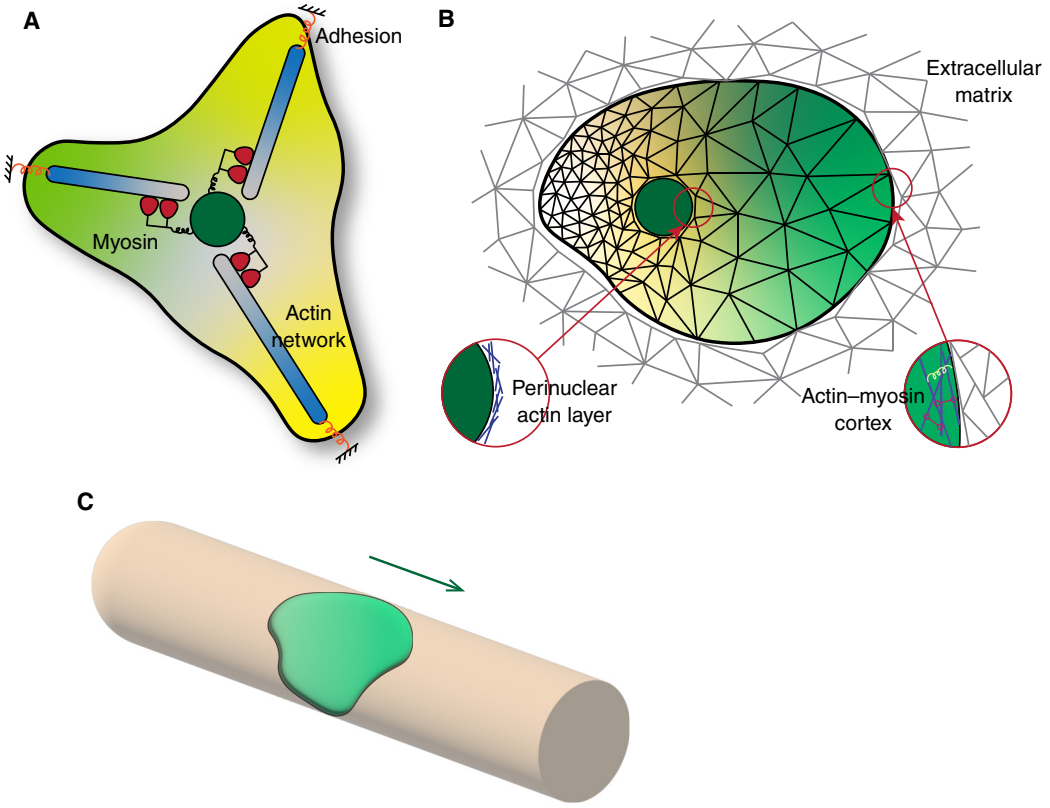

Figure 3. Mechanics of 3D cell motility. (*A*) Motor-clutch model of the cell motile mechanics: the cell has several motile appendages (arms) "grabbing and pulling" extracellular matrix (ECM) fibers. Each arm consists of an actin network that connects the cell body/nucleus, by myosin motors, to the adhesion complex (clutch). (*B*) Several models simulate the motile cell interior as an active link-node mesh, with links expanding on one side of the cell and contracting on the other. ECM is modeled as a passive link-node network. The latest models become complex and layered, differentiating between several types and dynamics of actin and myosin networks in the cell. (*C*) Phase-field models simulate the cell as a motile "active blob" migrating on a curved surface of an ECM fiber.

that glioblastoma cells balance motor/clutch ratios to enable effective migration. The authors identified 18 genes that correlated with the mechanical model parameters, suggesting that transcriptomic data alone could potentially predict the mechanics and speed of migration (Hou et al. 2024).

