Mathematical Modeling of Eukaryotic Cell Migration: Insights Beyond Experiments

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Abstract

A migrating cell is a molecular machine made of tens of thousands of short-lived and interacting parts. Understanding migration means understanding the self-organization of these parts into a system of functional units. This task is one of tackling complexity: First, the system integrates numerous chemical and mechanical component processes. Second, these processes are connected in feedback interactions and over a large range of spatial and temporal scales. Third, many processes are stochastic, which leads to heterogeneous migration behaviors. Early on in the research of cell migration it became evident that this complexity exceeds human intuition. Thus, the cell migration community has led the charge to build mathematical models that could integrate the diverse experimental observations and measurements in consistent frameworks, first in conceptual and more recently in molecularly explicit models. The main goal of this review is to sift through a series of important conceptual and explicit mathematical models of cell migration and to evaluate their contribution to the field in their ability to integrate critical experimental data.

Contents

THE QUESTS FOR MODELING MIGRATION

The ability to migrate in space is among the most fundamental functions of eukaryotic cells and thus is one of the best studied phenomena in biology. Migration is captivating also because of its aesthetics. Since the first developments of microscopes permitting the observation of cellular dynamics, the plethora of cell shapes and the strategies to morph between them have fascinated generations of researchers. Progress in cell migration research in fact has always been in a symbiotic relation with progress in imaging. New microscopy methods led to the discovery of novel aspects of cell migration, whereas open questions concerning the mechanisms of migration have driven innovation in microscopy. Thus, not only is cell migration one of the most densely populated research fields, it is also among the most technologically advanced and data rich.

It is probably safe to say that the majority of both molecular parts as well as elementary processes underlying cell migration are known. Moreover, many of the properties of these parts and processes are well characterized. Thus, migration is an attractive field for modelers to step in and conceptualize a wealth of information by mathematical formalism; however, entering a data-rich field comes with inherent challenges and responsibilities. Models must be data integrators, i.e., they should link experiments and reconcile different measurements with theory. Models must be molecularly explicit, i.e., they should generate hypotheses that stimulate concrete and realistic experiments. And models must be multifactorial, i.e., they should illuminate how different component processes cooperate to produce a particular migration behavior. All three quests originate from the fact that cell migration is driven by an immensely complex machinery, where chemical and mechanical processes interact across wide temporal and spatial scales, where processes integrate via nonlinear interactions, and where redundancy between processes yields a range of possible mechanisms that cause seemingly identical behavior. In such a scenario, investigator intuition falls short in the interpretation of experimental outcomes, let alone in predicting the outcome of new rounds of experiments under variable conditions. Therefore, although mathematical models are far from fulfilling these quests, they have been playing an important role in migration research since early days. The goal of this review is to provide a selective perspective on some of these modeling efforts and to highlight their contributions to the field, but also to pinpoint what they have missed.

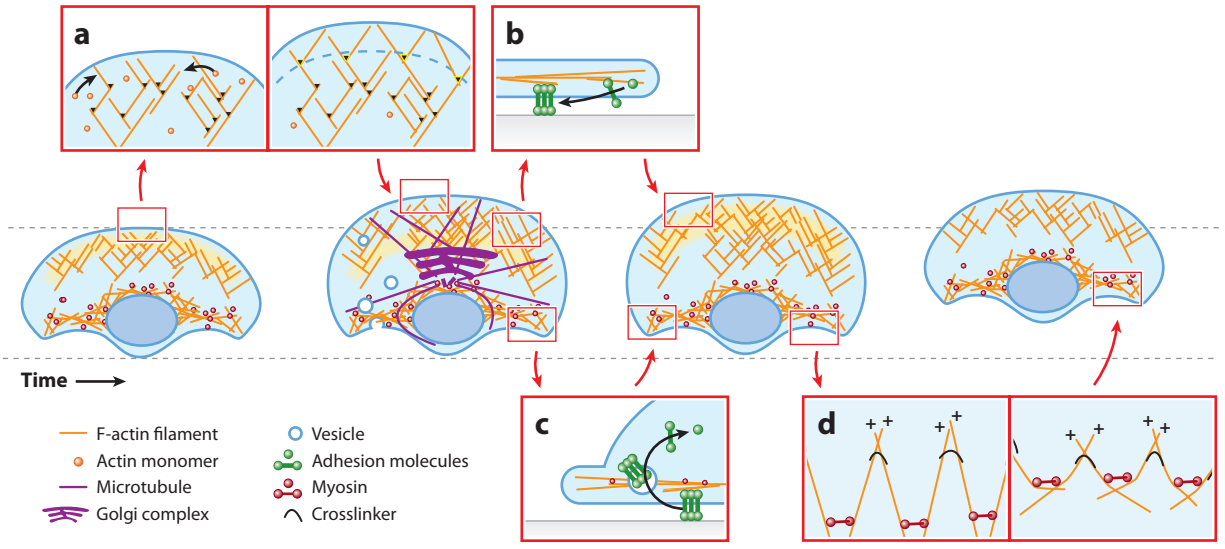

Figure 1

Revisiting the Abercrombie model of metazoan cell crawling. Cell migration is divided into discrete steps: (*a*) protrusion based on actin growth and polymerization force; (*b*) formation of new adhesions at the front; (*c*) release and recycling of adhesions at the rear; and finally, (*d*) actin-myosin-powered contraction of the cytoplasm, resulting in forward translocation of the cell body. We are showing schematically the centrosome and microtubules originating from it, as well as the Golgi complex and Golgi-derived microtubules that play important roles in guiding migration.

FROM ABERCROMBIE TO EARLY AND INTEGRATIVE MODELING

In his famous Croonian lecture, Abercrombie (1980) was the first to compile an integrated model of cell migration based on a series of fairly isolated experimental observations. Although the model was not mathematical, it has defined the framework for nearly all qualitative and quantitative models of migration to date. The model postulated that migration occurs in a cycle of four steps driven by interconnected but separate processes (**Figure 1**). Prerequisite to the cycle is that the cell is polarized (i.e., the cell has a well-defined front and rear). The Croonian lecture did not address the mechanisms of polarization; however, it offered the speculation that chemical and/or mechanical cues could be responsible for a differential distribution of molecular factors along the axis of movement that may cause the separation of processes. Today, it is well established that cells can sense gradients in chemical, mechanical, and other extracellular cues and define the front and rear.

Once the cell is polarized, step one in the migration cycle is the protrusion of a lamellipodium at the leading cell edge (**Figure 1*a***). In Abercrombie's time, it was not clear which molecules were driving the forward propulsion, although he already speculated that the growth of actin filaments at the cell front may be important. Step two consists of the formation of new adhesions at the cell front (**Figure 1*b***). These adhesions are required to balance propulsive forces at the leading edge as well as contractile forces elicited in step four. In step three, aging adhesions are released (**Figure 1*c***). The final step is the contraction of the cell (**Figure 1*d***). Abercrombie proposed that this process is mediated by actomyosin machinery similar to the molecular machinery implicated in muscle contraction. Given a front-to-back gradient in adhesion strength, contraction will lead to preferential forward movement of the rear. Importantly, it may also stall or even retract the leading edge, dependent on the overall adhesion strength and the rate of lamellipodial extension. Indeed,

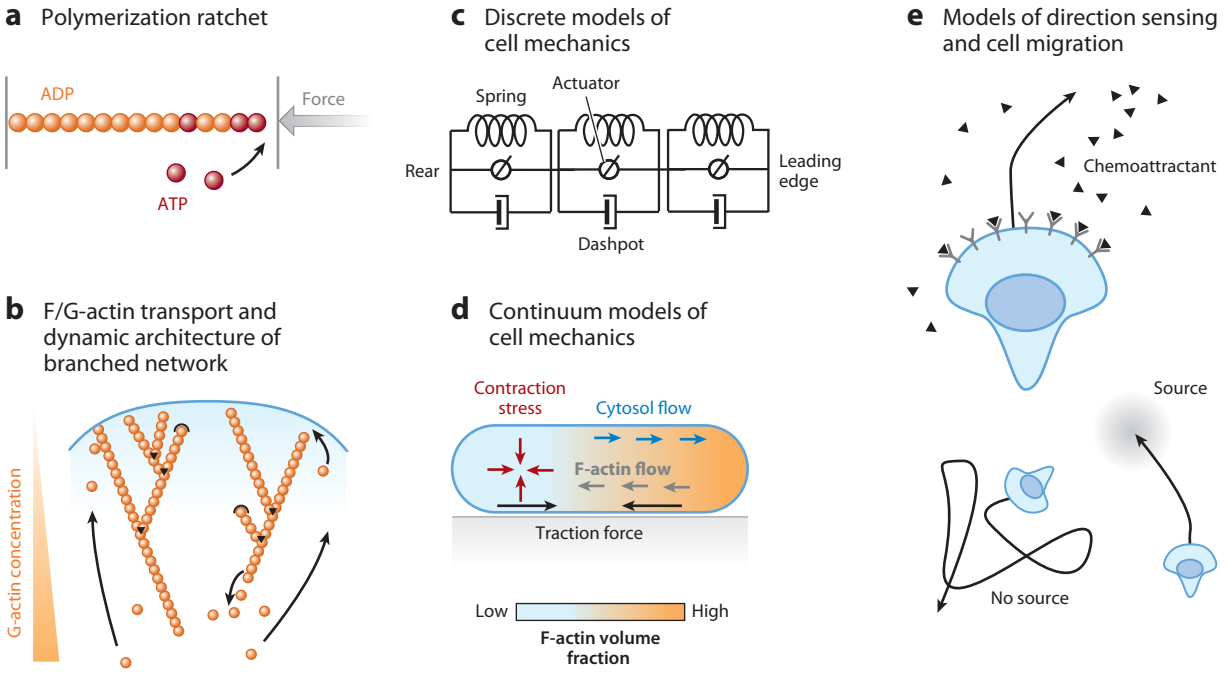

Figure 2

Schematics of early models that critically advanced the understanding of mechanisms of cell migration through mathematical modeling. (*a*) Ratchet model of force generation by actin polymerization (Hill 1981, Peskin et al. 1993). (*b*) Modeling of F-actin branching, mediated by Arp2/3 complex (*black chevrons*), capping (*black semicircles*), disassembly, and G-actin diffusion down its gradient (*arrows*), added to the polymerization ratchet model, put the dendritic-nucleation model of lamellipodium into a quantitative framework (Carlsson 2001, Mogilner & Edelstein-Keshet 2002). (*c*) Whole-cell models using discrete mechanical components comprised of springs, dashpots, and actuators (motors) (DiMilla et al. 1991) preempted current whole-cell models. (*d*) Whole-cell continuum models, such as the two-phase fluid model (Herant & Dembo 2010), integrate the contractile stress, F-actin, and cytosol flow with traction forces and cytoskeletal densities. (*e*) Early models of chemotaxis and long-term cell migration (Tranquillo et al. 1988).

