Nanoscale hydrodynamics in the cell: balancing motorized transport with diffusion

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One of the central problems in the cell is how to transport molecules around the cell to desired locations. Since low Reynolds number conditions apply and diffusional times are large, without the aid of molecular motors to transport the fluid quickly cells could not survive, yet diffusion is still essential for the ultimate delivery of the goods. This paradox of low Reynolds number/large Peclet number has been solved by the algal weed *Chara corallina* in ingenious ways, as the recent paper by Goldstein, *et al.* [*Proc. Natl. Acad. Sci.* 105, 3663–3667 (2008)] discusses at a deep but accessible way using modern hydrodynamic modeling.
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I have a couple of memories from graduate school at the University of Illinois that have some relevance to this paper by Goldstein *et al.* (2008) I knew some smart fellow grad students at the University of Illinois, smarter than me by a long shot, one of them was Larry Nodulman. One day, as we were leaving Loomis Labs, Larry looked at a typically Urbana summer sky with scattered puffy clouds and wondered: why are the clouds so distinct and sharp against the atmosphere; why isn't the water vapor just all blurred out into a haze? The other memory comes from when I first entered biological physics as a grad student, retreating from depression about the direction experimental high energy physics was going. I took a biochemistry course, and in the classic biochemistry textbook by Lehninger (Lehninger *et al.*, 2004) there is a cross-sectional scanning electron microscope (SEM) image of a cell with something like 20 nm resolution: it is unbelievably chock full of objects! I was stunned: how could something so small (20 μm) be so complex, and how did all the parts communicate with each other? The recent paper by Goldstein (Goldstein *et al.*, 2008) gives an intriguing answer to some of the physics of this process.

My fairly recent work in nanotechnology and nanofluidics has helped me answer Larry's question: the sharp edges of clouds are largely due to Newton's Law of motion, $\vec{F}=m(d\vec{v}/dt)$. It looks so simple, but it is not, because $d\vec{v}/dt$ is a total derivative of the vector $\vec{v}$ and that means the spatial as well as time dependence of the vector plays a major role in the evaluation of the derivative as one follows the velocity vector as it snakes around space. The full velocity derivative when written out has a term nonlinear in velocity of the form v^2/R; where R is the radius of curvature (you know this as the centripetal acceleration) and this nonlinearity gives rise to turbulence and puffy clouds and all sorts of horrible mathematical difficulties. However, in Lehninger's cell things are different: the nonlinear term in Newton's acceleration is small compared to linear viscous damping terms, and we say that we are in a regime of low Reynolds number flow. As Goldstein *et al.* point out, this means that the terrible nonlinear Navier–Stokes equation, which is Newton's acceleration plus the drag due to viscous flow, becomes what now looks like a relatively harmless equation for the motion of a fluid volume element which is linear in velocity

$$\frac{\partial\vec{v}}{\partial t}+\nabla P-\eta\nabla^2\vec{v}\sim 0, \qquad (1)$$

which is again an equation linear in $\vec{v}$. The new constant (it is not always constant) we have included here, the viscosity η, connects the shearing of the fluid by an object moving through it with the transverse transfer of momentum that must happen in shear. Shear is a critical concept in hydrodynamics because it provides the dissipative forces which dampen the momentum of a particle by sucking kinetic energy out of the motion. At the simplest level of a planar flow $\vec{v}_x$ of a liquid parallel to the (x,y) surface, the shear vector $\vec{S}$ in the $\hat{z}$ perpendicular to the surface is computed by taking the spatial derivative $\vec{S}=\partial v_x/\partial z\hat{z}$. Shear causes the drag on an object when it moves through a fluid. If the shear drag is sufficiently great, then Eq. (1) describes the motion of the fluid volume elements and we say that the fluid is a low Reynolds number flow if $R_e<1$, where the Reynolds number R_e is a dimensionless number given by

$$R_e \sim \frac{\rho \bar{v} \bar{L}}{\eta}, \qquad (2)$$

where ρ is the (constant) density of the fluid, $\bar{v}$ is the average flow speed, and $\bar{L}$ is the average distance over which the velocity $\vec{v}$ changes its direction. I am trying to be careful here because in reality the Reynolds number R_e in a complex flow is not a constant but is a function of space (Batchelor, 2000). In any event, if you put some numbers in Eq. (2) for typical speeds of fluid flow in cells of about 10 μm/s and typical dimensions of the cell of 10 μm and assume the medium is water (actually the internal fluid in a cell is much more viscous than water) you find that $R_e \sim 10^{-4}$ and so Eq. (1) is an excellent approximation. The implications of low R_e flow in biology has been famously described by the physics Nobel Laureate Edward Purcell in "Life at Low Reynolds Number" (Purcell, 1977), a title we stole in a paper with Ray Goldstein in a paper called "Biotechnology at Low Reynold's Number" (Brody *et al.*, 1996), and which Goldstein *et al.* refer to in the paper under discussion here. The process of transporting matter using deterministic flows such as the laminar flow of Eq. (1) is known as advection.