Second, there are 3D models of mesenchymal motile cells on top of 2D surfaces. The surfaces are not necessarily flat; for example, they can be cylindrical ECM fibers (if a cell crawls along a single fiber) or inner cylindrical walls (if a cell crawls inside a channel) (Winkler et al. 2019). In a way, one can call such models

$$2\frac{1}{2}\mathrm{D}.$$

Three modeling strategies were used to simulate the mechanics of cell shape. (1) The most direct approach, faithful to the physical reality, is to consider a cell as a physical, elastic, and/or viscous body with a free boundary, the bulk of which deforms under the action of both passive and active (myosin-powered) forces, and the boundary of which protrudes and retracts as

prescribed (Stolarska et al. 2009; Herant and Dembo 2010). Two main disadvantages of such models are the great computational challenge of simulating realistic mechanics on complex meshes and too many assumptions and parameters that are hard to constrain because of the lack of data on cell rheology. (2) Cellular Potts framework—representing the cell as a 3D set of pixels and minimizing hypothetic mechanical energy of the cell (the sum of the volume, surface, and adhesion energies) by stochastically adding and deleting surface pixels—was applied by adding protrusion and retraction forces to mimic a 3D motile cell (Fortuna et al. 2020). The advantage of this model type is in the relative ease of 3D simulations because the model is essentially a 2D model of a deformable cell surface embedded into the 3D space and clear intuitive qualitative connections to biological reality. The disadvantage is that it is not easy (but possible) (Rens and Edelstein-Keshet 2019) to connect the hypothetical energy to actual physical forces. (3) Phase-field models avoid simulating complex 3D meshes by representing dynamic cell shape as a deformable "blob," the boundaries of which smoothly protrude and retract according to evolving densities of reacting and diffusing abstract densities inside the blob (Fig. 3; Cao et al. 2019; Winkler et al. 2019). These densities can, for example, represent an activator/inhibitor pair (Cao et al. 2019) or a vector field responsible for local actin polarity (Winkler et al. 2019). The pluses and minuses of these models are somewhat like those of the cellular Potts models—ease of simulation tempered by vague connections to physical and biological realities. Impressively looking simulations of one of such models (Fig. 3) showed how ECM fiber curvature and topography modulate the cell's speed, shape, and actin organization (Winkler et al. 2019). Another model closely mimicked three observed morphodynamic behaviors of motile *Dictyostelium* cells by simply varying a couple of parameters (Cao et al. 2019).

Third, cellular Potts model cells were embedded into and made to transiently adhere to either a deformable discrete mesh of ECM fibers (Scianna et al. 2013; Tsingos et al. 2023) or deformable cells of the surrounding tissues (Bernadskaya et al. 2021). For example, Tsingos et al. (2023) made the contractile cellular Potts model cell pull with discrete adhesion sites on bead-spring ECM fiber networks. The model reproduced experimentally observed spatiotemporal fiber densification and displacement on characteristic viscoelastic ECMs.

Fourth, there are mechanical models of 2D cross-sections of 3D cells (Tozluoğlu et al. 2013; Zhu and Mogilner 2016; Maxian et al. 2020), in which the cell mechanics are modeled crudely with a simple elastic or viscoelastic cytoskeleton-like network. A pioneering model of this kind (Tozluoğlu et al. 2013), which was accompanied by experiments, represented the pressurized cell surrounded by a cell cortex membrane contour with the nodes connected by viscoelastic springs, which could either stretch, forming blebs that pried apart the ECM pores, or fold into lamellipodia-like protrusions adhering to the ECM elements. Another model of this kind (Zhu and Mogilner 2016) had a nucleus surrounded by an elastic node-link network, such that the links at one side of the nucleus contracted while expanding on the other side (Fig. 3). The cell membrane transiently adhered to the ECM node-link network. By varying parameters of this model, six different modes of locomotion were reproduced, for example, contracting the cytoskeletal mesh around the nucleus to squeeze the nucleus forward using it as a ram to push through the ECM. The disadvantages of these kinds of models are (1) reduced 2D representation of the 3D phenomenon, and (2) numerous ad hoc assumptions.