Abercrombie suggested that the reported rearward transport of cytoplasmic material would be associated with cell contraction. A few years later, Wang (1985) identified this transport as the retrograde flow of actin filaments. The Croonian lecture left open whether steps one through four were sequential and, if so, how they would be temporally coordinated. By now, it is well established that many mechanochemical signals couple the steps and that, in most motile cells, all steps run concurrently and are spatially coordinated (Ridley et al. 2003).

Numerous mathematical models were implemented to translate the propositions of the Croonian lecture into quantitative predictions. Among the first fairly complete models is a description of a cell as a chain of discrete viscoelastic and contractile elements connecting an adhesive pseudopod at the front to an adhesive uropod at the rear (DiMilla et al. 1991) (**Figure 2*c***). The model explicitly makes the assumption that the affinity of integrin receptors linking the cytoskeletal elements to the substrate is higher at the front than at the rear. Thus, the adhesion gradient is a model input rather than an outcome. However, the model included several equations governing the substrate binding and unbinding of integrins, as well as the recycling of integrins from the back to the front via receptor diffusion in the membrane and endocytic vesicle transport. Critically, following Bell's (1978) seminal description of adhesions, the rate of integrin unbinding was assumed to increase exponentially with the force exerted on the bond. This functionally coupled the strength of

adhesion to the level of contractility and led to an implicit feedback between the coupling states of individual integrins. The model offered two insights: First, dependence of migration efficiency on adhesiveness is biphasic. Too-weak adhesion causes both the front and rear to slip, whereas too-strong adhesion stalls both the front and rear. Optimal migration efficiency occurs in an intermediate regime, a prediction that would be experimentally validated six years later by modulation of the concentration of the integrin ligand fibronectin and by application of function-blocking antibodies against integrins (Palecek et al. 1997). Second, for a given level of adhesiveness, the migration efficiency was predicted to depend biphasically on the contractility (DiMilla et al. 1991). Too-weak contraction prevents tail retraction, whereas too-strong contraction results in retraction of both the front and rear. Thus, for optimal migration, a cell must sense the strength of its adhesion and adjust the level of actomyosin activity, a prediction that was confirmed in experiments by Rajagopalan et al. (2004) and Gupton & Waterman-Storer (2006). The pathways that promote autoregulation of contraction and adhesions in cells are still largely unknown.

Concurrent with DiMilla's work, Dembo and colleagues developed a continuum model (**Figure 2*d***) of the contractile and viscoelastic cytoplasm that could explain the relation between cytoplasmic flows, substrate adhesion, and protrusion dynamics (Alt & Dembo 1983, Dembo & Harlow 1986). The culmination of this line of work was a two-phase fluid model with moving boundaries (Alt & Dembo 1999) that integrated the dynamics of actin-filament assembly/disassembly and flow with the force balance between cytoplasm, adhesive substrate, and membrane. Numerical simulations of the model in 1D captured critical features of cell morphodynamics, including the formation of ruffles, protrusion, and retraction cycles at the leading edge and the spatial distribution of actin retrograde flow and traction forces.

Neither of these two model types explicitly addressed Abercrombie's step one. Whereas DiMilla & Lauffenburger's model focuses entirely on the interplay between contraction and adhesion, and thus does not consider cell-front advancement, protrusion in the Alt & Dembo model is generated by hydrostatic pressure. Clearly, pressure gradients do play a role in certain forms of migration (Bergert et al. 2012); however, there is general agreement in the field that, especially in adherent cells, lamellipodial growth and protrusion are mostly driven by assembly of actin polymers at the leading edge. First experiments directly showing the relation between actin assembly and protrusion were performed in the mid-eighties and early nineties, relying on innovative new modes of live-cell fluorescence imaging (Theriot & Mitchison 1991, Wang 1985). In parallel, biophysical models emerged that explained how the free energy of monomer binding to the growing filament tip is converted by a ratchet mechanism into mechanical work pushing the leading edge membrane (Hill 1981, Peskin et al. 1993) (**Figure 2*a***). These first ratchet models triggered a long series of very detailed work, explaining force production by actin polymer networks of a wide range of organizations (**Figure 2*b***), as well as complex phenomena like protrusion-retraction cycles and wave propagation (Ryan et al. 2012). Thus, although neglected by the earliest models of cell migration, today cell protrusion is probably the best understood of the four Abercrombie steps.

A third line of modeling stimulated by Abercrombie's work focused less on the mechanical processes but rather on the premise that cell migration requires the functional integration of several spatially and temporally distributed modules. Many of these models used the framework of stochastic simulations to test how specific rule sets describing the interaction between modules generate emergent properties of whole-cell migration. In one of the earliest of these models, Tranquillo et al. (1988) proposed a set of rules to define how spatial differences in cell-surface-receptor occupancy are translated into lamellipodial activation and cell turning (**Figure 2*e***). The model could explain the persistence time and orientation bias observed with leukocyte motion in either a uniform distribution or a gradient of receptor ligands. In contrast to Tranquillo's model, Arrieumerlou & Meyer (2005) relied on a rule set that defined the stabilization of randomly

protruding pseudopods under chemo-attractor gradients. Thus, this model was among the first to predict not only the motion of the cell centroid but also the morphodynamic behavior. As a continuation of this approach, Yu-Li Wang's lab published a more complete description of cell-shape dynamics (Satulovsky et al. 2008). Here, a rule set defines how the cell shape evolves stochastically under the influence of a combination of local protrusion and global retraction signals. Quite remarkably, by variation of model parameters, the authors showed that the same set of rules could mimic the shape and motility of amoeboid cells, keratocytes, neurons, or fibroblasts. The critical lesson learned from this exercise is that, as predicted by Abercrombie, cell migration can be explained through the integration of a few functional modules that are connected in a simple circuit.

On the quest for molecular detail and for quantitative agreement between model and experiment, most of the more recent modeling work has quit the path of integrating Abercrombie's elementary processes. Instead, it focuses on very specific aspects of individual steps. In the following, we review some of these models and discuss ways by which the community begins to return to integration, but at a higher level of complexity. We start with a general overview of modeling concepts used in the field, followed by discussion of specific models of the three Abercrombie steps, protrusion, contraction, and adhesion. Next, we review approaches for integration based on the example of keratocyte motility, before we return to the initiating step of polarity and to signaling. We conclude with an outlook to future work, including modeling of 3D motility.

KEY MODELING CONCEPTS

All mechanistic models of cell migration are built using several physical and conservation laws. The most fundamental of those are the principle of force balance (**Figure 3*a***, *left*) and the law of mass conservation (**Figure 3*a***, *right*). All cell-biological processes take place in aqueous medium at such small spatial scales (tens of micrometers at most) and speeds (a few micrometers per second at most) that inertia is negligible. Thus, a limited number of active and passive forces have to be balanced at every point in space and time. In the context of cell migration, two of the forces are active (i.e., their generation consumes energy from ATP hydrolysis and/or protein binding): First, at the cell periphery, polymerization of actin filaments into a meshwork produces a force that pushes the cell edge outward. Second, myosin motors operate on the actin-filament meshwork, which generates contractile stresses that pull the meshwork inward. Four other forces are passive (i.e., they dissipate or conserve energy): traction force from the drag between cytoskeleton and adhesion complexes, membrane tension resisting the polymerization force, viscoelastic stresses from deformations in the actin network, and viscous drag between the actin-filament and cytosolic fluid flows. The mass conservation law—basically an accounting principle—determines that the number of molecules of a certain type in any small volume can change owing only to transport (diffusion and drift/flow) of these molecules in and out of this volume and to chemical reactions inside the volume (**Figure 3*a***, *right*).

Given the fundamental nature of these laws, they are usually not controversial. Much harder and often requiring a leap of imagination is the writing of constitutive relations that complement the force balance and mass conservation equations with additional assumptions. It is imperative that they are stated and discussed explicitly. If this is done, then even a model based on a wrong assumption is useful because it shows what does not work.

