Current Topics in Biophysics (BPHS 2090)

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References/Acknowledgement:
- Weiss (1996)
- Berg (1993)
- Waigh (2014)
“Anomalous diffusion”

Question:
So how can we tell the difference between passive and active?

Answer:
How “normal” is your diffusion?

Fig. 1. Thermal diffusion (blue line) of a particle in a liquid is characterized by an MSD given by $\langle \Delta x^2(\tau) \rangle = 2D\tau$, where the displacement $\Delta x(\tau) = x(t + \tau) - x(t)$ along one axis is measured over a time interval $\tau$. In equilibrium, this linear dependence on $\tau$ is only expected for motion in simple liquids. In viscoelastic materials, such as polymer solutions, subdiffusive motion (red) is expected in equilibrium. By contrast, superdiffusive motion (green) often indicates partially or fully directed motion (e.g., for transport along a substrate) (11).
Rough analogy... (ignore convective currents)
Moving on....

**Question:**
What differences are there for micro- vs. macroscopic motors?

**Life at low Reynolds number**

E. M. Purcell  
*Lyman Laboratory, Harvard University, Cambridge, Massachusetts 02138*  
(Received 12 June 1976)

*American Journal of Physics, Vol. 45, No. 1, January 1977*

But I want to take you into the world of very low Reynolds number—a world which is inhabited by the overwhelming majority of the organisms in this room. This world is quite different from the one that we have developed our intuitions in.

Note: Purcell (1912-1997) won the 1952 Nobel Prize for his work on NMR
Reynolds number $(R)$ is a dimension-less number that indicates the ratio of inertial to viscous forces.

\[ R = \frac{\frac{avp}{\eta}}{\nu} = \frac{av}{\nu} \]

For water, \( \nu = 10^{-2} \text{ cm}^2 \text{ sec}^{-1} \)
Chapter 5

Life in the slow lane: the low Reynolds-number world

The Focus Question for this chapter is:

*Biological question:* Why do bacteria swim differently from fish?

*Physical idea:* The equations of motion appropriate to the nanoworld behave differently under *time reversal* from those of the macroworld.
Aside: Viscosity

Let’s firm this up a bit more....

Linear relationship in fluid velocity
(i.e., fluid flows in “layers” $\rightarrow$ laminar flow)

\[ v_x(y) = \frac{v_x(h)}{h} y \]

\[ F_x = \eta A \frac{\partial v_x}{\partial y} \bigg|_{y=h} \]

$\rightarrow$ Viscosity ($\eta$) is the constant of proportionality between applied force and shear

Berg (1993)
Connection point: Viscosity and diffusion are related

Recall:

\[ P(x)dx = \frac{1}{(4\pi Dt)^{1/2}} e^{-x^2/4Dt} dx \]

\( t = 50 \)

- smaller \( D \)
- larger \( D \)

Pop quiz
- How are the two types of plots (above versus left) related?
- The yellow circle corresponds to what above?
- How does this all relate to a “concentration gradient”??
Connection point: Viscosity and diffusion are related

“In 1851, George Gabriel Stokes derived an expression, now known as Stokes' law, for the frictional force – also called drag force – exerted on spherical objects with very small Reynolds numbers (i.e. very small particles) in a viscous fluid. Stokes' law is derived by solving the Stokes flow limit for small Reynolds numbers of the Navier–Stokes equations”

- wikipedia (Stoke’s Law)

\[ F_d = 6\pi \mu RV \]

Pop quiz
- If \( F_d \) is a force, and \( R \) and \( V \) is the radius and velocity of sphere respectively, what must the units of \( \mu \) (the “dynamic viscosity”) be?

Answer: \([\mu] = \text{kg/(m*sec)}\)
**Connection point: Viscosity and diffusion are related**

**Stokes’ Law**

\[ f_{sphere} = 6\pi \eta a \]

*f* is the “viscous friction coefficient” (tells you about the viscous drag force of dragging that sphere)

**Stokes-Einstein Relation**

relates the diffusion constant \( (D) \) to viscosity \( (\eta) \)

(this is one thing Einstein derived in 1905)

\[ D_{sphere} = \frac{kT}{6\pi \eta a} \]

Compare back to:
(what’s the difference?)

Berg (1993)
Connection point: Viscosity and diffusion are related

Stokes-Einstein Relation
relates the diffusion constant ($D$) to viscosity ($\eta$)
(this is one thing Einstein derived in 1905)

$D_{sphere} = \frac{kT}{6\pi\eta a}$

“[this eqn.] states that the fluctuations in a particle’s position are linked to the
dissipation, or frictional drag, it feels. The connection is quantitative and universal: it’s
always given by the same quantity $kT$ appearing in the ideal gas law, no matter what
sort of particle we study. For example, the right-hand side of [this eqn.] does not depend
on the mass $m$ of the particle. Smaller particles will feel less drag (smaller $f$) but will
diffuse more readily (bigger $D$) in such a way that all particles obey [this eqn.].”

