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# Do Cell Membranes Flow Like Honey or Jiggle Like Jello?

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**Cell membranes experience frequent stretching and poking: from cytoskeletal elements, from osmotic imbalances, from fusion and budding of vesicles, and from forces from the outside. Are the ensuing changes in membrane tension localized near the site of perturbation, or do these changes propagate rapidly through the membrane to distant parts of the cell, perhaps as a mechanical mechanism of long-range signaling? Literature statements on the timescale for membrane tension to equilibrate across a cell vary by a factor of ≈$10^6$. This study reviews and discusses how apparently contradictory findings on tension propagation in cells can be evaluated in the context of 2D hydrodynamics and poroelasticity. Localization of tension in the cell membrane is likely critical in governing how membrane forces gate ion channels, set the subcellular distribution of vesicle fusion, and regulate the dynamics of cytoskeletal growth. Furthermore, in this study, it is proposed that cells can actively regulate the degree to which membrane tension propagates by modulating the density and arrangement of immobile transmembrane proteins. Also see the video abstract here https://youtu.be/T6K7AIAqqBs.**

## 1. Introduction

Cell membranes consist of lipids, transmembrane proteins, and an assortment of other organic molecules. Do the mechanical properties of cell membranes resemble the properties of a purified lipid bilayer, perhaps with parameters adjusted to account for solutes? Or are there ways in which transmembrane and membrane-associated proteins fundamentally change the mechanics?

Two analogies may be useful: Most aqueous solutions flow pretty much like water, at up to ≈30% by weight of low molecular weight solutes.[1] Corrections to compressibility, viscosity, specific heat, and most other physical or thermodynamic parameters depend only weakly on solute concentration at such low concentrations. On the other hand, some aqueous gels can act as a semisolid, even at 1% gel by weight. For example, 1% agarose gel bears little mechanical resemblance to its primary component, water. Which analogy is a better description of the cell membrane? Is it a lipid bilayer, modestly perturbed by protein solutes? Or is it a 2D protein gel, permeated by interstitial lipid? Of course, cell membranes are wonderfully diverse, so answers may vary.

The fluid mosaic model, first proposed in 1972,[2] posits a cell bilayer membrane that can flow within its plane, but that has elastic properties when stretched or bent. In the initial version of this model, transmembrane proteins diffused freely within the plane of the bilayer (**Figure 1**A). Experiments later showed that many transmembrane proteins do not diffuse in cells,[3,4] and for those that do, diffusion coefficients are 10–100-fold lower than in pure bilayers.[5–7] Revisions to the model gradually added an increasing number of constraints due to specific interactions of membrane proteins with other membrane proteins, with lipid domains, or with cytoskeleton and extracellular matrix (Figure 1B,C).[8,9] While the presence of many types of membrane constraints in cells is well documented, the implications for membrane mechanics can be surprising. In this article, we consider effects of membrane constraints on membrane flow and stretching. We argue that in most cases, the cell membrane behaves more as a stretchy gel than as a flowing fluid.

The mechanical response properties of cell membranes are important because the mechanical tension in the cell membrane is a fundamental regulator of many membrane signaling and transmembrane transport processes.[10] Every protein conformational change that affects the projected area of the membrane is, in principle, sensitive to membrane tension. Tension also interacts with vesicle fusion, dynamics of the cytoskeleton, and cell growth and motility. Extensive literature has documented the importance of membrane tension as a cell biological parameter.[10–14] There is also a practical implication: pipette aspiration or tether pulling are sometimes used to perturb membrane tension in cells, for example, to study mechanosensitive ion channels.[15] One would like to understand how far and how fast these localized perturbations propagate.

## 2. A Conceptual Framework for Membrane Tension Propagation in Cells

The published literature contains widely divergent statements about how local changes to membrane tension propagate across a cell, ranging from “forces on the membrane at any point

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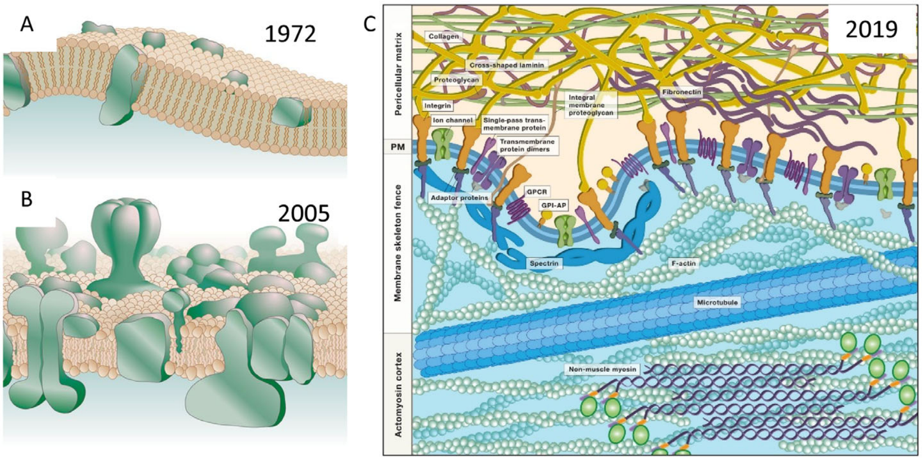

**Figure 1.** Evolving picture of cell membrane structure. A) A lipid bilayer contains a sparse distribution of freely diffusing transmembrane proteins. B) A lipid bilayer contains a dense and heterogeneous array of transmembrane proteins with localized domains containing distinct protein and lipid components. Adapted with permission.[2] Copyright 1972, American Association for the Advancement of Science and adapted with permission.[102] Copyright 2005, Springer Nature. C) The membrane comprises a dense and heterogeneous array of transmembrane proteins with strong interactions with the cytoskeleton and the pericellular matrix. These interactions suppress lateral motions and impose complex non-equilibrium patterns of membrane curvature. Adapted with permission.[103] Copyright 2019, Elsevier.

equilibrate within milliseconds"[16] to "there is no long-range propagation of membrane tension in cells over ≈10 min timescales"[3] (**Table 1**). These statements differ by a factor of $\approx 10^6$ in the claimed timescale. How can there be so much disagreement over so basic a question?

Here we summarize a conceptual framework for thinking about tension propagation in cells. In the sections below, we justify and expand on these results. Let $\sigma$ be the tension in the membrane. In the presence of a tension gradient $\nabla\sigma$, a membrane will flow at a velocity $\mathbf{v} = \frac{k}{\eta}\nabla\sigma$, where $k$ is the Darcy permeability of the array of obstacles and $\eta$ is the 2D membrane viscosity. The ratio $\frac{k}{\eta}$ is the 2D membrane mobility (the inverse, $\frac{\eta}{k}$ is the 2D membrane drag). In two dimensions, the Darcy permeability is approximately[17]

$$k \approx -\frac{a^2\,[1 + \ln(\phi)]}{8\phi} \qquad (1)$$

where $a$ is the radius of the obstacles and $\phi$ is their area fraction. At low $\phi$, the 2D Darcy permeability diverges as $k \approx \frac{a^2}{8}\phi^{-1}\ln(\phi^{-1})$. In three dimensions, the Darcy permeability of an array of immobile spheres at low $\phi$ is $k \approx \frac{2a^2}{9}\phi^{-1}$.[18] The 3D $\phi^{-1}$ scaling diverges significantly slower compared to the 2D $\phi^{-1}\ln(\phi^{-1})$ scaling.