A first example of constitutive relations is shown in **Figure 4*a***, based on Chan & Odde's (2008) model of a molecular clutch, which links actin filaments pulled by myosin and deformable substrate via dynamic adhesions. After the forces of myosin contraction and adhesion and substrate deformations are equilibrated, which results in two equations for five unknown variables, three

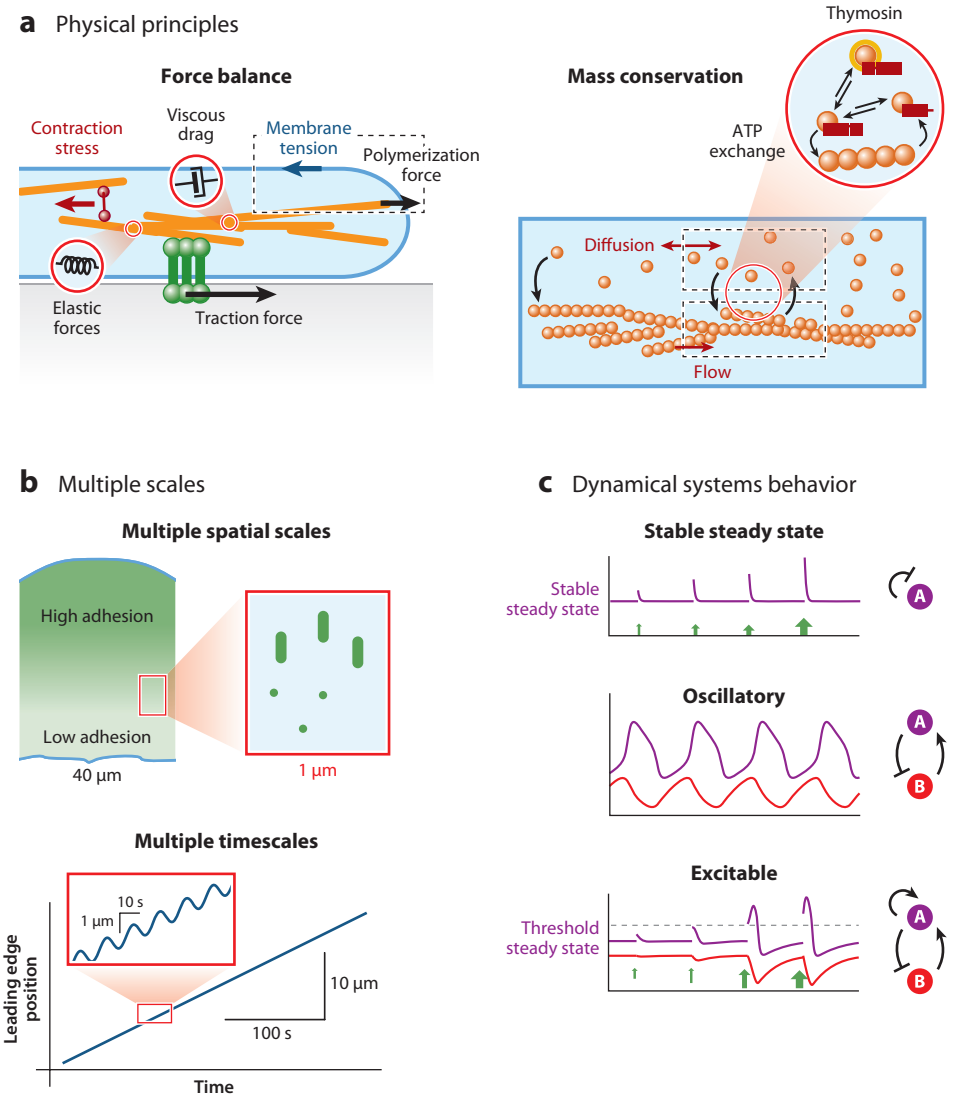

Figure 3

Ingredients of mathematical models. (*a*) Physical principles. (*Left*) At cellular scales, inertia is insignificant, and imbalances of forces quickly dissipate, leading to the force balance principle: The total force on any object or any subcellular region (e.g., *dashed box*) sums to zero. (*Right*) Mass conservation. In any region of space (e.g., *dashed box*), the total amount of a substance can dynamically change only if it is transported out, for example, by diffusion, advection, or active transport, or changes form, for example, by polymerizing or depolymerizing oligomers. (*b*) The same process or quantity appears differently at different scales. (*Top*) The adhesion pattern in cells varies spatially. On the scale of the whole cell, adhesion is strong at the front and weak at the rear. At smaller scales, fine structure of individual focal adhesion sites can be resolved. (*Bottom*) Many cells exhibit cycles of protrusion and retraction at small timescales; however, at larger timescales, the result is smooth net migration forward. (*c*) Dynamical systems behaviors, including steady states, excitability, and oscillations. Green arrows indicate pulsatile activation of the systems.

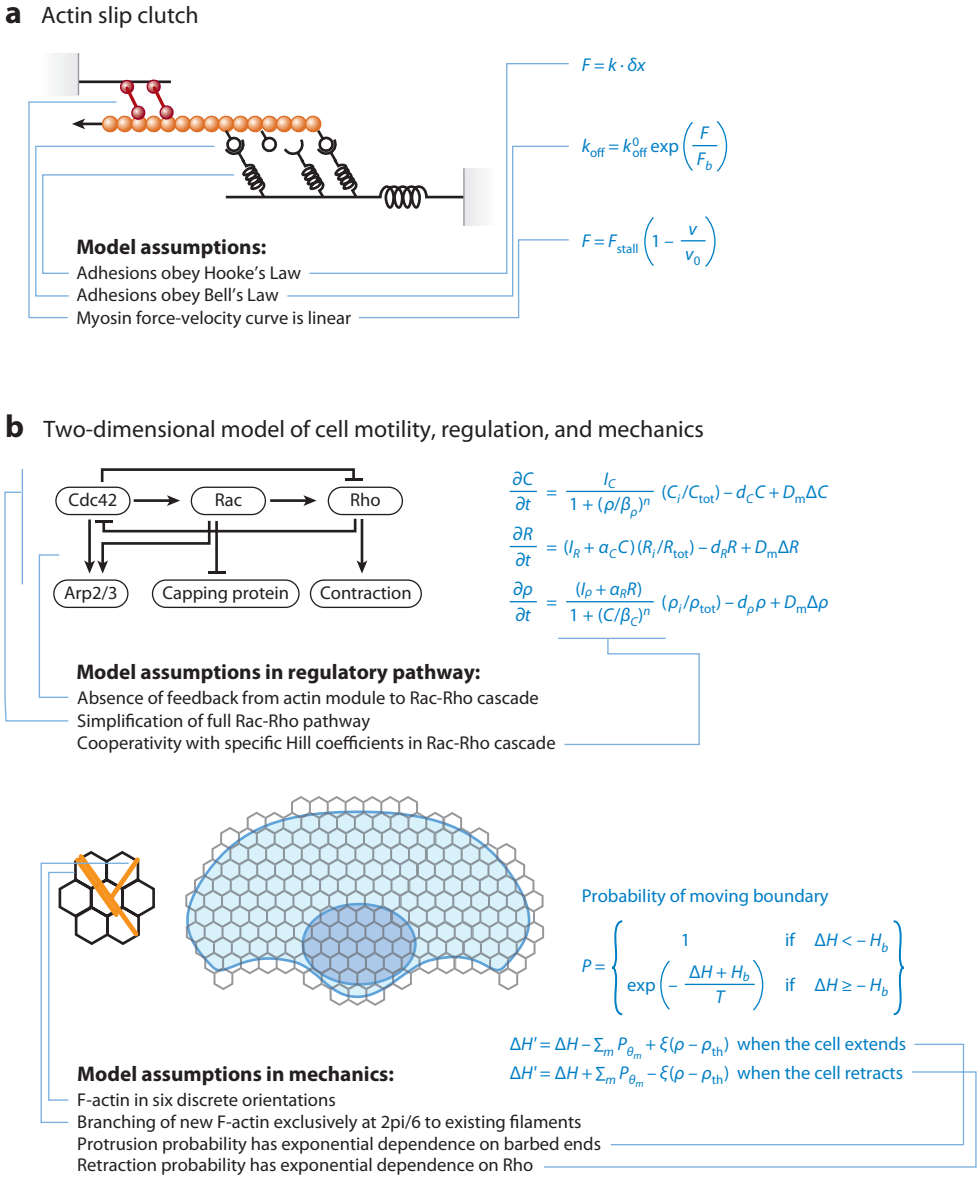

Figure 4

Examples of mathematical models and assumptions that the models are built on. (*a*) Stick-slip adhesion (Chan & Odde 2008). (*b*) Cell shape, movement, and polarity governed by signaling reaction–diffusion system (Marée et al. 2006).

additional mechanical equations are necessary to mathematically define the system. The equations are shown in **Figure 4*a***. The first equation relates the force in an adhesion to the elastic deformation of the substrate, the second equation defines the dissociation rate of bonds between adhesion and cytoskeleton to the level of transduced force, and the third equation defines the force-velocity relation for myosin motors. All three equations represent simplifications of a very complex reality,

and considerable data are needed to verify their validity. Often, such data are not available, which does not invalidate the model. However, caution is used when interpreting model predictions. Another example is based on the work by Marée et al. (2006), shown in **Figure 4*b***. To model shape and movement of a whole cell, equations for reactions between the activity of Rho GTPase signals and actin accessory proteins must be written using generally reasonable, but in detail relatively arbitrary, assumptions about the Michaelis-Menten reaction kinetics and the geometry and movements of the actin-filament meshwork. As long as all assumptions are transparent, the value of such a model lies in the quantitative hypotheses that are being generated. Such hypotheses will highlight the need for future experiments and even may define their order of priority.

Modeling cell migration was popular for decades and is increasingly important because intuition often fails when we try to think about multiple temporal and spatial scales on which the motility processes unravel (**Figure 3*b***). Also, whereas many motile processes are stable and steady, others exhibit complex, dynamic behavior, such as periodic oscillations and excitable pulses (**Figure 3*c***). Nonlinear feedbacks and network motifs behind these dynamics are best tackled with the tools of mathematics. Moreover, the mechanics, transport, and reactions in migrating cells are stochastic and heterogeneous, and so modeling is often very helpful in integrating, interpreting, and understanding the data. In the following, we review how, in the past few years, simple conceptual models have answered qualitative questions raised by experimental observation, and detailed, systems-like models have recapitulated the data, helping to illuminate the steps of motility.