Connection point: Viscosity and diffusion are related

Stokes-Einstein Relation
relates the diffusion constant ($D$) to
viscosity ($\eta$)

$D_{\text{sphere}} = \frac{kT}{6\pi\eta a}$

(this is one thing Einstein derived in 1905)

“Einstein also checked whether the experiment he was proposing was actually doable. He reasoned that in order to see a measurable displacement of a single 1 $\mu m$ colloidal particle, we’d have to wait until it had moved several micrometers. If the waiting time for such a motion were impractically long, then the experiment itself would be impractical. Using existing estimates of $k$, Einstein estimated that a 1 $\mu m$ sphere in water would take about a minute to wander a mean-square distance of 5 $\mu m$, a convenient waiting time. Einstein concluded that colloidal particles occupy a window of experimental opportunity: They are large enough to resolve optically, yet not so large as to render their Brownian motion unobservably sluggish. Very soon after his prediction, Jean Perrin and others did the experiments and confirmed the predictions. As Einstein put it later, “Suddenly all doubts vanished about the foundations of Boltzmann’s theory [of heat].”

Connection point: Viscosity and diffusion are related

Fig. 2. Recorded random walk trajectories by Jean Baptiste Perrin [72]. Left part: three designs obtained by tracing a small grain of putty (mastic, used for varnish) at intervals of 30 s. One of the patterns contains 50 single points. Right part: the starting point of each motion event is shifted to the origin. The figure illustrates the pdf of the travelled distance $r$ to be in the interval $(r, r + dr)$, according to $(2\pi\xi^2)^{-1} \exp(-r^2/[2\xi^2])2\pi r \, dr$, in two dimensions, with the length variance $\xi^2$. These figures constitute part of the measurement of Perrin, Dabrowski and Chaudesaignes leading to the determination of the Avogadro number. The result given by Perrin is $70.5 \times 10^{22}$. The remarkable œuvre of Perrin discusses all possibilities of obtaining the Avogadro number known at that time. Concerning the trajectories displayed in the left part of this figure, Perrin makes an interesting statement: “Si, en effet, on faisait des pointés de seconde en seconde, chacun de ces segments rectilignes se trouverait remplacé par un contour polygonal de 30 côtés relativement aussi compliqué que le dessin ici reproduit, et ainsi de suite”. [If, veritably, one took the position from second to second, each of these rectilinear segments would be replaced by a polygonal contour of 30 edges, each itself being as complicated as the reproduced design, and so forth.] This already anticipates Lévy’s cognisance of the self-similar nature, see footnote 9, as well as of the non-differentiability recognised by N. Wiener.
Reynolds # \((R)\)

For “swimmers”, \(R\) varies quite a lot depending upon size.....
Low Reynolds # \((R)\)

\[ R = 3 \times 10^{-5} \]

\[ \eta = 1 \text{ centipoise} \quad \nu = 10^{-2} \text{ cm}^2/\text{sec} \]

You stop swimming, you *stop*

\[
\begin{align*}
\text{coasting distance} &= 0.1 \text{ Å} \\
\text{coasting time} &= 0.3 \text{ microsec.}
\end{align*}
\]
Low Reynolds # \((R)\)

- When \(R\) is small, “weird” things can happen.....

Figure 5.1: (Photographs.) An experiment showing the peculiar character of low Reynolds-number flow. (a) A small blob of colored glycerine is injected into clear glycerine in the space between two concentric cylinders. (b) The inner cylinder is turned through four full revolutions, apparently mixing the blob into a thin smear. (c) Upon turning the inner cylinder back exactly four revolutions, the blob reassembles, only slightly blurred by diffusion. The finger belongs to Sir Geoffrey Taylor.[Copyrighted figure; permission pending.][From (Shapiro, 1972).]
Low Reynolds # ($R$)

Wait, you can simply “unmix” by “reversing” time?

→ Mixing is hard!

→ Tied to that: swimming is different!

Figure 5.2: (Schematics.) Shearing motion of a fluid in laminar flow, in two geometries. (a) Cylindrical (ice-cream maker) geometry, viewed from above. The central cylinder rotates while the outer one is held fixed. (b) Planar (sliding plates) geometry. The top plate is pushed to the right while the bottom one is held fixed.

Low Reynolds # ($R$)

Think of this as a statement of Newton’s 2\textsuperscript{nd} law for fluids

\begin{align*}
\text{Navier-Stokes:} \\
- \nabla p + \eta \nabla^2 \vec{v} = \frac{\partial \vec{v}}{\partial t} + \rho \left( \vec{v} \cdot \nabla \right) \vec{v}
\end{align*}

\begin{itemize}
  \item Pressure + viscous forces
  \item Inertial forces
\end{itemize}

If $R \ll 1$:

\begin{quote}
Time doesn’t matter. The pattern of motion is the same, whether slow or fast, whether forward or backward in time.
\end{quote}


American Journal of Physics, Vol. 45, No. 1, January 1977
Low Reynolds # ($R$)

If $\mathcal{O} \ll 1$:

Time doesn't matter. The pattern of motion is the same, whether slow or fast, whether forward or backward in time.