Equation (1) is asymptotically correct at low $\phi$, matches more detailed calculations within 25% for $\phi < 0.2$,[17,19–22] and breaks down (predicts $k \leq 0$) for $\phi \geq 0.37$. There are few published measurements in cells of $a$ and $\phi$.[9,23]

If a membrane is pulled and it encounters resistance to flow, the membrane can stretch. A stretched membrane experiences a change in tension $\Delta\sigma = E\frac{\Delta A}{A}$, where $E$ is the stretch modulus, and $\frac{\Delta A}{A}$ is the fractional change in membrane area. Note that $E$ and $\sigma$ have the same units but represent different physical quantities. Membrane stretch is a highly nonlinear process, that is, the stretch modulus can vary depending upon the initial state of the membrane or the physiological state of the cell. Few published measurements directly assess the stretch modulus of cell membranes. Micropipette aspiration of neutrophils gave a membrane stretch modulus of 40 pN $\mu m^{-1}$[24,25]—substantially lower than the ≈100 000 pN $\mu m^{-1}$ stretch modulus of purified lipid bilayers.[26,27]

Once a membrane is stretched, it gradually flows past any obstacles to relieve the stretch. The balance of stretch and viscous forces causes tension to propagate diffusively, with a tension diffusion coefficient

$$D_\sigma = \frac{Ek}{\eta} \qquad (2)$$

Arguments over the speed of tension propagation boil down to different assumptions about the parameters $a$, $\phi$, and $E$ that go into calculation of $D_\sigma$ (there is less controversy about $\eta$).

Our experiments in five cell types found very small values of $D_\sigma$ in each, for example, 0.024 $\mu m^2\ s^{-1}$ in HeLa cells, implying little propagation of tension over biologically relevant timescales.[3] Some of the discrepancies between this finding and other reports may stem from genuine biological variation. Cells may dynamically regulate the number and position of transmembrane obstacles, affecting $k$. Cells may also dynamically regulate reservoirs of unstretched membrane, affecting $E$. Together these processes could lead to orders of magnitude variations in $D_\sigma$, with these variations occurring between cell types, over time within individual cells, or in different subcellular regions. Whether such variations in $D_\sigma$ actually occur remains to be determined.

## 3. How Does a Membrane Flow? Stokes' Paradox Brought to Life

Viscously dominated flows in two dimensions have unique properties, qualitatively different from in three dimensions.

**Table 1.** Literature statements on propagation of membrane tension in cells.

| Reference | Statement | Cell type |
|---|---|---|
| **Fast equilibrium of membrane tension** | | |
| Keren et al. "Mechanism of shape determination in motile cells." *Nature* **2008**, *453*, 475. | "Forces on the membrane at any point equilibrate within milliseconds." | Fish epithelial keratocytes |
| Mueller et al. "Load adaptation of lamellipodial actin networks." *Cell* **2017**, *171*, 188. | "However, lateral membrane tension cannot act locally as it equilibrates instantaneously across the cell surface." | Fish epithelial keratocytes |
| Ofer et al. "Actin disassembly clock determines shape and speed of lamellipodial fragments." *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 20394. | "Because membrane tension equilibrates rapidly, we assume that tension is spatially homogenous along the boundary." | Fish epithelial keratocytes |
| Houk et al. "Membrane tension maintains cell polarity by confining signals to the leading edge during neutrophil migration." *Cell* **2012**, *148*, 175. | "This tension rapidly propagates throughout the cell to act as a long-range inhibitor of leading-edge formation." | Neutrophils |
| Winkler et al. "Membrane tension feedback on shape and motility of eukaryotic cells." *Phys. D* **2016**, *318*, 26. | "...membrane tension acts as a global mechanical feedback that may constitute a conduit for rapid–note that tension relaxes on the time scale of few milliseconds–information transfer across the cell." | Simulations |
| Kozlov and Mogilner "Model of polarization and bistability of cell fragments." *Biophys. J.* **2007**, *93*, 3811. | "Since the membrane has properties of a 2D fluid, the tension $\gamma_{\mathrm{mem}}$ is isotropic and constant in the membrane plane." | Theory |
| Lieber et al. "Membrane tension in rapidly moving cells is determined by cytoskeletal forces." *Curr. Biol.* **2013**, *23*, 1409. | "Force equilibration within the membrane is rapid ($\approx$ milliseconds), so that a local increase in the force exerted on the membrane leads to an almost global increase in membrane tension." | Fish epithelial keratocytes |
| Schweitzer et al. "Theoretical analysis of membrane tension in moving cells." *Biophys. J.* **2014**, *106*, 84. | "...under static conditions, the lateral tension ... has to be isotropic and homogeneous throughout the whole membrane. Yet, membranes of moving cells undergo a complex in-plane flow..., which implies existence of tension gradients along the membrane surface." | Theory |
| Huse "Mechanical forces in the immune system." *Nat. Rev. Immunol.* **2017**, *17*, 679. | "...tensional changes in one region can propagate almost instantaneously to distal domains; this enables the rapid transmission of physical information from one side of the cell to another." | Leukocytes (Review) |
| Pontes et al. "Membrane tension: a challenging but universal physical parameter in cell biology." *Semin. Cell. Dev. Biol.* **2017**, *71*, 30. | "It is assumed that under static conditions, membrane tension is isotropic and homogeneous throughout the entire membrane." | (Review) |
| Sens and Plastino "Membrane tension and cytoskeleton organization in cell motility." *J. Phys. Condens. Matter* **2015**, *27*, 273103. | "3.3. Is membrane tension uniform in a given cell?<br>Since the cell membrane is a fluid, gradients of membrane tension should lead to membrane flow from regions of low tension towards regions of high tension, giving a rapid equilibrium of membrane tension over the cell surface. ... Experimentally there is to date little evidence for gradients in membrane tension." | Motile cells (Review) |
| Keren "Cell motility: the integrating role of the plasma membrane." *Eur. Biophys. J.* **2011**, *40*, 1013. | "The integrating role of membrane tension as a global mechanical regulator is analogous to the role of the cell's membrane potential as a regulator of its electrophysiological behavior." | (Review) |
| Diz-Muñoz et al. "Use the force: membrane tension as an organizer of cell shape and motility." *Trends Cell Biol.* **2013**, *23*, 47. | "Membrane lipids flow like a liquid and can almost instantaneously equilibrate $T_m$ [membrane tension] across the cell." | (Review) |
| Saha et al. "Joining forces: crosstalk between biochemical signalling and physical forces orchestrates cellular polarity and dynamics." *Phil. Trans. R. Soc., B* **2018**, *373*, 20170145. | "The protrusive forces from the actin growth lead to a nearly fourfold increase in membrane tension, which is thought to equilibrate rapidly across the cell." | (Review) |
| **Local variations in membrane tension** | | |
| Shi et al. "Cell membranes resist flow." *Cell* **2018**, *175*, 1769. | "...there is no long-range propagation of membrane tension in cells over $\sim$10-min timescales." | HeLa, 3T3 fibroblasts, MDCK, mBEC, neurons |
| Morris and Homann "Cell surface area regulation and membrane tension." *J. Membr. Biol.* **2001**, *179*, 79. | "...a local step tension perturbation is not felt instantaneously over the entire plasma membrane." | (Review) |
| Basu et al. "Cytotoxic T cells use mechanical force to potentiate target cell killing." *Cell* **2016**, *165*, 100. | "Although the fluid nature of lipid bilayers generally promotes rapid equilibration of applied force, local interactions with the cytoskeleton have been shown to generate inhomogeneities in tension." | T cells |