ACTIN-FILAMENT DYNAMICS AND PROTRUSION

Actin-based protrusion has attracted a lot of modeling efforts because of the rich biochemical and mechanical data, on the one hand providing detailed quantitative information to parameterize models and on the other hand needing models for integration and validation. The key question that must be addressed by models of actin-filament dynamics and protrusion relates to the origin of the pushing force generated by the growing actin meshwork. Early conceptual ratchet models were developed to explain how thermal bending, growth, and subsequent elastic pushing by individual actin filaments generate a force against the resisting cell-edge membrane (Mogilner & Oster 1996, Peskin et al. 1993) and then against effective resistance of filaments transiently attached to the surface being pushed (Mogilner & Oster 2003). Following these early descriptions, increasingly detailed models (Alberts & Odell 2004, Carlsson 2003, Schaus & Borisy 2008, Smith & Liu 2013, Weichsel & Schwarz 2010) started to simulate branching and capping dynamics of the growing actin network as a whole and discovered that a delicate balance between ratcheting filament forces, branching/capping kinetics, and geometry of the meshwork edge causes effective network strengthening, which explains the observation that the growth rate of the actin network is insensitive to the load (Parekh et al. 2005). These theories also allowed understanding of why the protruding network is ordered angularly: Filaments grow predominantly at 35° relative to the protrusion direction (Maly & Borisy 2001). The reason is that evolution of filaments in various directions is interdependent, and mother filaments and their daughters growing at the relative angle of 70° are optimally abutting the leading edge and protected from capping if they grow symmetrically ($\pm 35°$), whereas at other angles, filaments lose competition with neighbors.

Another class of physical models examined elastic deformations of actin gels near the growing surface that were ignored by the advanced ratchet theories. These elastic propulsion models (Gerbal et al. 2000, Marcy et al. 2004) approximated the gel as a continuous elastic medium with stress generated at the surface by growing F-actin and showed that near curved surfaces, squeezing elastic forces propel the surfaces forward. These models explained the force-velocity curve generated by the actin network growing around spherical beads (Marcy et al. 2004).

In a sense, the ratchet models are microscopic, considering individual filaments, whereas elastic models are macroscopic, considering actin gel as a continuum. Mesoscopic models must account for forces from both the individual ratcheting filaments and viscoelastic deformations and the stresses of effective gel at which surface these filaments grow (Zimmermann et al. 2010). It was unclear what experimental data would require this challenging mesoscopic modeling until Lacayo et al. (2012) reported a fascinating observation: Ellipsoidal beads were propelled by actin tails both lengthwise and sidewise. Elastic theories predict that an elongated bead would be squeezed from the sides and propelled forward along its length, whereas the ratchet theories posit that the branching actin network would spread along the widest possible surface, thus pushing the bead wide-side forward. Only combined mesoscopic theory correctly predicts the observed orientations (Zhu & Mogilner 2012), making the point that the known or assumed protrusion mechanisms are not mutually exclusive. Rather, the cell likely uses several redundant mechanisms, and the future challenge for models and experiments is to understand design principles behind this complexity. Another lesson is that we still must better understand multiscale mechanical behavior of actin gels.

Besides the mechanisms mentioned above, there are many more theories, including, but not limited to, pushing by excluded volume effects (Schreiber et al. 2010), swelling gel pressure of liquid dendritic clusters (Lee & Liu 2009), and hydrostatic pressure (Bergert et al. 2012). One of the earlier ideas was that actin filaments generate pushing force, not alone, but by linear growth under the control of processive proteins at their tips (Dickinson et al. 2004). Recently, a model of this kind was used to explain why Ena/VASP-mediated actin-filament elongation is saturated at high actin monomer concentration: The growth is limited by the rate of the Ena/VASP EVH2 domain recruiting actin monomers from solution and subsequently transferring the subunit onto the barbed end (Breitsprecher et al. 2011). A similar idea led to a thermodynamic model predicting that, in the presence of the processive capper formin, variation of a single physical parameter—the effective elastic energy of the formin-capped barbed end—results in the observed diversity of polymerization rates (Shemesh & Kozlov 2007).

Two models mentioned in the previous paragraph signify another trend: To understand the full mechanism of protrusion, it will be necessary to move from conceptual to detailed models of actin growth that include accessory proteins. Such models are useful only if they are integrated with detailed experimental data. A good example of such a joint study is the recent investigation of the density and speed of the actin comet tails that propel beads coated with the Wiskott–Aldrich syndrome protein (WASp) (Ditlev et al. 2012). Through a combination of fluorescence imaging and exhaustive computational modeling, the authors demonstrated that, as the local density of adaptor protein Nck increases, actin polymerization increases in a nonlinear manner as the result of a previously unappreciated 4:2:1 Nck/WASp/Arp2/3 stoichiometry. Ditlev et al. (2012) used the data to definitively find all functional dependencies of chemical reactions, which is very rare and normally remains guesswork in models, and to reverse engineer molecular details of the crucial Arp2/3-mediated pathway of F-actin-network protrusion.

While trying to understand the dynamic properties of actin networks, one should not forget that the dynamics of individual actin filaments is not understood completely yet. Early modeling of the ATP-hydrolysis cycle coupled to the actin treadmill (Bindschadler et al. 2004, Vavylonis et al. 2005) predicted that the actin network dynamic structure and force production depend critically on the nucleotide state of F-actin (Footer et al. 2007). Recently, high-resolution structural reconstruction (Fujii et al. 2010, Galkin et al. 2010, Murakami et al. 2010) revealed complex cooperative and allosteric properties of the actin filament, specifically very strong interactions between protomers along the two filaments' helices, whereas interactions between the two strands of the filament turned out to be weaker than expected. The first relevant model (Yogurtcu et al. 2012) explored mathematically the mechanical properties of filaments by modeling two helical strands

interconnected by longitudinal and diagonal bonds and a rate of ATP conversion depending on the elastic energy of the filament. Yogurtcu et al. (2012) found ADP-actin filaments to be softer than ATP-actin, which shed light on the possibility that actin filaments are not only force generators but also mechanosensors (Greene et al. 2009).

HOW DOES ACTOMYOSIN CONTRACTION WORK?

In the large majority of cell-migratory systems, contraction is driven by myosin motors, although evidence for motor-independent contractility has been found (Italiano et al. 1999, Ofer et al. 2011, Sun et al. 2010, Wilson et al. 2010). Over many years, in vitro studies (Bendix et al. 2008, Condeelis & Taylor 1977, Janson et al. 1991, Reymann et al. 2012) demonstrated that collapses of disordered arrays of actin and myosin filaments generate contractile force, but molecular mechanisms of this contraction remained unclear until recently: It is not obvious that a network of filaments with active force-generating elements will contract rather than expand or simply churn isometrically.

A few conceptual models suggested hypothetical mechanisms for how the action of myosin motors could yield contraction. Some models rely on the fact that actomyosin stress fibers, which generate significant contractile forces in motile cells, have periodic sarcomeric organization, similar to striated muscle (Naumanen et al. 2008). Mathematical models of stress fibers (Stachowiak & O'Shaughnessy 2009) couple myosin force with elastic and viscous drags to predict force-velocity properties that are in agreement with experimental observation. But how do actin and myosin filaments self-organize into a sarcomeric structure? One proposal is that motors do not slide off the barbed filament ends (Zumdieck et al. 2007). Hence, when a few filaments of opposite polarity engage with one motor cluster, they will be slid into a configuration resembling a mini-sarcomere. Contraction is then produced by interaction of multiple mini-sarcomeres. Even without this property, a mixed-polarity filament bundle is predicted to be self-sorted by myosin into a periodic arrangement with alternating filament polarity (Craig et al. 2011, Stachowiak et al. 2012, Zemel & Mogilner 2009): Filaments with a polarity opposite to the polarity of the majority are propelled out, leading to spatial segregation of filaments into regions of equal polarity. As Friedrich et al. (2012) correctly noted, in such a self-sorted bundle, myosin motors accumulate in the wrong locations for contraction (i.e., at the barbed ends between equal-polarity regions). Friedrich et al. (2012) resolved this puzzle in a thought experiment where end-tracking crosslinkers permanently attach to the barbed ends of actin filaments, while still allowing polymerization. They demonstrate that this would lead to self-organized and contractile sarcomeric structures. Which of the many actin-crosslinking molecules may have such properties remains to be determined.

It is widely acknowledged that stress fibers form predominantly in cells with large focal adhesions that tend to stall cell motility (Burridge & Wittchen 2013). Stress fibers are less often observed in cells with high migration efficiency. In these cells, rear and front are connected by contractile zones that often contain transversal arcs of actomyosin bundles as well as diffuse interspersion of crisscrossed actin filaments and small clusters of myosin motors (Lim et al. 2010). These organizations of actomyosin contractile machineries have been best characterized in fish keratocyte cells, where it was first argued, based on a combination of electron and light microscopy, that actin networks contract when filament pointed ends decouple from the network by disassembly, whereas the respective barbed ends remain crosslinked by myosin clusters (**Figure 1*d***) (Verkhovsky et al. 1999a). These network-contraction dynamics intrinsically lead to a self-organizing transition from crisscrossed to more and more bundled actin filaments where the bundle axes tend to be orthogonal to the direction of network growth. Hence, transversal arcs in contractile zones may be understood as the final product of actomyosin contraction accompanied by filament disassembly. Indeed, Mendes et al. (2012) recently combined experimental imaging and biophysics with modeling to

demonstrate how actin-myosin bundles can contract. The authors showed that net contraction or expansion depends on a delicate balance. Severing of filaments near their pointed ends, combined with dynamic crosslinking and myosin-driven sliding, tips this balance towards net contraction.