Fifth, there is a state-of-the-art, truly 3D, impressively detailed model (Fig. 3) of invadopodia (Kim et al. 2022), elongated ventral membrane protrusions that allow cancer cells to physically widen the ECM pores creating channels for migration (early, simpler models of invadopodia, i.e., Enderling et al. [2008], paved the way for Kim et al. [2022]). The authors of Kim et al. (2022) filled the 3D cell volume with the fine and layered mesh of nodes connected by lines. The lines in these structures are simulated with "spring-dashpot in parallel" elements. This viscoelastic mesh consists of triple surface layers

of (1) cell membrane, (2) force transduction layer, and (3) actin cortex layer. Underneath this triple layer is the intracellular branched actin network and the double layer of the nuclear envelope (perinuclear actin layer and nuclear membrane surface). The virtual energy method was used to compute elastic forces between the actin networks, cross-linking molecules, and myosin motors at each time step; balancing them with viscous forces generated deformations. There is a protrusive phase driven by F-actin polymerization, a retractile phase due to the contractile action of perinuclear myosin motors, and an actin disassembly phase in the model. The ECM is also a fine viscoelastic mesh. Compared to stunning images of realistically looking model cells in Kim et al. (2022), the findings from the simulations are modest, qualitative, and expected (i.e., that invadopodia speeds become faster as the protrusive phase becomes longer, and that it is impossible to generate contractile force without cross-linkers).

MACHINE LEARNING APPROACHES TO CELL MIGRATION

Traditional bottom-up models reviewed above have a relatively low-dimensional parameter space and are appropriate for understanding simple features of modest amounts of data. However, modern high-throughput cell biological methods generate data sets that contain enormous volumes of quantitative data characterized by a very high-dimensional parameter space (Rafelski and Theriot 2024). One of the tasks of modern theoretical research is to project raw data onto low-dimensional space while extracting features from the data that are relevant to studied phenomena. ML is ideally suited for this task. For example, ML was recently used to identify lamellipodia and other types of protrusion from raw images (Moshkov et al. 2024), to predict migratory trajectories from dynamic cell shapes (Schoenauer Sebag et al. 2015), to find metastatic melanoma cells (Zaritsky et al. 2021), and to predict 3D migratory behavior from 2D cell motility features (Baskaran et al. 2020).

Here, we focus on two rapidly developing applications of ML to the problem of cell migration: prediction of TFs and analysis of cell trajectories. Cells move on elastic substrates by generating contractile and protruding forces and pulling on the substrates to propel themselves; maps of these forces reveal what motility mechanisms cells use (Mogilner and Savinov 2023). The ingenious traditional method to obtain TFs is to place a cell on an elastic film with embedded fluorescent beads, measure displacements of the beads, and solve an inverse problem of elasticity theory (reverse-engineer the forces from the displacements they cause) (Dembo and Wang 1999). This method, used for decades with spectacular results, suffers from the mathematical ill-posedness of the inverse mathematical problems, especially from the difficulty of separating mechanical and measurement noise from meaningful signals.

ML offers a conceptually straightforward and promising alternative way that harnesses supervised learning (using labeled training data to map a feature to a label) to measure TFs (Fig. 4). Simply speaking, the method could work as follows: (1) make a model to generate thousands of active force distributions, (2) in each case solve the well-posed direct mathematical problem of predicting the distributions of (a) reactive forces of the elastic substrate (these are TFs), and (b) deformations of the substrate, (3) train an ML network by thousands of (a–b) pairs, and (4) test the ML network by presenting it with measured substrate deformation distribution and asking it to predict respective TF distribution. This program was successfully implemented (Wang and Lin 2021) where the authors used a simple mathematical model of a dynamic motile cell (Satulovsky et al. 2008) to generate active forces along the cell periphery, apply these forces to the elastic substrate, compute the substrate's elastic deformations, and train a neural network by the substrate's deformation–force pairs' data. The trained neural network was tested by generating additional data, as above, presenting the substrate's deformations map, asking the network to predict the TFs, and comparing the predicted and computed TFs. The authors found, however, that the traditional TF calculation method and ML method outperform each other in different cases