(*Continued*)

**Table 1.** Continued.

| Reference | Statement | Cell type |
|---|---|---|
| Lieber et al. "Front-to-rear membrane tension gradient in rapidly moving cells." *Biophys. J.* **2015**, *108*, 1599. | "Overall, our results indicate that even though membrane tension equilibrates rapidly and mechanically couples local boundary dynamics over cellular scales, steady-state variations in tension can exist in the plasma membranes of moving cells." | Fish epithelial keratocytes |
| Cox et al. "Removal of the mechanoprotective influence of the cytoskeleton reveals PIEZO1 is gated by bilayer tension." *Nat. Commun.* **2016**, *7*, 10366. | "...the tension in the bilayer can be modified by cytoskeletal proteins and linkages to the extracellular matrix." | HEK293 cells |
| Fogelson and Mogilner "Computational estimates of membrane flow and tension gradient in motile cells." *PLoS One* **2014**, *9*, e84524. | "The implicit assumption in most of the literature is that the plasma membrane flows forward effortlessly in motile cells. However, this assumption was never critically examined." | Theory |
| Sachs "Mechanical transduction by ion channels: A cautionary tale." *World J. Neurol.* **2015**, *5*, 74. | "Cortical forces are shared by the bilayer, the cytoskeleton and the extracellular matrix." | (Review) |
| Wu et al. "Membrane shape-mediated wave propagation of cortical protein dynamics." *Nat. Commun.* **2018**, *9*, 136. | "...increasing actin polymerization in our model enhanced local membrane/cortex tension...." | RBL-2H3 cells |
| Alimohamadi et al. "The role of traction in membrane curvature generation." *Mol. Biol. Cell* **2018**, *29*, 2024. | "the tangential traction captures the effect of local membrane tension and curvature." | Theory |
| Ellefsen et al. "Myosin-II mediated traction forces evoke localized Piezo1-dependent $Ca^{2+}$ flickers." *Commun. Biol.* **2019**, *2*, 298. | "cellular traction forces generate local increases in membrane tension that activate Piezo1 within spatial microdomains." | Human foreskin fibroblasts, mouse embryonic fibroblasts, and neural stem/progenitor cells |

This mathematical distinction has far-reaching biological implications.

Suppose a sphere is slowly dragged through a large tank of viscous liquid. Here "slow" means that viscous forces greatly exceed inertial forces (technically, that the Reynolds number $Re \ll 1$). In 1851, Stokes calculated the drag on the sphere,[28] and in 1905, Einstein used Stokes' result to determine the relation between the radius of the sphere and its Brownian diffusion coefficient.[29] Stokes' calculation showed that the flow velocity in the liquid decreases inversely with distance from the sphere. If the sphere is more than ≈10 radii from walls of the tank, it moves as if the walls were barely there. This is true both for drift under external forces and for Brownian motion.

In two dimensions, however, the flow-field of a slowly dragged disk decays much more gradually with distance $r$ from the disk—as $\ln(r)$, in fact. Since the logarithm function diverges at large $r$, it is not possible to have a disk moving at finite velocity and a flow profile that asymptotically approaches zero velocity at large distances from the disk. In the idealized 2D world, the boundaries affect the flow no matter how far away they are. This mathematical breakdown is called Stokes' paradox.

For 70 years, Stokes' paradox stymied efforts to apply Einstein's calculation to 2D diffusion, for example, of a transmembrane protein in a lipid bilayer. In 1975, Saffman and Delbrück proposed that, even for an isolated transmembrane protein, the flow is not purely 2D.[30] The aqueous media on both sides of the membrane have finite viscosities, and transfer of stress to these media quenches the logarithmic divergence at a characteristic length scale, the so-called Saffman–Delbrück length, $l = \mu' h/\mu$, where $\mu'$ is the 3D membrane viscosity, $h$ is the membrane thickness (≈5 nm), and μ is the viscosity of the surrounding aqueous media. Viscosity is 100–1000-fold higher in membranes than in cytoplasm, so the characteristic length scale is $l \approx 1$ μm. The 3D membrane viscosity, $\mu'$ (N s $m^{-2}$), is related to the often-used 2D viscosity $\eta$ (N s $m^{-1}$) by $\eta = \mu' h$. Experiments have confirmed the Saffman–Delbrück predictions for pure bilayers with dilute tracers.[31]

### 3.1. Drag from a Random Array of Obstacles

Consider a membrane punctuated by a random array of immobile obstacles, for example, transmembrane proteins attached to the cytoskeleton (**Figure 2**A). We seek to impose a membrane flow relative to the obstacles, but the no-slip boundary condition requires that the flow velocity be zero at the surface of each obstacle. If the obstacles are closely spaced compared to the Saffman–Delbrück length $l = \eta/\mu$, then each obstacle imposes a logarithmically decaying perturbation to the flow that reaches to the neighboring obstacles. From a hydrodynamic perspective, a 2D membrane with an array of immobile obstacles is equivalent to a 3D fluid with parallel immobile fibers, that is, a gel. The Stokes' paradox qualitatively explains why a solution of fibers quickly forms a semisolid gel while a solution of spheres remains fluid to high concentration. Lipid flow in cell membranes should be exquisitely sensitive to immobile obstacles, even at very low obstacle densities.

To make these ideas quantitative, we seek to estimate the Darcy permeability $k$ in the relation $\mathbf{v} = \frac{k}{\eta}\nabla\sigma$. The Darcy permeability has units of area, and the only length scale in the problem is the radius of the obstacles, so we can write $k = a^2 f(\phi)$, where $f(\phi)$ is a dimensionless function of obstacle area fraction $\phi$.

Calculation of the 2D drag function, $f(\phi)$, for a random array of obstacles is a hairy problem. The theory of flow through