A combination of in vitro biophysical investigation and modeling has offered complementary views on the mechanisms of actin-bundle formation and contraction: Random shuffling of actin filaments by myosin in disordered bundles generates both compressive and tensile stresses. However, compressive stresses are relieved through filament buckling and severing, keeping only tensile forces and, thus, driving contraction in the presence of crosslinkers (Lenz et al. 2012, Murrell & Gardel 2012). Although filament severing and actin disassembly may not be required, actin crosslinking is crucial for contraction (Bendix et al. 2008, Dasanayake et al. 2011, Thoresen et al. 2011). Overall, relative to the numerous models explaining detailed aspects of actin network assembly and protrusion, we are at only the beginning of an era that should generate a comprehensive and unifying model of the actomyosin arrangements required for pulling the cell rear toward the protruding front.

ASSEMBLY, DRAG, AND MECHANOSENSING OF ADHESIONS

Adhesions between the cytoskeleton and substrate are dynamic chains of specialized proteins that assemble in nascent structures in protrusions, undergo complex processes of maturation and turnover, and are released at the cell rear. Besides these mechanical roles in generating tractions, adhesions are also involved in mechanosensory functions of cells and numerous cell-signaling pathways (Parsons et al. 2010). At first sight, two fundamentally different types of adhesions exist: cell-matrix adhesions and cell-cell adhesions. The former primarily feature integrins as the transmembrane receptors (Vicente-Manzanares et al. 2009), whereas the latter are mediated by the family of cadherins (Gumbiner 2005). However, data increasingly suggest that these adhesion types share many commonalities in composition, structure, and function despite their different receptor systems.

Cell-matrix adhesions have been much more accessible to experimental investigation, especially high-resolution imaging. Cell-matrix adhesions spontaneously assemble in cells cultured on microscope coverslips. Coating coverslips with specific extracellular matrix components can elicit formation of particular subclasses of cell-matrix adhesions. However, structure and function of cell-matrix adhesions in less artificial environments than glass coverslips are still largely unexplored. Novel imaging and analysis approaches are required to address these questions (Harunaga & Yamada 2011). Moreover, mathematical modeling may be indispensable for sorting out how the kinetics of adhesion formation, stabilization, and disassembly may vary between different mechanical environments (Walcott et al. 2011). So far, models of adhesions have barely scratched the surface of these complex and adaptive molecular machines. Even less work has been done on cell-cell adhesions in which biochemical and biophysical data still are largely missing owing to the difficulties in probing kinetic and mechanical properties with sufficient resolution. In the following, we highlight two aspects that have received particular attention: adhesion strength and mechanosensing.

The strength of the adhesions is crucial for migration. Protrusion is the result of actin polymerization minus centripetal rearward flow of the actin network. To determine the magnitude of rearward flow, the net force exerted on the actin-filament meshwork by actin-filament assembly and actomyosin contraction is divided by the effective drag from the adhesions. Thus, at the leading edge, the adhesion acts like a clutch: If the drag is high, the centripetal flow is slow, and polymerization translates into the protrusion. If the drag is low, the centripetal flow cancels the polymerization, and the actin network simply treadmills. Gardel et al. (2008) accomplished the first direct analysis of this relationship by measuring traction forces simultaneously with the distribution

of the actin centripetal flow rates adjacent to the cell leading edge. Surprisingly, they found that, whereas the flow decreased away from the leading edge, the traction force first increased with distance from the cell edge and started to decrease together with the flow rate at only 3–5 μm. This indicated that adhesions were slipping at the leading edge, whereas away from it adhesions were gripping. Two mathematical models (Li et al. 2010, Sabass & Schwarz 2010) explain this behavior based on the rich work in tribology. The models posit that the adhesion molecules are basically sticky, linear elastic springs transiently attaching to the actin network. Their deformation by the flowing actin creates elastic force, the average magnitude of which is proportional to the number of the attached springs and to the spring elongation. At slow flow, many springs are attached, so the adhesion is gripping, but the spring elongation before spontaneous detachment is small, proportional to the flow rate; thus, the effective adhesion drag is almost a constant. At fast flow, however, attached springs stretch and detach quickly, because the increasing force accelerates detachment exponentially (Bell 1978). Consequently, the net adhesion drag is low and slipping.

Very similar modeling ideas were used to start addressing the phenomenon of adhesion mechanosensing (Geiger & Bershadsky 2001): Adherent cells adjust their adhesion strength to the mechanical and geometric properties of their microenvironment, in particular to stiffness (Pelham & Wang 1997). From a mechanical perspective, this behavior is counterintuitive. The reaction forces exerted on a stationary adhesion and its proteins do not depend on the substrate rigidity. Hence, the activation of such an adhesion site should not be regulated by substrate rigidity. One explanation to resolve this paradox posits that adhesions are not stationary. Accordingly, early hypotheses of adhesion mechanosensing relied on the dynamic coupling of two springs (Bruinsma 2005, Schwarz et al. 2006). Assuming that an elementary adhesion represents a sticky spring, and that the substrate represents another spring in series, force generation by myosin or actin assembly yields an expansion of the adhesion spring that depends on the stiffness of the substrate spring. The effective rate of adhesion detachment prescribed by the Bell equation, in turn, depends on the rate of adhesion-spring expansion. This provides a mechanism for the self-adjustment of the adhesion strength to the substrate properties. Indeed, Chan & Odde (2008) demonstrated that this concept of adhesion mechanosensing was relevant in an experimental study (**Figure 4*a***) using the adhesion of filopodia as a simple model system that could be numerically replicated by stochastic simulations. On stiff substrates, actomyosin contraction stretches the sticky adhesion springs rapidly on the unyielding substrate, so the springs slip, and the density of bound adhesion springs is low. As a result, a fast, steady retrograde flow of actin ensues, accompanied by low traction forces. In contrast, on a soft substrate, actomyosin activity stretches the sticky adhesion springs very slowly because most of the stretch is absorbed by the deforming substrate. As a result, the adhesion springs stick, and the density of bound adhesion springs grows until some of the springs snap. This triggers a chain reaction in which other springs break, which leads to an oscillatory load-and-fail dynamics with slower retrograde flow and higher traction forces on soft substrates.

At the whole-cell level, even simpler mechanosensing models are conceivable that do not depend on spring detachment. One such model (Marcq et al. 2011) posits that the cell consists mechanically of two effective elastic (actin) and contractile (actomyosin) elements connected in parallel with each other and in series with the elastic substrate. In such a system, the adhesion and intracellular forces are balanced, coupling both myosin strength and cytoskeletal elasticity to the substrate stiffness. Nicolas et al. (2004) proposed another whole-cell model that includes the notion of strain-sensing. The model accounts for the fact that, if a cell deforms the substrate by application of a contractile force, F, then the energy of deformation, proportional to F^2/k, depends on the substrate stiffness expressed by the spring constant, k. The ratio of this energy to the change in elastic energy at adhesions when new adhesion proteins are added can govern

the dynamics of adhesion-complex formation. Implicitly, this connection renders the assembly of adhesion dependent on the substrate stiffness.

Several efforts have begun to incorporate these simple ideas into more complex models that consider geometrically explicit adhesion complexes. A key finding from these analyses is that the softer the substrate is, the closer to the boundary of the complex the adhesion force concentrates. This in turn directly affects the dynamics of adhesion-complex remodeling (Gao et al. 2011, Qian et al. 2009). Other, more complex models of mechanosensing are based on the idea that polarized cell shapes, cell contractility, and adhesion sliding induce cytoskeletal shear that depends on the substrate stiffness (Friedrich & Safran 2012, Walcott & Sun 2010, Zemel et al. 2010). Hence, actin filaments and stress fibers would be aligned with the axis of polarity. One of the early partial tests for this idea is the recent experimental finding that the contractile deformations change the anisotropy of the cell cytoskeleton globally, which in turn changes active cytoskeletal forces and adhesion distributions in a substrate-stiffness-dependent manner (Trichet et al. 2012). However, as described above, the actomyosin machinery is organized differently in many migrating cell types, which also suggests that these more complex models are still fairly remote from the actual cell behavior. Future models of mechanosensing must integrate the rapidly growing experimental data on the force-dependent kinetics and molecular hierarchy of adhesion formation. Similar to the most complex models of the protrusion machinery, the role of mathematical modeling here will be to integrate and test the consistency of many diverse experimental data points and to elucidate which of the existing, more conceptual hypotheses of mechanosensing will survive. A second factor that must be incorporated into future modeling is feedback between mechanical forces, structural adaptation of adhesions, and signaling. Although experimentalists continue to acquire more and more quantitative information regarding the functional linkages between force, ultrastructure, and signals (Burridge & Wennerberg 2004), the mathematical models that would conceptualize these data are still lacking. Notable attempts over the past few years in the direction of molecularly explicit models of adhesion formation (Macdonald et al. 2008) and adhesion-mediated signaling (Cirit et al. 2010) have been turned a bit obsolete already by a steady inflow of new experimental data. This indicates how excitingly rapidly our knowledge of adhesions changes.