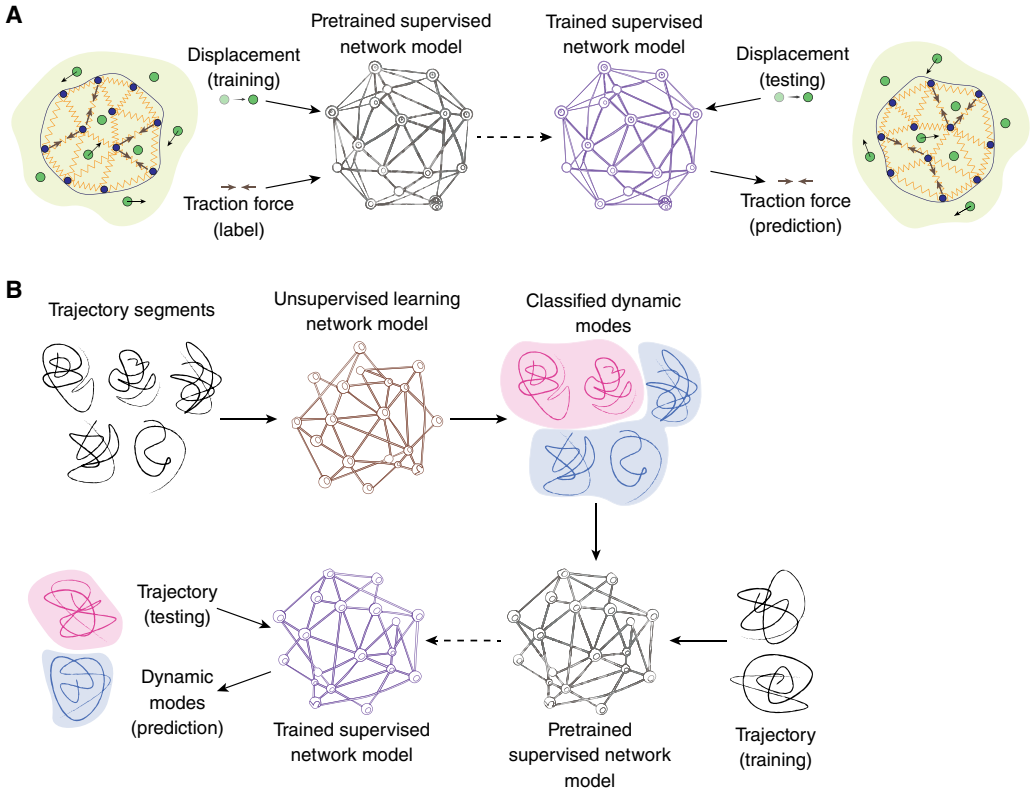

Figure 4. Applications of machine learning to study cell migration. (*A*) A neural network is trained to reverse-engineer traction forces from measured substrate displacements as follows: a traditional computational model is used to generate active intracellular forces that are applied to the deformable substrate generating both displacements and forces in the substrate. Each of a great number of intracellular force distributions generates a unique pair of displacement and force patterns in the substrate. The process of supervised learning presents the network with the training patterns of displacements and pairs each of these patterns with the corresponding pattern of forces (label). The trained network can then be tested by being presented with a displacement pattern not used in the training process and comparing the predicted traction force pattern with the traction force distribution corresponding to the displacement pattern, both of which come from one simulation of the computational model. (*B*) Training of a neural network to quantify cell migratory trajectories starts with an unsupervised learning process, in which the network uses geometric metrics to classify trajectory segments. This results in clustering the trajectories into several dynamic modes, which are then applied, together with previously unused trajectory data, in the second, supervised learning stage of the training process. The fully trained network is then able to predict switches between dynamic modes of motility along the experimentally obtained migratory trajectories.

and their accuracies are generally the same. Hence, ML offers no obvious advantage yet. Conceptually similar approaches are reported in Pielawski et al. (2020) and Duan and Huang (2022).