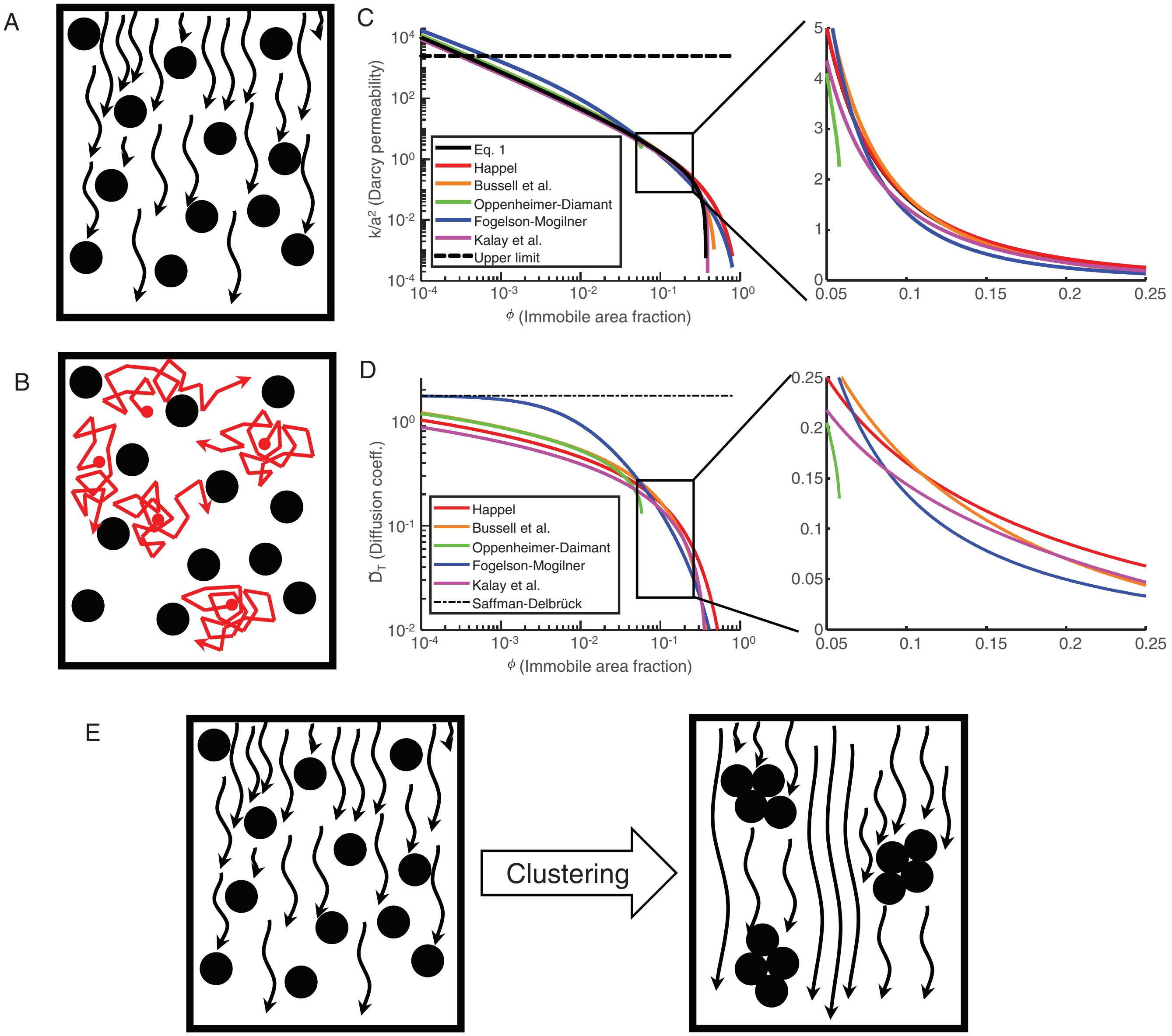

**Figure 2.** Effects of obstacles on membrane flow and tracer diffusion. A,B) Cartoons showing the influence of protein obstacles (black circles) on A) lipid flow and B) tracer diffusion. Obstacles can suppress bulk flows while tracers can still pass relatively unhindered. C) Effect of obstacle density on dimensionless Darcy permeability. At $\phi \approx 0.12$, $k/a^2 \approx 1$. The "upper limit" is set by viscous drag in the thin film of cytoplasm between the membrane and the underlying cytoskeleton. This limit was calculated assuming a Saffman–Delbrück length $l = 1000$ nm, spacing between the membrane and the cytoskeleton $d = 10$ nm, and an obstacle radius $a = 2$ nm. Details of the calculation for each curve are in the Supporting Information. D) Effect of obstacle density on dimensionless tracer diffusion coefficient, $\tilde{D}_T = \frac{\pi\eta}{k_B T} D_T$. Happel and Fogelson–Mogilner calculated Darcy permeabilities that were recast to diffusion coefficients using Equation (3). E) Clustering of obstacles enhances membrane flow without increasing $\phi$. Clustering obstacles into groups of $N$ increases Darcy permeability by a factor of $N$.

a porous medium was first developed almost 100 years ago by Kozeny[32] and Carman,[33] in the context of hydraulic engineering. Happel[17] adapted the Kozeny–Carman approach to an array of parallel rods. Howells[34] performed a more detailed calculation for the same geometry. Bussell et al.[19] applied the Howell calculation to cell membranes. More recently, Fogelson and Mogilner[22] performed numerical simulations of membrane flow past a random array of obstacles and developed asymptotic expressions to fit the low and high $\phi$ regimes.

### 3.2. Tracer Diffusion Is Related to Membrane Mobility

A common response to the assertion that cell membranes strongly resist flow is "but tracer diffusion studies clearly show that the membrane is fluid!" Can a membrane appear microscopically fluid for diffusion of molecular-scale tracers, while still appearing almost solid-like for bulk flows?

Let us compare the effects of obstacles on tracer diffusion and on bulk flow (Figure 2). The Einstein and Saffman–Delbrück theories together correlate the tracer diffusion coefficient ($D_\mathrm{T}$) with the drag force per obstacle ($\zeta$) through $\zeta = \frac{\ln(l/a_\mathrm{T})-\gamma}{\ln(l/a)-\gamma} \cdot \frac{k_\mathrm{B}T}{D_\mathrm{T}}$. Here $a_\mathrm{T}$ is the radius of the tracer, $k_\mathrm{B}$ is Boltzmann constant, and $T$ is the absolute temperature. If the tracers have the same size as the obstacles, then $\zeta = \frac{k_\mathrm{B}T}{D_\mathrm{T}}$ . The total drag force from $N$ obstacles, $N\zeta$, should equal Brinkman's mean-field drag force, $\frac{\eta}{k}A$, where $A$ is the area of the membrane.[35] The number-density of obstacles is related to their area fraction by $\phi = \frac{N\pi a^2}{A}$ . Making this substitution leads to the relation between tracer diffusion and the Darcy permeability[19]

$$\frac{k}{a^2} = \frac{\pi\eta D_\mathrm{T}}{k_\mathrm{B}T\phi} \tag{3}$$

The factor of $\phi$ in the denominator of Equation (3) implies that bulk flow is far more sensitive to obstacle density than is tracer diffusion. At low $\phi$, $D_\mathrm{T}$ scales as $\ln(\phi^{-1})$, whereas $k$ scales with $\phi^{-1}\ln(\phi^{-1})$.

Figure 2C,D quantitatively illustrates the drastic difference between Darcy permeability ($k$) and tracer diffusion ($D_\mathrm{T}$) in their sensitivities to $\phi$: when $\phi$ increases from $10^{-4}$ to 0.1, $D_\mathrm{T}$ decreases by approximately tenfold (Figure 2D), while $k$ decreases by ≈10 000-fold (Figure 2C). For the same reason, Darcy permeability can be many orders of magnitude lower in cellular versus purified membranes, but tracer diffusion typically differs by a factor of only 10–100. In a cell membrane, facile diffusion of tracers can coexist with almost complete suppression of flow. The familiar 3D analogy is that a drop of dye will diffuse almost unhindered through an agarose gel, though macroscopically the gel appears as a solid.

Several efforts have incorporated hydrodynamic coupling into calculations of tracer diffusion.[19–21] Oppenheimer and Diamant[20] calculated an interpolation between the Saffman–Delbrück diffusion coefficient and the obstacle-dominated diffusion coefficient, thereby avoiding the $\ln(\phi^{-1})$ divergence of $D_\mathrm{T}$ at $\phi = 0$. Kalay et al.[21] combined numerical simulations and analytical calculations to tackle the same problem, including the effect of discrete lipid size. Equation (3) permits us to interconvert calculations of tracer diffusion and of membrane mobility.