Last, but not least, there are several models that explicitly complement experimental approaches in understanding how adhesions, actin flow, and cell protrusion are co-organizing in space and time. Traction forces peak at a characteristic distance of 1–3 μm from the leading edge. The peak essentially colocalizes with a peak of adhesion density (Alexandrova et al. 2008, Gardel et al. 2008). The importance of these peaks is that they demarcate the boundary between lamellipodial and lamellar actin networks (Ponti et al. 2004). In the first computational model to explain this observation, Shemesh et al. (2012) posited that nascent adhesion complexes grow if the force applied to them exceeds a threshold, whereas they disintegrate and detach from actin with a rate exponentially increasing with force if the force is below threshold. Simulation of this model showed that very near the leading edge, nascent adhesions wither because of the lack of force. Gradually, though, the actin flow slows down and adhesions start to grip and grow because of the forces exerted by the drag of the actin filaments. Adhesions aggregate to a narrow band because they effectively take on the whole force of the actin-network recoil. Behind the band, the flow of the disintegrating actin network is so slow, and thus forces are so low, that adhesions cannot grow again.

Ji et al. (2008) provide another example of a model that integrates experimental data to decipher the balance between forces, actin flow, and cell edge movement. They assumed that spatiotemporal variations in the measured actin network flow of a cell result from spatiotemporal variations in adhesion, contraction, and propulsive forces exerted on the growing network. This allowed the reverse engineering of all forces, including membrane tension, from actin movements alone. They first validated their approach by correlating the location of predicted adhesion forces to the

molecular dynamics of adhesion sites and by correlating the location of predicted contraction forces with myosin aggregation. This modeling approach offered several intriguing insights into the mechanical regulation of cell protrusion: While the cell edge moves in cycles, an initially weak rate of actin-network assembly is sufficient to push the membrane forward; but then, as the membrane tenses, adhesions start to grip, predicting that even on a timescale of a few tens of seconds, adhesion assembly is controlled by force feedback. As the increasingly anchored actin network continues to push the membrane forward, the tension reaches a threshold beyond which the adhesion grip is no longer sufficient. The cell edge stalls forward movement, and the still-assembling actin network only slips backward. At the same time, the membrane tension begins to relax, permitting the onset of the next protrusion cycle. An important prediction from these time-shifted peaks in forward movement of the cell edge and in membrane tension is that the power output (membrane tension times motion velocity) of the protrusion machinery is maximal after fastest protrusion but before maximal membrane tension. Because the work of the protrusion machinery is accomplished by polymerization of actin filaments, this prediction implies that the rate of fastest filament assembly must also be delayed relative to the time point of fastest edge movement. Indeed, the authors were able to confirm this prediction experimentally by measuring the spatiotemporal variation of actin assembly concurrent with the actin network flows. In combination, this model and the data suggest that, for a sustained forward movement of the leading edge in productive protrusion cycles, the actin assembly must be reinforced in a temporally precise fashion to allow continued growth of the actin network against increasing membrane tension. Hence, the regulation of actin-network assembly itself must be mechanosensitive. Future work will have to reveal whether this sensitivity is a property of the actin network structure alone (Risca et al. 2012) or whether mechanoresponsive activation of regulatory signals is required to support the protrusion process.

ORGANIZATION OF THE ACTIN TREADMILL

The gradual remodeling of the actin network from the leading edge toward the cell rear and the recycling of actin units and other molecular factors from the rear to the front are essential parts of cell migration. As the leading edge of the cell moves forward, newly assembled parts of the actin network are left behind and start to disassemble, converting F-actin into G-actin. The latter diffuses in the cytoplasm and assembles onto uncapped filament barbed ends, the majority of which are at the leading edge. This cycle of assembly, disassembly, and reassembly is referred to as the actin treadmill (Pollard & Borisy 2003). The sites of assembly and disassembly and the aging of the actin network in between are spatially distributed over the lamellipodium. In the fast and steadily moving keratocyte cells, the lamellipodium spans nearly the entire cell (Svitkina & Borisy 1999); however, in most other cells, the lamellipodium is a structure only a few micrometers wide that morphs into a wider lamellar network in a marked transition of kinetic, kinematic, and molecular properties (Giannone et al. 2007, Iwasa & Mullins 2007, Ponti et al. 2004).

Following early models of actin-network self-organization into the treadmilling lamellipodial array (Carlsson 2001, Mogilner & Edelstein-Keshet 2002) (**Figure 2*b***), Stuhrmann et al. (2011) recapitulated the lamellipodial-to-lamellar transition. They considered continuous and deterministic distributions of length and nucleotide states of actin filaments from the front to the rear, as well as processes of branching, capping, hydrolysis, and cofilin and tropomyosin binding. The model suggests, for example, that all shorter filaments from the leading edge disassemble rapidly, leaving only longer filaments farther away from the front, and that fast binding-unbinding of cofilin to aging filaments creates a zone of disassembly. Surviving longer filaments associate with slowly binding tropomyosin, which stabilizes the lamellar network. Another model predicts sequences of discrete and stochastic events in the dynamics of network growth-retraction cycles owing to the

effects of random capping (Zhuravlev & Papoian 2009). And the previously discussed model by Shemesh et al. (2012) explains the mechanical rather than chemical features of the lamellipodium-lamellum transition. Perhaps the general lesson from these models is that the complex process of the actin treadmill must be examined quantitatively, experimentally, and theoretically in specific systems, to make sure that we first understand cell-specific details and then try to generalize.

To date, a detailed quantitative understanding through rigorous combinations of experiment and theory has been achieved only for simplified systems. An excellent example of such work is the study by Reymann et al. (2011) in which microscopy and modeling were combined to investigate mechanistically the distribution of cofilin along growing actin comet tails. The model is based on measured kinetics of actin assembly in the presence of profilin; kinetics of ATP hydrolysis and phosphate release from actin filaments; kinetics of capping protein incorporation, which controls actin-filament length within branched actin networks; and kinetics of interaction between ADF/cofilin and actin filaments, as well as the acceleration of phosphate release from neighboring subunits after ADF/cofilin binding. In agreement with the experimental results in this paper, the model could account for the spatial separation of the young, growing actin network; the aging ADP-loaded region; and the fragile, crumbling network at the very rear of the tail, with filament fragments rather than actin monomers floating away. This abrupt disintegration of the actin network at the rear, noticed also by Berro et al. (2010) and Smith & Liu (2013) and predicted theoretically for the first time by Michalski & Carlsson (2011), probably plays a significant role in the process of pulling the cell rear forward.

Along with the chemical mechanism of actin-network disassembly, myosin-induced disassembly is very significant (Vallotton et al. 2004, Wilson et al. 2010). The molecular mechanisms for a myosin-accelerated disassembly have remained enigmatic; an attractive possibility is that myosin forces break the filaments of an already weakened network into pieces, generating naked pointed ends with ADP-subunits that tend to depolymerize quickly. To map the assembly/disassembly in epithelial and keratocyte cells (**Figure 5*a***), respectively, both Vallotton et al. (2004) and Wilson et al. (2010) used a model based on mass conservation, which predicts locations of high network turnover from measured actin network flow and rates of net increase/decrease in actin density. They then discovered that zones of high disassembly colocalize with high myosin density (Wilson et al. 2010) and that acute activation of myosin motors results in a rapid increase in the rate of network disassembly, significantly before the disintegrating network also accelerates contractile flows (Vallotton et al. 2004). These data highlight the tight integration of mechanical and chemical cues in the regulation of the actin treadmill.

KERATOCYTE: INTEGRATED MODELS OF THE MECHANICS OF WHOLE-CELL MIGRATION

One of the greatest challenges for mathematical models is the integration of local models of protrusion, contraction, adhesion, and the actin treadmill. There are a growing number of such models (reviewed in Holmes & Edelstein-Keshet 2012), but so far most of them, though elegant and thought provoking, lack experimental verification. Not surprisingly, the simplest motile cell—the fish epidermal keratocyte—was the first to face theoretical scrutiny. This cell moves rapidly and steadily and has a characteristic, canoe-like shape (**Figures 4*b*** and **5*a***). Besides steady locomotion, its great advantages for quantitative understanding are the simplicity of its actin-network organization in a flat, treadmilling lamellipodium and a well-defined contractile zone consisting of a tight transversal arc of actomyosin bundles. For decades, this cell has remained among the favorite model systems for studying the biophysics of cell motility. A wealth of accumulated data (reviewed in Pollard & Borisy 2003) has attracted modelers and experimentalists receptive to modeling insights