Another relevant study (Tao et al. 2024) proposed a different approach to circumvent the problems of destabilizing noise and of not knowing the exact substrate's rheology. Tao et al. (2024) found that ML can very accurately predict the cell shape and substrate displacements from the shapes and displacements of several previous time frames. Importantly, this prediction process averages the noise out. Then, TF can be computed by the traditional approach of solving the inverse elasticity theory problem

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starting from the predicted smooth displacement map.

Schmitt et al. (2024) went one step further. The authors of that state-of-the-art study asked the question: Can spatial distribution of a key protein predict TF directly? They adapted the so-called U-net neural network (Ronneberger et al. 2015; Falk et al. 2019) to predict TF using the spatial distribution of zyxin, a focal adhesion protein, as input. The procedure introduced in Schmitt et al. (2024) is to (1) measure spatial maps of zyxin distribution and substrate displacements, (2) compute TFs by using the traditional approach of solving the inverse elasticity theory problem with the measured displacements as the initial condition, and (3) train U-net on the resulting zyxin-TF data. It turned out that the trained network could then predict TFs from zyxin distributions without the displacement data. Interestingly, when other key proteins (i.e., actin, myosin, and paxillin) were used to train U-net, the prediction quality became worse; combinations of zyxin with a non-zyxin protein at most performed as well as zyxin alone.

Schmitt et al. (2024) went even further: besides using the trained U-net as a "black box," they developed a "physical bottleneck neural network," which incorporated a minimal elastic model combined with the neural network. This network allowed computing the "adhesion strength functional," Y, which is a function of both spatial coordinate and zyxin distribution, such that TF, **F**, can be computed from the displacement field, **u**, from a linear equation: $\mathbf{F} = Y\mathbf{u}$. Computing TF from this equation is not as accurate as using the "black box" neural network but is easier and offers mechanistic insight. Lastly, they used a neural network based on physical rules but agnostic to a particular physical hypothesis, called "Green's function neural network." Such a network derived a nonlinear functional relation between zyxin distribution as input and TF as output. Using this relation, TF can be predicted with almost 80% accuracy, while using just 10 model parameters compared with about 10^5 times greater number of parameters of the unconstrained "black box" U-net.

Analysis of cell migratory trajectories is also very amenable to the use of ML (Fig. 4). One of the relevant questions is whether and how the trajectories can be quantified and classified. In other words, while the whole set of trajectories constitutes multidimensional data, we would like to project these data onto a low-dimensional space, preserving the most essential and relevant features of the data and clustering the trajectories into several informative and intuitive classes. An example of implementation of this general task is a recent study (Song et al. 2023) where, first, unsupervised learning was used to recognize the trajectory type of dendritic cells moving in 2D. The authors computed several features (i.e., radius of gyration, end-to-end distance, and statistics of direction turning) quantifying the trajectories segmented into equal-length tracks and used the quantifiers as the input of an unsupervised ML model to cluster the trajectory segments into different modes. They found that the data are best categorized into three dynamic migratory modes: slow diffusion, and slow and fast persistent migration. Then, they trained the supervised ML model with the trajectory segments set as the input and the dynamic modes as the output, which are learned from the unsupervised part of the study and applied the trained network to analyze the entire trajectories. The analysis showed that the cells switched with certain frequencies between the three motility modes, depending on the cells' developmental stage.