Experiments in artificial model membranes with added obstacles have explored in detail how obstacle density and size affect tracer diffusion.[36,37] Tracer diffusion studies in cells are broadly consistent with these theoretical predictions.[19]

### 3.3. Comparison of Theoretical Predictions of Membrane Mobility

All published calculations show similar trends for the dimensionless Darcy permeability $k/a^2$, as a function of obstacle area fraction $\phi$ (Figure 2C). Each calculation has its own domain of validity. All literature results, except for Fogelson–Mogilner, are consistent at $\phi < 0.05$. Fogelson–Mogilner gives incorrect scaling of $f(\phi)$ at low $\phi$ because their analytical approximation did not include the long-range hydrodynamic coupling special to two dimensions. Kalay et al., Happel, and Fogelson–Mogilner are within a factor of 2 of Bussell et al. for $0.02 < \phi < 0.20$. Kalay et al. breaks down at $\phi > 0.38$, and Bussell et al. breaks down at $\phi > 0.47$. Fogelson–Mogilner and Happel remain consistent with each other up to $\phi \approx 0.80$. While some specialized membrane structures, for example, bacteriorhodopsin plaques, have nearly close-packed proteins,[38] in most cases, the density of immobilized transmembrane proteins is $\phi < 0.25$.[9]

The dimensionless tracer diffusion coefficient, $\tilde{D}_\mathrm{T} = \frac{\pi\eta}{k_\mathrm{B}T}\ D_\mathrm{T}$, varies much more slowly as a function of $\phi$ (Figure 2D). Oppenheimer–Diamant breaks down at $\phi > 0.058$ but is the only calculation to correctly interpolate tracer diffusion between Saffman–Delbrück and obstacle-dominated regimes in the low $\phi$ limit. Comparison of Figure 2C,D highlights the different sensitivities of membrane flow and tracer diffusion to obstacle density.

Despite the differences between the various calculations, there is little motivation to further improve concordance among the theories because the underlying assumptions (a random distribution of equal-sized circular obstacles) are unlikely to apply with high accuracy in the real world anyway. For instance, single-particle tracking experiments in cell membranes have suggested a heterogeneous array of “corrals” that lead to nonclassical diffusion.[4,39–41] At present, data on the microstructure of membrane obstacles are lacking. When such data become available, numerical simulations will likely be needed to make accurate inferences about membrane mobility.

### 3.4. Corrections due to Cytoplasm Viscosity

The calculations discussed above break down in the limit of very low $\phi$. Viscous drag between the membrane and the cytoskeleton introduces an additional impediment to membrane flow. The details of this interaction are likely complex, but as a first approximation, one can model the situation as a membrane atop a solid boundary, separated by an aqueous film of thickness $d$. The relation between tension gradient and membrane velocity for this scenario is $\mathbf{v} = \frac{d}{\mu}\nabla\sigma$, where $\mu$ is the viscosity of the cytoplasm. This membrane–cytoskeleton drag dominates if $k/\eta > d/\mu$, or equivalently if $k > d\,l$, where $l = \eta/\mu$ is the Saffman–Delbrück length. Since $d \approx 10$ nm[42] while $l \approx 1$ µm, membrane–cytoskeleton drag becomes important for $k^{1/2} > 100$ nm. Assuming an obstacle radius $a \approx 2$ nm, then reference to Figure 2C shows that membrane–cytoskeleton drag dominates over drag from in-membrane obstacles for $\phi < 10^{-4}$–$10^{-3}$. We anticipate that such low values of $\phi$ are rarely, if ever, found in intact cell membranes.

### 3.5. Estimates of Membrane Mobility

The 2D viscosity of lipid bilayers is approximately $\eta \approx 0.001$–$0.01$ pN s µm$^{-1}$.[43,44] What about $\phi$ and $a$? Widely divergent values have been used in the theoretical analyses of membrane flow. **Table 2** gives these estimates, along with the resulting estimates for membrane mobility ($k/\eta$). The mobility estimates vary by a factor of $>10^4$. At present, it is not clear whether these different results reflect genuine variations between cell types, or if some of the published numbers are incorrect.

Shi et al., Bussell et al., and Kalay et al. estimated membrane mobilities of $k/\eta \approx 1\ \mu\mathrm{m}^3\ \mathrm{nN}^{-1}\ \mathrm{s}^{-1}$. To gain an intuition for this

**Table 2.** Estimates of membrane mobility according to published theoretical analyses.

| Reference | Cell type | $a$ [nm] | $\phi$ | Membrane mobility $k/\eta$ ($\mu m^3$ $nN^{-1}$ $s^{-1}$) |
|---|---|---|---|---|
| Shi et al.[3] | HeLa, fibroblasts, epithelial, endothelial, neurons | 2 | 0.18 | 0.6 |
| Bussell et al.[19] | Erythrocytes, lymphocytes | 2 | 0.1–0.2 | 2.2–0.5 |
| Kalay et al.[21] | Unspecified | <2 | 0.22 | <0.4 |
| Fogelson and Mogilner[22] | Fish keratocytes | 20 | 0.1 | 220 |
| Oppenheimer and Diamant[20] | Unspecified | 5 | $10^{-3}$–$10^{-2}$ | 7300–440 |

Values for $a$ and $\phi$ are given as approximations or ranges in most articles. For all articles, we calculated Darcy permeability, $k$, using the formulae from Bussell et al. (see the Appendix in Supporting Information), and calculated mobility $k/\eta$ assuming $\eta = 0.003$ pN s $\mu m^{-1}$.

level of mobility, one can imagine a cell membrane where the tension on one side is of order the value typically measured in cells ($\approx$10 pN $\mu m^{-1}$)[45] and gradients of this magnitude occur over cellular dimensions ($\approx$10 μm). Then membrane flows would be only $\approx$1 nm $s^{-1}$. Without invoking any specialized structures—just a random arrangement of protein-sized obstacles at biologically realistic density—we see that cell membranes can be highly resistant to flow. On the other hand, Fogelson and Mogilner assumed tenfold larger obstacle radius, and Oppenheimer and Diamant assumed 10–100-fold lower obstacle area fraction. These differing assumptions lead to drastically less resistance to flow.

### 3.6. Biological Regulation of Membrane Mobility: Clustering and Immobilization

The scaling of Darcy permeability with $a$ and $\phi$ in Equation (1) may have profound implications because these parameters can be dynamically regulated in cells. Receptor clustering is associated with many signaling pathways.[46,47] Clustering of obstacles into aggregates would increase the effective value of $a$ while keeping $\phi$ constant (Figure 2E). Specifically, clustering obstacles into groups of $N$ would increase the Darcy permeability by a factor of $N$. Protein-rich but widely spaced focal adhesions or adherens junctions impose far less resistance to flow than would the same number of immobile proteins uniformly spread throughout the membrane. Increases in membrane flow may be a previously unrecognized consequence of receptor clustering. Clustering of a substantial portion of transmembrane proteins will also facilitate diffusion of other transmembrane proteins not affiliated with the clusters (one should then treat the tracers and obstacles as having different sizes ($a_T \neq a$) in calculations leading to Equation (3)).

Receptor immobilization has also been associated with signaling. For instance, lateral mobility of AMPA receptors is regulated by intracellular $Ca^{2+}$ concentration in neurons;[48] and activation of the high-affinity IgE receptor FcεRI suppresses its diffusion in mast cells and basophils.[49] Converting a mobile receptor to an immobile one increases $\phi$ without affecting $a$. Immobilization of a substantial number of transmembrane proteins will suppress membrane flow, and will also suppress (to a less extent) diffusion of other transmembrane proteins even if not specifically bound. On the other hand, during major cytoskeletal remodeling events (e.g., mitosis, cell migration), immobile transmembrane proteins may detach from the cytoskeleton, resulting in a drastic increase of membrane flow. Indeed, removal of membrane-binding myosin leads to an apparent increase in lipid flow.[50]

## 4. How Does a Membrane Stretch?

If a membrane is tugged and it encounters resistance to flow, then the membrane will stretch with a stretch modulus $E$. We now consider stretching forces.