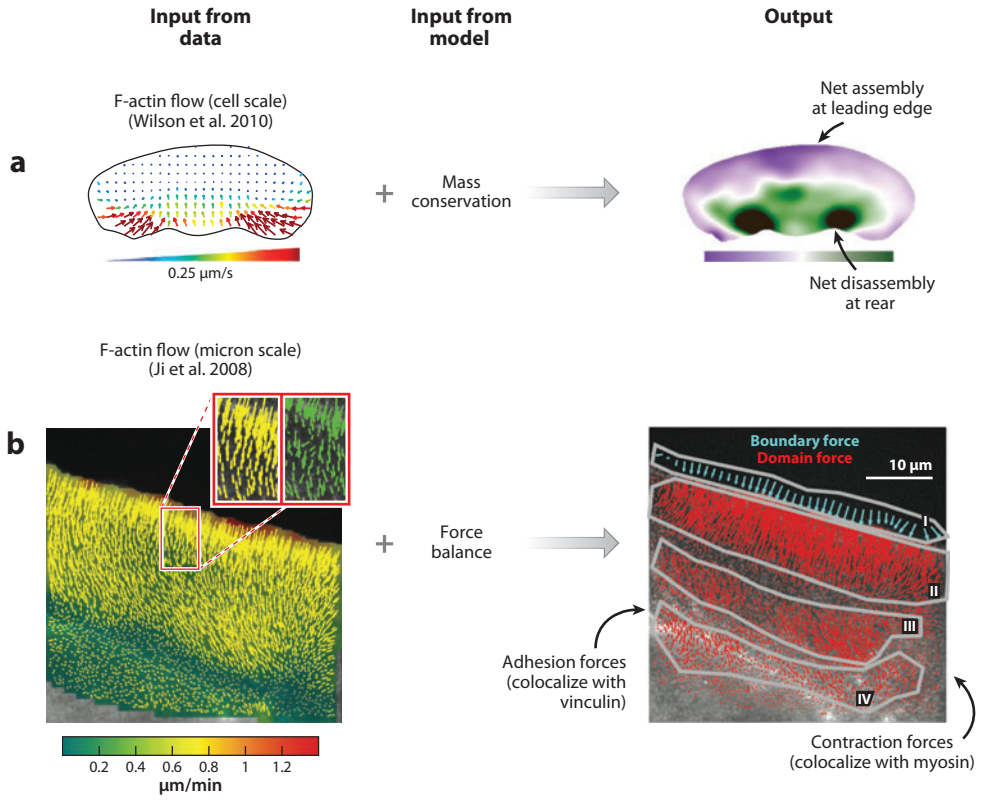

Figure 5

Mathematical models as data integrators. One role of mathematical modeling is that it allows data on a directly observable variable, such as the F-actin flow field (*left*), to inform another quantity of interest and ultimately yield biological mechanisms. (*a*) Wilson et al. (2010) developed a simple mathematical model based on mass conservation. When combined with the cell-scale F-actin flow field, the model predicted a distribution of net F-actin assembly and disassembly that revealed a role for myosin in F-actin disassembly. (*b*) Ji et al. (2008) developed a model based on force-balance principles, along with other assumptions, such as the short-timescale elasticity of the F-actin network. Micrometer-scale F-actin flow fields then allowed the calculation of intracellular force distributions. Together with further assumptions regarding the orientation of adhesive friction, this permitted elucidation of spatiotemporal distribution forces generated by actomyosin contraction, polymerization at the cell boundary, and adhesions.

to collaborate toward an integrated understanding of cell locomotion. A few key experimental findings laid down the agenda for modeling. First, Lee et al. (1993) discovered the geometric principle of keratocyte locomotion: graded radial extension, in which the actin network extends at the front and retracts at the rear in directions locally normal to the boundary. Thus, the peculiar shape of the motile keratocyte originates in graded extension-retraction rates in space. At the center of the leading edge, the net extension rate is maximal, and then the rate decreases along the front toward the sides, where the net retraction rates increase from the sides to the center of the rear. Second, Verkhovsky et al. (1999a) suggested that small clusters of myosin motors contract and bundle the treadmilling lamellipodial actin network (see network-contraction model in the section, How Does Actomyosin Contraction Work?). As the cell glides forward, these clusters move rearward in a cell frame of reference and accumulate in the transversal arc in front of a mechanically largely

passive cell body. Contractions within the elementary actomyosin clusters and bundles bend the transversal arc forward. In combination with myosin-mediated disassembly of the lamellipodial actin network, this geometry creates a graded retraction of the rear. Third, Grimm et al. (2003) observed that the density of actin filaments is graded at the leading edge, decreasing from the center to the sides, and proposed that, as a result, greater membrane resistance per filament toward the edge slows down actin polymerization, which would explain the curved form of the leading edge.

The earliest mathematical model of keratocyte motility, unfortunately largely overlooked, simply simulated strands of treadmilling actin filaments oriented precisely in one direction and wrapped in an elastic ring representing the membrane (Sambeth & Baumgaertner 2001b). Despite ignoring myosin and several essential elements of lamellipodial organization, including the unrealistic nature of long, treadmilling filaments rather than a treadmilling actin array, this model reproduced the slightly bent, rectangular shape of the motile keratocyte remarkably well. One valuable lesson from this early model was that it is hard to keep the total area of the virtual cell restrained. In this model, the rather idealistic assumption of an elastic membrane ring served to contain the lamellipodium.

For several years, the control of the cell area remained the central puzzle for modeling efforts. It was first solved by Keren et al. (2008) and definitely proven by Lieber et al. (2013) in works that combined experiment and model. Using the variability of cell shapes across large populations of motile keratocytes, Keren et al. (2008) found that the area of the motile cell remains constant because the lamellipodium is enveloped in an inextensible membrane bag. Moreover, they proposed that the actin band at the leading edge is self-organized by branching, capping, and lateral flow of actin into an array with an inverted parabolic density. The cell sides are demarcated by the critical density at which the small number of actin filaments is stalled by the membrane tension. Variations in cell shapes can be explained by variations in the filament density at the front, multiplied by the stall force per filament, and divided by the membrane tension: When this ratio is high, the cell is more canoe-like and faster and has a smoother shape, whereas cells with a low ratio are ragged, slow, and more disc-like. Hence, in the case of the keratocyte, a property as complex as cell shape can be reduced to a single elementary relation between global rate of actin assembly and membrane tension. Further evidence for this theory has come from studies of cytoskeletal fragments lacking a nucleus and organelles (Ofer et al. 2011). Ofer et al. (2011) demonstrated that the membrane tension and fragment shape evolve simultaneously from the balance of forces between the stalled filaments at the side pushing the membrane from within and the membrane tension crashing the weakened actin network at the rear. Finally, Rubinstein et al. (2009) and Barnhart et al. (2011) simulated centripetal flow of the viscous actin network powered by myosin contraction at the rear. By comparing the cell shapes on surfaces with higher and lower adhesion strengths and stronger and weaker myosin, they found that the centripetal flow is graded, which helps to maintain the cell shape, as foreseen by Verkhovsky et al. (1999a). The qualitative bottom line of these models is the insight that three mechanical modules, (*a*) graded actin treadmill in the inextensible membrane bag, (*b*) graded actin-myosin contraction, and (*c*) actin disassembly, maintain the steady and rapid locomotion of keratocytes.

Keratocyte locomotion is so beautiful from the physical point of view, and presents such a great example of a free-boundary problem from the mathematical point of view, that a score of sophisticated computational models drawing on the lessons described above have sprung up. These models also draw on the active polar gel theory that generalized the dynamics of actin filaments contracted by myosin motors (Kruse et al. 2005). Compared with those of Barnhart et al. (2011) and Rubinstein et al. (2009), who treated the actin network as an isotropic viscous fluid and adhesion drag as a parameter, these models started to explicitly include anisotropy of the partially aligned actin filaments and discrete slip-and-grip adhesions (Kuusela & Alt 2009,

Shao et al. 2012, Ziebert et al. 2012). One interesting lesson from this modeling surge is that multiple models with very different underlying assumptions can predict the same observed cell-motile behavior. For instance, Wolgemuth et al. (2011) demonstrated that four completely different assumptions about the control mechanisms of cell shape lead to the same shape. This means, first, that without feedback between experiment and theory one cannot understand motility. Second, multiple redundant mechanisms likely are at play, and one should not claim greater generality of any discovered mechanism than is warranted by the data at hand.

MODELING POLARITY AND SIGNALING IN MIGRATION

For the mechanical steps of cell migration to occur, the cell has to be polarized: Its front, sides, and rear must be defined. The problem of cell polarity in general is much wider than the polarization related to the onset of motility, and there is a wide repertoire of general polarization mechanisms (Nelson 2003). Hence, one of the great challenges is to understand which specific polarization mechanism or combination of mechanisms works in a specific system. Combined with experiments, modeling was, is, and will remain relevant to address this question. In addition, polarization mechanisms necessarily involve multiple nonlinear feedbacks on multiple spatiotemporal scales. Thus, modeling is frequently crucial to support the intuitive interpretation of experimental data. Owing to space limitations, we cannot do justice to all relevant aspects (for instance, we are not discussing the important polarity-driving processes of endo- and exocytosis, microtubules, symmetry breaking in actin gels, stochastic polarization, and mechanochemical patterns). Instead, we direct the reader to recent reviews covering these aspects (Asnacios & Hamant 2012, Diz-Muñoz et al. 2013, Goehring & Grill 2013, Vignaud et al. 2012) and concentrate on only a couple of topics.

The first of those is the fundamental question: How does the actin dendritic network stay polarized, with barbed ends oriented forward? The answer is not known, but a few conceptual mathematical models suggest plausible mechanisms. The earliest of those (Sambeth & Baumgaertner 2001a) is based on the possible autocatalytic character of the branching actin growth and on relevant competition for resources. For example, if both the length of existing filaments and the concentration of Arp2/3 complexes are limiting factors for the branching rate, and if there are two coexisting arrays, one made of right-oriented and another of left-oriented filaments, and if one of these arrays has a greater total filament length, then this dominating array will bind a disproportionally higher number of Arp2/3 complexes and branch off a greater number of nascent filaments. Those, in turn, will bind an even higher number of Arp2/3 complexes, and the math suggests that the ensuing positive feedback will eliminate one of the arrays, concentrating all F-actin in one polarized network.

Another model (Atilgan et al. 2005) shows mathematically that if branching occurs when Arp2/3 is bound to membrane-bound WASp and the Cdc42 signaling complex, and if transmembrane receptors involved in the recruitment of the Cdc42/WASP complex are conical or trapezoidal in shape, preferentially residing at the curved regions of the plasma membrane, then the spatial orientation of the Arp2/3 complex is restricted to the leading edge during each branching event. In that case, positive feedback is established at the leading edge: Growing actin filaments stretch and curve the membrane, and the Arp2/3 complex localizing to the region of highest membrane curvature produces nascent filaments, further increasing the curvature. Another plausible positive feedback, already mentioned above (Maly & Borisy 2001), that could lead to polarization depends on the assumption that barbed ends facing away from the load are more likely to be capped. Last, but not least, it was recently discovered in vitro that the Arp2/3 complex initiates nascent branches predominantly on the convex side of bent actin filaments (Risca et al. 2012), and the model in this

study suggests that the protruding actin array can stay polarized because the leading filaments are bent by the membrane load. Hence, nascent filaments branch off mostly from the mother filament side facing the leading edge.