Another study (Korabel et al. 2022) started from simulating multiple trajectories of cells engaged in the so-called fractional Brownian motion (in which the average displacement of a cell increases proportionally to time in power α, where α is the so-called anomalous diffusion exponent), and then used these data to train the neural network to identify the anomalous diffusion exponents. The authors applied the trained network to analyze hemocyte cell trajectories in 3D in live *Drosophila* embryos and found that the cells were engaged in super-diffusive motility on average ($1 < \alpha < 2$). Also, the motility was heterogeneous, in the sense that the anomalous diffusion exponent fluctuated, both in time and between different trajectories.

OUTLOOK

Integrative approaches to modeling cell migration are still mostly the future; for now, this research mostly follows a tested and reliable reductionist approach, according to which the migration process can be reduced to the problems of polarity, directionality, and motility. In conclusion of our review, we discuss the strengths and limitations of the different modeling endeavors and principal open questions, as well as the challenges of integrating multiprocess models and data.

Cell Polarity

The strength of the models of the MT-related cell polarization models that we discussed is excellent integration of theory and experiment: many of these models are introduced in experimental studies, where modeling was judiciously used to discriminate between alternative hypotheses and to interpret biophysical measurements.

One limitation of these models is that constitutive mechanical relations, for example between relevant stresses and strains, are rarely based on measurements, and so there is a lingering doubt whether assumed mechanical relations were chosen as such for better fits.

An interesting open question about polarity models relates to the curse of specificity in cell biology—so far, unifying theories of cell migration, of the sort that physics is accustomed to, remain elusive, and having an adequate polarization model of one motile cell type helps little in elucidating the directional motility onset of another cell type. The great future modeling challenge is to start revealing general design principles of integration of mechanochemical cell parts into diverse polarization events.

Directional Sensing

The models of galvanotaxis are in their infancy, compared to rich traditions of modeling cell mechanics and polarity. Considering that chemotaxis is very closely related to galvanotaxis and that computational modeling of chemotaxis is thriving for decades, the most promising direction would be focusing on one cell type and integrating microscopy, genetic, biophysical, and computer tools to elucidate three interacting modules of galvanotaxis: EF-sensing machinery on the cell surface, respective signal transduction pathways, and cytoskeletal response to respective signals.

Mechanics of Cell Motility

The main strength of the models of 3D cell motility that we reviewed is in the diversity of approaches to the cell mechanics, from considering the cell as a set of contractile adhesive "arms," to minimizing a sum of volume-, surface-, and adhesion-related energies of a "trembling blob," to simulating a mesh mimicking dynamic cytoskeletal scaffolds. This diversity allows us to look at the pliable modes of cell migration from different angles, each bringing an additional sliver of understanding.

The challenge we are facing is that increasingly detailed models become hopelessly cumbersome and unwieldy to be used to nimbly test multiple hypotheses.

Among many open questions about the future of mechanical modeling, the one we would like to highlight is how do we overcome the tremendous computational expense of solving coupled equations of nonlinear mechanics and stochastic cytoskeletal dynamics, exacerbated by the need to scan multidimensional parameter spaces?

Embracing Machine Learning

The strength of traditional bottom-up models, such as those we reviewed in the sections on polarity, motility, and directional sensing, is in bringing mechanistic insights into cell migration. These models, simply speaking, explain gears of subcellular machines in an intuitive way and generate clear hypotheses for future experiments.

However, the main limitation of such models is that even the most detailed of them are still too simplistic to embrace the complexity of the multiscale cell migration process. On the other hand, the data-driven approaches, which are often not constrained by laws of physics and

chemistry, are excellent for embracing complexity, finding key features of cell migration, and predicting migration mechanics from "big data." Yet, these approaches rarely bring mechanistic understanding.

Likely, the way forward is to augment traditional models with data science and ML methods, as discussed in Choi et al. (2021) and Brückner and Broedersz (2024). Lastly, the big open question is: Is it possible to use nascent artificial intelligence (AI) to build multiple detailed traditional models from data, simulate them faster, and use data to discriminate between alternative models automatically, freeing human researchers from routine technical tasks.

COMPETING INTEREST STATEMENT

The authors declare no competing interests.

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