To measure the stretch modulus, one applies a tension change ($\Delta\sigma$) and measures the fractional response in membrane area $\frac{\Delta A}{A}$. The stretch modulus is $E = \frac{\Delta\sigma}{\Delta A} A$. When stretching a cell membrane, a key question is: what to use for $A$? This area should correspond to the region impacted by the applied tension change, but if one does not know how the tension propagates, one cannot estimate $A$.

To avoid this quandary, one can apply a global tension change to the entire cell membrane through techniques such as cell stretching/squeezing, or full cell aspiration.[24] Then, $A$ corresponds to the projected membrane area of the full cell. When local tension perturbations are applied, one should treat "$A$" as the area of a small subcellular region of size determined by the spreading of the tension propagations.[51]

In various cell types including neurons,[52] fibroblast,[53] outer hair cells,[54] neutrophils,[55] fish epithelial keratocytes,[56] and microglial cells,[57] membrane tethers of length up to $\approx$10 μm can be pulled with nearly constant pulling force, implying an effective stretch modulus $E \approx 0$. In this regime, there is negligible propagation of membrane tension since membrane tension is not perturbed by tether pulling. The very small value of $E$ is explained by the presence of reservoirs of folded or tubular membrane that maintain a nearly constant tension under increase in projected membrane area.[11,51,58,59] These membrane reservoirs should be considered as reservoirs local to the pulled tether. Next, we discuss models for interpreting these experimental results.

### 4.1. Models of Membrane Stretching

In a free membrane, thermal fluctuations cause undulations in the membrane topography (**Figure 3**A). Stretching suppresses these undulations, decreasing the configurational entropy. Under strong stretch, the restoring force comes primarily from the intermolecular interactions within the lipid bilayer. Stretch moduli of pure lipid bilayers are $E \approx 100\,000$ pN $\mu m^{-1}$, implying that membranes are almost inextensible under cellular forces.[26,27] Simple mathematical models of these processes[60] are in quantitative agreement with experiments in purified bilayers,[26,27] and set an upper bound for membrane stretching modulus in cells.

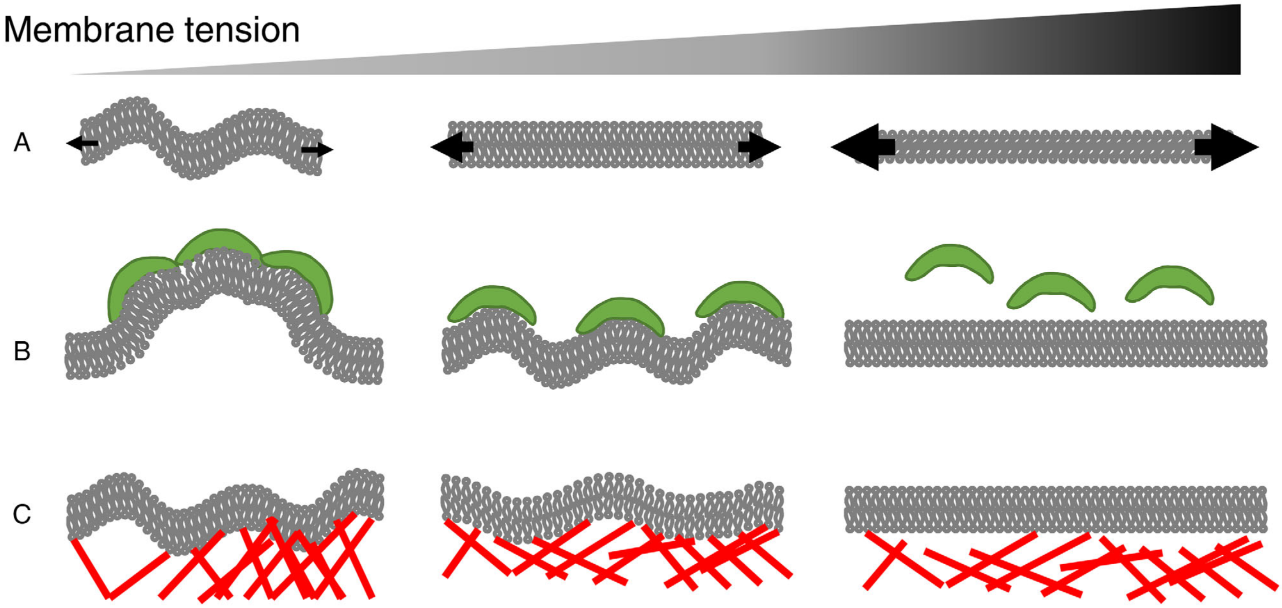

**Figure 3.** Contributions to membrane tension in cells. A) In an isolated bilayer membrane, stretch suppresses thermal fluctuations and then deforms the internal structure of the bilayer. B) When membrane-bound proteins induce curvature, stretch disrupts in-plane protein-protein interactions and then causes proteins to dissociate from the membrane. C) Stretch distorts the cytoskeleton, and then disrupts cytoskeleton-membrane attachments.

Proteins can change this picture radically, through several mechanisms (Figure 3B). Proteins that bend the membrane can introduce transverse ruffles,[61] or in extreme cases, can even nucleate tubes[62,63] or pinch off vesicles.[64,65] These proteins introduce a coupling between the bending energy (of the protein–membrane complex) and the stretching.

Several protein molecules might introduce bends of the same sense into a membrane. Under low tension, there is then an effective attraction between the proteins due to the ability to share elastic membrane deformation energy when closely spaced.[66] Changes to the configurational entropy of the membrane can also induce Casimir-like attractive interactions between proteins.[67] Under high tension, however, large regions of high curvature are disfavored, causing the protein domains to break up.[68,69] Thus there is also a coupling between the in-plane translational entropy of the proteins and the membrane stretching.

Finally, for proteins that can equilibrate between membrane-bound and free-solution states, changes in membrane tension can tilt this equilibrium (Figure 3B).[61] If the bound form of the protein introduces curvature into the membrane, then membrane tension favors the unbound state. For instance, membrane tension can drive disassembly of aggregates of Bin/amphiphysin/Rvs (BAR)-domain proteins[68,70,71] and dissociation of coating proteins such as clathrin or caveolin from the membrane.[72,73] BAR domain-coated membrane tubes have recently been proposed to control membrane tension during bleb formation.[51] On the other hand, if the bound form of the protein increases the membrane geometrical area (e.g., by inserting a span across the membrane), then tension can favor the bound state. This may occur, for instance, in insertion of epsin N-terminal homology domain (ENTH) proteins or $\alpha$-synuclein into membranes.[74,75]

Cytoskeleton introduces yet another change in the stretching properties of the membrane (Figure 3C). Cytoskeletal elements can poke or pull on the membrane. As above, tension seeks to smooth these deformations. However, in the case of the cytoskeleton, the perturbing elements are semisolid, so stretching of the membrane is accompanied by deformation of the cytoskeleton.[76] When the cytoskeleton is dynamic, membrane stretch may drive local rearrangements of the cytoskeleton,[50] or may break cytoskeleton–membrane interactions. Thus, the apparent stretch modulus of the membrane depends sensitively on details of cytoskeletal mechanics and cytoskeleton–membrane interactions. Transfer of membrane tension to cytoskeletal elements can drastically alter the tension experienced by mechanosensitive ion channels.[77]