So far, so good for mathematics since nonlinear equations are notoriously difficult to solve (a point lost on Al Gore), but bad for the cell. Why? It is bad because a low Reynolds number flow cannot mix contents because there is no vorticity. Back to Larry's clouds! Clouds form in the atmosphere because the full-on version of $m(d\vec{v})/dt$ allows for the fluid to circulate around in a circle, creating the famous atmospheric water cycle shown in Fig. 1. But, no such circulation, called vorticity, is possible in Eq. (1) because it is an equation with a potential function solution. Mother Nature is aware of this problem and motorized the fluid: the cytoplasma of eucaryotes is full of motors which pump the fluid around the cell, creating a net circulation within the cell, as schematically shown by Fig. 2. This active pumping of the cytoplasma solves a number of physics problems: advection of cell contents is now driven by metabolically powered motors rather then a pressure gradient in Eq. (1) (it is very hard to create pressure gradients

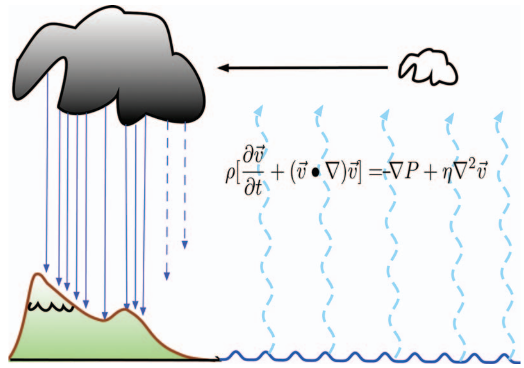

Figure 1. The circulation of water in the atmosphere. Transport of the water vapor is driven by the Navier–Stokes equation.

in a closed volume!), contents can circulate around the cell rather than just in and out, and the motion can be controlled and directed. But we would warn the reader that symmetry plays a role in these equations through the spatial derivatives, and that the simplified equations is still a vector differential equation and not easily solved without playing very close attention to boundary values of the flow, as Goldstein *et al.* are careful to point out.

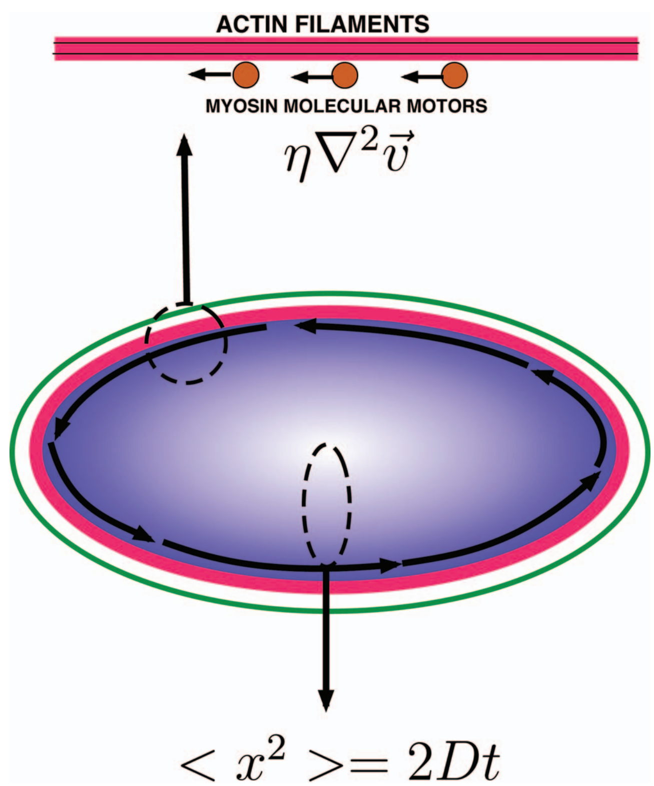

Figure 2. The motorized transport of contents in the cell (Lodish *et al.*, 2000). Myosin molecular motors run along actin filaments and drag the fluid of the cell using the viscous drag term in the Navier–Stokes equation (upper), while molecules diffuse from the laminar streams according to Einstein's relation (lower).

However, even if Mother Nature is a master at working with these differential equations for low R_e motorized fluids she still is left with a physics problem. Even with a motorized fluid, the flow is still low R_e, and thus laminar and deterministic. How can you get small objects out of the laminar flow lines to other places? For that we need Albert Einstein and his most cited paper (Einstein, 1906), on Brownian motion as a transport of particulates due to thermal motion and the hydrodynamic drag exerted on particles. Thermal diffusion can spread molecules and objects around a cell. The actual subject of Brownian motion is quite complex, but the simple relationship that everybody knows equates the second moment $\langle x^2 \rangle$ of a particle's position x versus time

$$\langle x^2 \rangle = 2Dt, \tag{3}$$

where the diffusion coefficient D is connected to the viscous drag coefficient ξ an object feels as it moves at low Re speed v through a liquid and the thermal energy $k_B T$. The trick is to combine the (deterministic) transport of particles that Eq. (1) represents with the diffusional blurring represented by Eq. (3). This is again a very difficult problem to solve, but there is a famous dimensionless number called the Peclet number P_e that characterizes the ratio of the time needed for an object to diffuse a root-mean-square distance Z to the time for the fluid transporting the particle to advect the same distance Z if the mean flow speed is $\bar{v}$,

$$P_e = \frac{t_{diffuse}}{t_{advect}} \sim \left[\frac{Z^2}{D} \bigg/ \frac{Z}{\bar{v}} \right] = \frac{\bar{v}Z}{D}. \tag{4}$$