The phenomena discussed so far are local. An interesting and fundamental question on the global scale is whether motility starts by polarizing the cell from the front (i.e., by creating a dominant protruding pseudopod) or by defining the rear first and only then establishing protrusion at the opposite side (Cramer 2010). At least in keratocyte cells and fragments, the data clearly point toward a rear-driven mechanism (Verkhovsky et al. 1999b, Yam et al. 2007). While the cell shape is still symmetrical, the centripetal actin flow accelerates at the future rear, followed by invagination of the edge, and only then does the opposite edge start to protrude. Existing mathematical models (Kozlov & Mogilner 2007, Wolgemuth et al. 2011, Ziebert et al. 2012) explain this as follows: If myosin density is increased at one side of the cell, the inward actin flow accelerates and the actin network is bundled, resulting in inhibition of protrusion. The inward movement of the respective edge condenses all myosin, further enhancing this process, while at the opposite edge the membrane tension drops (owing to the collapse of the future rear), allowing polymerization of the previously stalled branched-actin network to accelerate and protrusion to start. Recent experiments indeed confirmed that membrane tension is a crucial regulator of cell polarization (Houk et al. 2012). In fibroblasts, where polarization also often starts from the rear (reviewed in Cramer 2010), the mechanism is different and seems to be preceded by self-alignment of stress fibers stretching across the cell. Friedrich & Safran (2012) explain this alignment by considering the cell cytoskeleton as an anisotropic elastic body in which myosin-powered contraction, coupled with elastic deformation of the substrate, promotes fiber alignment.

Starting with Turing's seminal work in the fifties, many models have explained polarization as a result of a reaction-diffusion process involving the activator and inhibitor interacting and diffusing at different rates. For example, Marée et al. (2006) consider nonlinear interactions between diffusion of Rac, Rho, Cdc42, and PIP molecules in both cytosol and membrane (**Figure 4*b***) and signaling to the cytoskeleton dynamics downstream of the signal-polarizing module. Another model suggests self-polarization via autocrine signals, also upstream from the motile apparatus: Ligands released predominantly from one side of the cell activate receptors and intracellular signaling at the same active side, and near the opposite, inactive side, ligand shedding, receptor activation, and intracellular signaling are maintained at stably low levels (Maly et al. 2004). Yet other models propose that there is a reaction-diffusion system around the cell periphery inherent to the motile machinery itself, which does not require an upstream signaling module (Neilson et al. 2011).

Finally, a recent tour-de-force study (Ku et al. 2012) embraced the complexity of polarization by using modeling and experiment, without going into mechanistic details. Rather, this study used biochemical perturbations and high-throughput microscopy to explore causal interactions between front (actin), middle (microtubules), and back (myosin) modules in cells. By recording polarization levels of actin, tubulin, and myosin spatial distributions over multiple time points in 100,000 polarizing neutrophils, and by quantifying the degree to which perturbed response curves for marker-activity levels and spatial distributions deviated from control, this study revealed that a surprisingly simple circuit governs polarity: a feed-forward from the rear to the front, with microtubules signaling to both front and rear. This systems-level study creates a basis for future mechanistic understanding of polarization in this system.

Biochemical signaling not only permeates the polarity aspect of cell migration but also is intimately involved in all other steps of motility, especially guidance. The great majority of signaling models in cell motility address the phenomenon of chemotaxis (we refer to Iglesias & Devreotes 2012 for a recent review of such models). Modeling of other aspects of signaling in motility is

in its infancy, owing in part to scarce and confusing relevant quantitative data; however, novel experimental techniques, such as multiplexing, are starting to change this situation (Machacek et al. 2009).

FROM 2D TO 3D

Most models are limited to migration in 2D, justified by the flatness of the cell-motile appendages, or even 1D. The nature of this flatness is itself an open problem. Some technically very challenging 3D models of cells moving on flat surfaces have begun to emerge (Allena 2013, Herant & Dembo 2010, Zeng and Li 2011). The key challenge, however, is to understand how a 3D motile cell crawls through the extracellular matrix. Formidable difficulties faced by both modelers and experimentalists (Friedl et al. 2012) are that (*a*) classic polarized signaling and mechanical patterns that govern migration in 2D models often are not essential for efficient migration in 3D, (*b*) there are more modes of motility in 3D, (*c*) these modes of motility are very sensitive not just to the stiffness but also to the rheology and geometry of the extracellular matrix, and (*d*) microscopy data on spatiotemporal distributions of key molecules and force measurements are semiquantitative at best.

Nevertheless, a few models have started to examine mathematically the properties of 3D migration. In the pioneering work by Zaman et al. (2005, 2006), the virtual cell is but a material point describing the cell position in 3D space, which is associated with a vector describing the cell polarity and speed. The cell moves and turns according to a simplified force balance between the cell internal active and passive stresses and external passive stresses in the extracellular matrix. The model explains that, contrary to the 2D situation, the cell achieves maximal motility in the softest matrices, because the pore size of the extracellular matrix is the major limiting factor for the considered mode of crawling, and the matrix stiffness decreases with increasing pore size. Accordingly, matrix degradation by, for example, proteases may be a critical determinant of cell migration.

Borau et al. (2011) took the concepts in Zaman et al. (2005, 2006) one step further by considering the cell in 3D as a network of springs and contractile elements inside the extracellular matrix. The network adapts to the directions of the strain tensor in the matrix caused by cellular contractions and extensions, resulting in self-polarization and movement of the virtual 3D cell. The general insight from this model is that adhesion and contraction play fundamentally different roles in 2D and 3D, which is the emerging consensus of experimental studies (Even-Ram & Yamada 2005). Another model uses an assumption that only the cell-cortex contraction matters in 3D, and because the cortex has the topology of the spherical surface, the model becomes 2D (Hawkins et al. 2011). By considering myosin contractions and actin flow in the cortex, this model demonstrated that the actin flow converged to one of the cell poles. Coupled to the surrounding matrix, it is as if the cell generates a continuous rowing motion to propel itself forward, which was recently observed in a very specific system (Shih & Yamada 2010).

WHAT LIES AHEAD

Abercrombie (1980, p. 143) concluded his Croonian lecture by saying, "It seems to me that comprehensiveness is wanted in the subject [of migration], which is still inclined to suffer from fragmentation." Chances are that he would come to the same assessment again today. The past 35 years doubtless have brought much more detailed and, especially molecularly, more explicit understanding of the subprocesses driving cell migration. Our review highlights numerous examples in which phenomenological or physicochemical models have shed light on the mechanisms of protrusion, adhesion, and contraction. We had to leave out models of more specialized processes, such as blebbing and actin waves, as well as models that explain possible roles of other cellular components and processes, including microtubule dynamics and vesicle transport. Moreover, we

left out models that begin to address the differences between single-cell and collective migration. But these models do not change the fact that even now we have no quantitative understanding of how the subprocesses integrate and how this integration is affected by environmental cues. Building such a model will require a much deeper analysis of the dynamics of cellular signaling and its dependence on mechanical force feedback.

There are two key arguments for why it is worth it to build an integrated model of cell migration. First, the community needs a model for multiplexing experiments. The migration machinery consists of many more components than can be observed concurrently in space and time, today and in the foreseeable future. However, with a mathematical model in hand, data from a first experiment focusing on components *X* and *Y* can be merged with data focusing on components *Y* and *Z*, which can be tested for consistency with data from a third experiment focusing on *X* and *Z*. Second, an integrated mathematical model is needed to distinguish quantitative from qualitative origins of heterogeneity. Different cell types, but also different cells from the same cell type, can display significantly different migration behaviors. This includes the issue that the same cell type in different environments (e.g., 2D versus 3D) can display different behavior. Do these differences arise from fundamentally different interrelations between the elementary migration processes, or can they be explained by merely a shift in one or several parameters of the models describing particular elementary processes? Arguably, answering this question may be the most important contribution modeling should make toward unraveling the mechanisms of migration. Especially in view of the nonlinearity and redundancy of the pathways controlling migration, it is exceedingly difficult to address this question through experiment alone. Manipulation of one particular component of one elementary process may change the behavior of that process alone, but it may also affect the relationship between that process and several other processes, including their respective behaviors. As a result of this complexity, more and more experimental studies have produced apparently contradicting conclusions. But could it be that all these data describe the same overall system behavior, but at different operation points? Or are there truly different behaviors, and if so, where are the differences? We cannot think yet of an example in which modeling has been able to resolve these very issues. However, we designate this task as the ultimate quest in mathematical modeling effort.

With the capacity to explain heterogeneity will also come relevance of mathematical models for translational migration research. Models of this type could begin to provide answers to why the overexpression of the actin-bundling protein fascin enhances cell invasion and metastasis, or why the hyperactivation of ERK-MAPK signaling in bRaf-mutated cells leads to enhanced plasticity of cell migration. None of the mathematical models available today is anywhere near this level of prediction—and we suspect it will still take a while to get to this point. However, this is an exciting target for mathematical modeling. With a process as multifaceted as migration, it is nearly impossible to experimentally isolate the functions of disease-related distortions in pathways, whereas in silico experiments could screen millions of scenarios for how the aberration of a particular component of the machinery could translate into altered behavior. Even more powerful in silico experiments could screen these scenarios in different virtual environments, both mechanically and chemically, enabling the systematic investigation of mechanisms of cell adaptation that are of immense importance to disease progression but notoriously hard to capture experimentally. At this point, it is unknown how a model must look to make such predictions. The hope is that not every pathway must be described in complete molecular detail, but we do not know yet whether physiologically and pathologically relevant variation in cell migration behavior can be captured by higher-level principles. To make this fundamental choice in model design, modelers must interface their work and test hybrid descriptions of the cell-migration process in the context of quantitative data.

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