### 4.2. Do Cell Membranes Have a Stretch Modulus?

The very concept of a membrane stretch modulus may be ill-defined in the context of a cell. The stretch modulus is defined as the increase in membrane tension for a fractional increase in membrane area. Time does not appear in this definition. Implicitly, one assumes that the stretching happens slowly, so the membrane remains in thermodynamic equilibrium throughout. For an isolated membrane, this means waiting for the longest wavelength thermal fluctuations to relax: ≈0.1 s for a 10 µm vesicle.[78]

In the presence of proteins or cytoskeleton, the relevant dynamics can be much slower.[53] Binding of a protein to a membrane and rearrangement of proteins within a membrane might take seconds to minutes. Cytoskeletal rearrangements or making and breaking of cytoskeleton-membrane linkages could take minutes to hours. In these contexts, a step-wise increase in membrane area could lead to a slow and kinetically complex increase in membrane tension, and the membrane stretch modulus is no longer a well-defined quantity. Measurements on membrane tethers pulled from cells typically show an irregular and kinetically complex evolution of membrane tension in response to a transient extension of the tether.[3,53] When pulling a membrane tether, the apparent stretch modulus is ≈0 when the tether is short (typically ≈10 μm).[53] As one slowly stretches the tether, the stretch modulus of the cell membrane gradually increases to a non-zero value, likely represented by the stretch modulus measured by Needham and Hochmuth (40 pN $\mu m^{-1}$).[24] Eventually, as the stretching proceeds, the stretch modulus approaches that of pure lipid bilayers (≈100 000 pN $\mu m^{-1}$).[26]

Indeed, a substantial literature has explored the role of the cytoskeleton in "mechanoprotection" of the cell membrane.[77,79–81] Plastic (i.e., locally irreversible) disassembly of caveolae and disruption of membrane–cytoskeleton interactions provide a path for absorbing membrane stress while preserving the all-critical barrier integrity of the membrane. This behavior is reminiscent of the "crumple zones" engineered into modern cars to protect the passenger compartment in the event of a crash.

Evidence for mechanoprotective interactions comes from several directions. Tethers pulled from fibroblast membranes irreversibly altered the apparent membrane area, demonstrating that membrane stretch in cells has a plastic as well as elastic component.[53] Pharmacological perturbations to the cytoskeleton greatly decreased the overall stiffness of the membrane, but also led to more reversible increases in tension as a function of tether stretch.[53] Together, these experiments demonstrated that dynamic membrane–cytoskeleton interactions regulate the apparent stretch modulus of the membrane. Finally, creeping flow of a membrane relative to the cytoskeleton, as we saw above, leads to a slow and kinetically complex evolution of membrane area in response to a step-wise local perturbation to membrane tension, for example, from a pulled tether. In view of these complex effects, the membrane stretch modulus should not be viewed as an absolute property of a cell, but rather as a summary of the outcome of a specific measurement paradigm (stretch magnitude and duration) under defined physiological conditions.

## 5. Combining Stretching and Flow: Diffusion of Membrane Tension in Cells

It is not practical to impose a uniform tension gradient on a cell membrane. More typically, a perturbation to tension is applied locally, for example, by a cytoskeletal filament, a vesicle fusion event, or a focal adhesion to a substrate or other cell. The membrane can then respond in two ways: by stretching or by flowing. Initially, one expects the membrane to stretch locally. Flow then gradually causes the stress to relax.

Simple force-balance arguments show that this interplay of stretch and flow causes membrane tension to propagate following a diffusion-like equation, with diffusion coefficient $D_\sigma = \frac{Ek}{\eta}$ .[3] As we saw in Table 2, several theoretical estimates give a membrane mobility $k/\eta \approx 1\ \mu m^3\ nN^{-1}\ s^{-1}$ (though other estimates are $\approx 10^3$-fold higher). A value for the stretch modulus consistent with whole-cell aspiration experiments and tether pulling experiments in cells, $E \approx 10$ pN $\mu m^{-1}$,[24,25] gives a tension diffusion coefficient $D_\sigma \approx 0.01\ \mu m^2\ s^{-1}$. Our experimental measurements of tension diffusion gave $D_\sigma \approx 0.024\ \mu m^2\ s^{-1}$,[3] in reasonable agreement with this simple estimate.

This estimate implies a time of ≈10 min for tension to diffuse from one side of a 10 μm cell to the other, but only ≈1 s for tension to diffuse across a 400 nm dendritic spine head, and ≈0.1 s for a 100 nm presynaptic active zone. The steep dependence of $k$ on $\phi$ implies that modest changes in the density of transmembrane obstacles could have substantial impact on diffusion of tension. For instance, a tenfold decrease in the obstacle density from $\phi = 0.20$ to $\phi = 0.02$ is expected to lead to a 42-fold increase in $D_\sigma$; and a tenfold increase in $E$ to 100 pN $\mu m^{-1}$ would lead to a further tenfold increase in $D_\sigma$.

Similar arguments have been used to show that the hydrostatic pressure in the cytoplasm also propagates diffusively through cells, though the diffusion coefficient for pressure, $D_P \approx 50\ \mu m^2\ s^{-1}$, is ≈200-fold larger than our estimate for membranes on account of the correspondingly lower viscosity of the cytoplasm compared to the cell membrane.[82,83]

One must distinguish the diffusion coefficient of tension, $D_\sigma$, from the molecular diffusion coefficient, $D_T$, of a tracer particle within the membrane. These quantities have the same units, but they represent different physical processes. $D_\sigma$ depends on the stretch modulus of the membrane, while $D_T$ does not. Just as a drop of dye will gradually diffuse through a semisolid agarose gel, one can expect individual proteins or labeled lipids to diffuse in the plane of a cellular membrane, even when the membrane strongly resists bulk flow.

## 6. Experiments on Propagation of Membrane Tension

There have been few direct measurements of the propagation of membrane tension in cells. Early tether-pulling experiments examined the interaction of tethers successively pulled on opposite sides of a fibroblast.[53] These experiments suggested a shared membrane reservoir but did not assess the timescale of membrane sharing. Measurements on motility and shape determination in fish keratocytes[16] and in neutrophils[55] were consistent with models in which membrane tension rapidly equilibrated cell wide, but these experiments did not explicitly measure tension propagation.

Measurements of membrane tension propagation are complicated by the fact that local perturbations to the membrane could induce cytoskeletal deformations that might propagate rapidly to other regions of the cell.[84] For instance, during rapid changes in cell shape, the membrane and cytoskeleton stretch coherently, as in the folds of an accordion.[85] These changes lead to long-range propagation of changes in membrane tension, without sliding of membrane relative to cytoskeleton. Distinguishing membrane-mediated versus cytoskeleton-mediated conduction of mechanical signals is a challenging problem.

To probe tension propagation rigorously, one should perturb tension in one part of a cell, for example, by pulling a tether, and monitor tension elsewhere. In recent experiments, we used pairs of tethers to perturb and monitor tension.[3] We did not observe any signs of long-range tension propagation in HeLa cells, 3T3 fibroblasts, Madin–Darby canine kidney epithelial cells, mouse brain endothelial cells, and in the proximal dendrites of cultured rat hippocampal neurons. Measurements of tension relaxation in single tethers pulled from HeLa cells were consistent with a very small tension diffusion coefficient, $D_\sigma \approx 0.024$ µm$^2$ s$^{-1}$.