If the Peclet number is very large, advection is much more rapid then diffusion and little diffusional spreading occurs. However, since diffusion like erosion is a slow (but steady) process with a mean distance of blurring which only increases as the square root of time at high P_e number diffusion is not a particularly efficient way to spread goodies around inside the cell.

The solution that the algal weed *Chara corallina* has evolved is exceptionally ingenious, and Goldstein *et al.* give a beautiful mathematical analysis of the solution to the high P_e problem. There are two parts to the solution that I hope are now appreciated by the reader: (1) The motorized fluid inside the cell is set up to create a cycle of vorticity to move contents around, like the water cycle of the atmosphere. The "indifferent zone" within the cell is actually the dividing line between counter-flowing currents, and hence, a region of high shear. (2) Because the P_e is high, on the order of 100–1,000 or greater, advection moves things too rapidly for effective dispersal. To get around this, the diffusional distances are minimized by layering the laminar flows in the circulation in a helical manner, like the stripes of a barber pole, or perhaps better put, by moving the fluid along an inclined plane wrapped around an axis, so that adjacent laminar

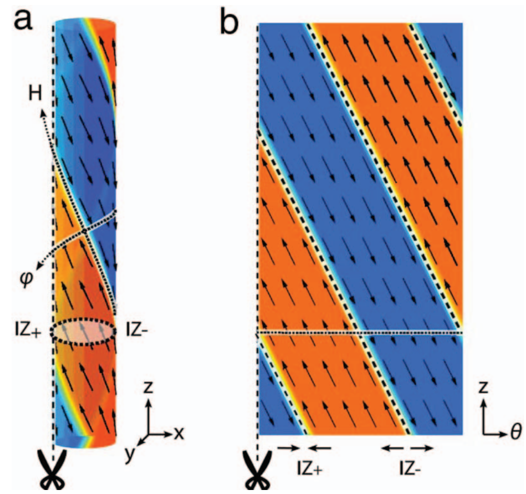

Figure 3. Taken from (Goldstein *et al.*, 2008), Fig. 2. Idealized spiraling flow in *Chara*. (a) Flow at the boundary, divided in an ascending band (red) and descending band (blue) separated by two indifferent zones. Vectors indicate the direction of flow along the bands. The shaded region corresponds to the horizontal section shown by its intersection with the boundary as a horizontal solid line in b and viewed along the cell axis in *c* and *d*. (b) Cylinder from (a), cut open along dotted line (as indicated by scissors) and flattened out. Ascending and descending regions now appear as diagonal bands. The two indifferent zones have a subtle difference in symmetry, which is reflected in the horizontal components of motion converging at one zone and diverging for the other, as indicated by the arrows at bottom.

flow lines are near each other, separated by the pitch of the helix (see Fig. 3). In this way, the effective P_e is reduced by the ratio of the pitched to the length of the helix, and much more effective diffusional mixing of the contents can occur. Figure 3 shows the interweaving of the helical flow lines, taken from (Goldstein *et al.*, 2008).

To actually do the calculations of the change in the mixing due to the helical twists around an axis requires some sophisticated transforming of the flow patterns in the radial expansions in terms of Bessel function components, rather like the way one solves periodic wave equations in terms of the Fourier components. This Bessel function analysis breaks down the solutions in terms of characteristic wavelengths λ of the flow, which can then be analyzed in terms of their diffusional broadening as they are advected around the helix axis by the motorized liquid. To quote the authors: "Our model calculations show that this wavelength/radius ratio is also a maximum in the nutrient uptake rate from the environment. It is then a plausible conjecture that nature has chosen helical flows to enhance the uptake rate, particularly at this significant developmental stage." We hope the significance of that statement is now clear!

We started talking about clouds and Newton's (nonlinear!) equations of motion at high Reynolds number, discussed how the length scale of fluid motion in cells restricts one to low Reynolds number flow and mentioned the masterful article by Purcell called "Life at Low Reynolds Number." The author of this appreciation originally worked with Goldstein and coauthored an article which used many of the techniques exploited by Goldstein *et al.* in the present article, and we called that earlier article "Biotechnology at Low Reynolds Number." Now Goldstein and his collaborators have taken that title and analysis a step further, and in their words: "the present analysis serves to highlight the unusual features of life at high Peclet numbers, in which advection dominates diffusion." I hope that this appreciation makes the full context of that last statement clear. For me, the wonder of that old SEM picture of a cell in Lehninger is all the more enhanced by this excellent paper.

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