Our results and the earlier work asserting sub-second tension relaxation in motile cells[16,55] are not necessarily inconsistent, because these experiments were performed on different cell types. To move, motile cells must translate the membrane relative to the cytoskeleton. These cells may have developed specialized structures to permit this flow to occur. Fish skin keratocytes,[16] neutrophils,[86] and the slime mold *Dictyostelium discoideum*[86] crawl at a speed of ≈0.1 µm s$^{-1}$. At a membrane mobility of 1 µm$^3$ nN$^{-1}$ s$^{-1}$, the tension gradient across a 10 µm-wide cell would be ≈1000 pN µm$^{-1}$. This tension gradient is comparable to the rupture strength of cell membranes.[87] Modestly lower density or greater spacing of membrane obstacles would protect motile cells from shredding their membranes and allow equilibration of membrane tension on the timescale of minutes. These possibilities suggest future work to characterize membrane obstacles in motile cells; and also to perform double-tether experiments to measure tension propagation directly in motile cells.

### 6.1. Needs for Tool Development

We are still far from having a dynamical picture of cell membrane tension and its subcellular regulation. The fact that variations in membrane tension can be substantial and long-lived within a single cell, raises the need for better tools to map membrane tension. Several recent reports of small-molecule[88,89] and protein-based[90] fluorescent reporters of membrane tension are thus very encouraging. A key challenge in the use of these reporters will be to distinguish in-plane membrane tension from changes in projected membrane density that would also affect the apparent brightness of the signal.

The dye-based tension reporter, FliptR,[88] can be used in a fluorescence lifetime imaging mode that is insensitive to dye concentration. However, all of the tension reporters' signals also depend strongly on the lipid composition, limiting their applications to relatively fast cellular events where local lipid compositions do not vary. To study processes such as inositol trisphosphate (IP3) signaling, tension-induced gene regulation, and the cell cycle, more accurate membrane tension reporters will be needed. Development of improved dye- or protein-based reporters of membrane tension should open a new era of probing this fundamental physical quantity throughout all aspects of a cell's life.

## 7. Speculations on the Role of Localized Membrane Tension

Localization of membrane tension in cells may have important biological implications. Tension localization may explain why activation of tension-sensitive Piezo1 channels appears to be primarily near focal adhesions.[91] More generally, local variations in membrane tension could provide a means to signal local mechanical inputs to the cell, possibly triggering local cytoskeletal or other signaling responses.

In neuronal synapses, vesicle release must be accompanied by endocytosis to maintain overall membrane area. Propagation of tension has been proposed as a possible pathway to couple exocytosis and endocytosis at neuronal synapses.[92–94] Changes in membrane tension have also been proposed to trigger insertion or removal of additional membrane as a means of maintaining tension homeostasis in other cell types.[95] The time- and distance-scales over which these mechanisms can act will depend on the tension diffusion coefficient.

For cells that are growing or changing shape, the degree to which the membrane can flow to accommodate these shape changes will impact the distribution of tension in the membrane. For instance, as red blood cells fold to squeeze through capillaries, the distribution of membrane tension will depend on membrane mobility. When primary cilia are deflected, the mechanical forces in the membrane depend on whether the membrane can flow.[96] The degree to which this flow occurs is not presently known.

Similarly, there would be great interest to map the distribution of tension in crawling or extravasating immune cells,[97] or in growing neurons.[52] Cytoskeleton–membrane interactions have been proposed to help bundle actin filaments,[98] though the range over which this bunding can occur will be affected by propagation of membrane tension. Formation of membrane blebs during cell migration, cell division, and apoptosis may provide a way for the cell to dynamically tune the rate of membrane tension propagation in these processes. The degree of locality of this coupling will depend on the diffusion coefficient of membrane tension.

Finally, we consider how propagation of membrane tension can affect the growth of filopodia and lamellipodia. Filopodia grow via actin locally poking on the plasma membrane, reminiscent of tether pulling experiments (**Figure 4**A). Filopodia typically contain 15–30 tightly packed actin filaments and grow at ≈0.1 µm s$^{-1}$.[99] Each actin filament provides ≈1 pN force. The same diffusion equations that described propagation of tension during tether pulling can also be applied to study tension propagation during growth of filopodia,[3] with the distinction that in filopodia, the internal actin bundle sets a minimum radius of the membrane tube.

As in membrane tether pulling, the first ≈10 µm of filopodia growth are expected to experience a constant membrane tension of ≈10 pN µm$^{-1}$ due to the presence of local membrane reservoirs ($E \approx 0$). Filopodia, are typically less than 10 µm long,[100] but some can grow to more than 70 µm.[101] Growth beyond ≈10 µm will lead to stretching of the membrane and an increase in membrane tension opposing further growth. The balance between actin polymerization forces and membrane tension will be influenced by the gradual viscous flow of membrane into the tether, coupled to radially outward propagation of membrane tension in the surrounding cell membrane. We suggest that there will be merit in comparing measurements of filopodial growth to numerical simulations that couple actin growth and propagation of membrane tension.

Growth of lamellipodia appears superficially similar (Figure 4B), but has some noteworthy differences due to the different geometry. Many bundles of actin work in concert

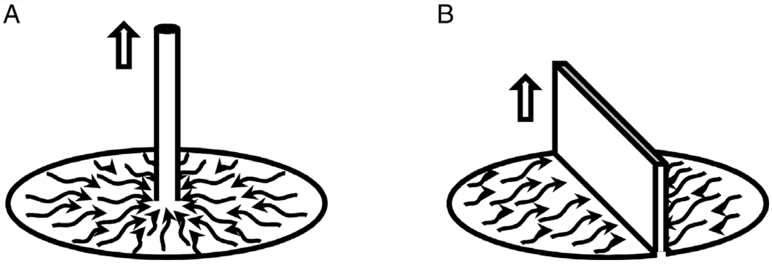

**Figure 4.** Resistance of cell membranes to formation of filopodia and lamellipodia. A) Illustration of filopodium formation, where lipid in the plasma membrane flows radially inward into a tube. B) Illustration of lamellipodium formation, where lipid in the plasma membrane flows into a sheet through a linear flow profile. These two modes of membrane transport are expected to evoke different membrane tension profiles in the cell membrane due to the difference between radial versus linear diffusion of membrane tension.

to extend a sheet-like protrusion from the cell membrane. As in the case of filopodia, the force balance arises from actin polymerization versus membrane tension. However, the different geometry is anticipated to lead to substantial differences in dynamics. In the case of filopodia, the plasma membrane flow was radially inward and the diffusion of tension was radially outward. In the case of lamellipodia, the membrane flow and tension diffusion are essentially 1D, along the line perpendicular to the junction between the lamellipodium and the rest of the cell membrane. This difference in dimensionality may have profound implications for how quickly the tension in the protrusion equilibrates, and how far across the cell the increase in tension propagates. These qualitative arguments illustrate how diffusion of membrane tension provides a conceptual framework for thinking about membrane-cytoskeleton interactions.

## 8. Conclusions and Outlook

In this review, we combined disparate literature discussions of membrane flows into a unified picture for thinking about membrane tension propagation in cells. We highlighted four parameters that determine how membrane tension propagates in cells: area fraction of immobile obstacles, $\phi$; size of the obstacles, $a$; membrane area stretch modulus, $E$; and membrane viscosity, $\eta$. These parameters govern the interplay of membrane flow and membrane stretching, and together set the rate at which local changes in membrane tension diffuse through a cell. We speculated on the biological implications of localized tension in cell membranes and on future studies to explore how cells might regulate these important biophysical parameters.

## Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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## Conflict of Interest

The authors declare no conflict of interest.

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