- “Reciprocal motion”

The Scallop Theorem

- A scallop wouldn’t be able to swim for low $R$

- Need more than one degree of freedom
Low Reynolds \# ($R$)

- A scallop wouldn’t be able to swim for low $R$

![Diagram](image)

**Figure 7.6** (a) A scallop with a single hinge is unable to move forward at low Reynold’s number due to the time translational symmetry of the Navier–Stokes equation. (b) Purcell’s hypothetical two hinge organism is able to propel itself forward using a series of conformational changes.

Waigh (2014)
Low Reynolds # ($R$)

- Possible motor designs....

Figure 5.5: (Schematic.) Three swimmers. (a) The flapper makes reciprocal motion. (b) The twirler cranks a stiff helical rod. (c) The spinner swings a stiff, straight rod.

Figure 5.9: (Schematic; photomicrograph.) (a) The bacterial flagellar motor, showing elements analogous to those of a macroscopic rotary motor. The inner part of the motor assembly develops a torque relative to the outer part, which is anchored to the polymer network (the “peptidoglycan layer”), turning the flagellum. The peptidoglycan layer provides the rigid framework for the cell wall; it is located in the periplasmic space between the cell’s two membranes. (b) Composite electron micrograph of the actual structure of the motor assembly. Top to bottom, about 75 nm. [Digital image kindly supplied by D. Derosier; see (Derosier, 1998).] [Copyrighted figure; permission pending.]

→ Provides some biophysical basis for why the motors are “designed” the way they are!
Low Reynolds \# ($R$)

**Figure 7.11** Range of different strategies used by micro-organisms for motility. (a) Amoeba use cytoplasmic streaming to crawl across a surface, (b) euglena have a single flagellum and the cell body acts as a propeller, (c) sperm cells use flagella to swim, (d) spirochetes swim using a cork screw motion, (e) chrysophytes (golden algae) have a hairy flagellum for propulsion, (f) paramecium use the coordinated beating of cilia in metachronal wave to propel themselves, and (g) chlamydomonas (green algae) swim with multiple flagellae.
Figure 7.10  Range of velocities used for transport in cells and micro-organisms. The mechanism of motility can be classified as crawling/swimming, extension/contraction and internal transport. [Copyright 2000 from Cell Components: From Molecules to Motility by Bray. Reproduced by permission of Garland Science/Taylor & Francis LLC.]
"Creeping flow past a falling sphere in a fluid (e.g., a droplet of fog falling through the air): streamlines, drag force $F_d$ and force by gravity $F_g$."

**Question:**
So if a small bead is getting jostled around, will it in fact “sink”?
Connection point: \( R \) & Stokes’ Law

**Question:**
So if a small bead is getting jostled around, will it in fact “sink”?

→ Similarly, shouldn’t milk (a colloid) settle? Or air molecules for that matter?

Need to also consider (re *sedimentation*):
- Buoyant forces (→ Archimedes)
- Thermal “agitation” (→ remember diffusion!)

Consider for a moment a different (but physically similar) problem: charges between two charged plates

*Figure 4.14: (Sketch.) Origin of the Nernst relation. An electric field pointing downward drives positively charged ions down. The system comes to equilibrium with a downward concentration gradient of positive ions and an upward gradient of negative ions. The flux through the surface element shown (dashed square) equals the number density \( c \) times \( v_{drift} \).* Nelson (2004)
Connection point: $R$ & Stokes’ Law

Consider for a moment a different (but physically similar) problem: charges between two charged plates.

$\Delta V$ Movement of charge is a balance of diffusion and electro-static forces

As such, an equilibrium distribution is set up over some distance

$\Delta (\ln c) \equiv \ln c_{\text{top}} - \ln c_{\text{bot}} = -q\Delta V_{\text{eq}}/k_B T.$  

Nernst relation

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Connection point: *R & Stokes’ Law*

\[ \Delta (\ln c) \equiv \ln c_{\text{top}} - \ln c_{\text{bot}} = -q\Delta V_{\text{eq}}/k_B T. \quad \text{Nernst relation} \]

For gravitational potentials (rather than electrical) and considering buoyant forces...

... one obtains an expression for an equilibrium profile

\[ c(x) \propto e^{-m_{\text{net}} g x / k_B T}. \quad \text{sedimentation equilibrium, Earth’s gravity} \]

**In short** (and in rough analogy to diffusion)
- There are ultimately two “scales” here: time & space
- The equation above indicates the spatial scale at (temporal) equilibrium
- Stokes’ drag determines how long it takes to reach that spatial equilibrium *(Svedberg equation)*

Weiss (1996)
Connection point: $R$ & Stokes’ Law

→ Centrifuges speed things up!
“Current Topics”

- Let’s see how the topics covered so far relate to some “current” articles in the 11/17/15 issue of the Biophysical Journal....
Basic idea is that diffusion is important for drug delivery. But the structure of tissue affects the effective permeability....
Diffusion Regulation in the Vitreous Humor

![Diagram of a human eye and vitreous humor](image)

**FIGURE 1** Schematic overview of a mammalian eye (a) and vitreous preparation process for SPT (b–e). (a) The vitreous humor of the mammalian eye mainly consists of collagen fibrils, as well as the GAGs HA and HS, both of which carry several negative charges. From fresh ovine eyes (b), the vitreous humor is carefully removed (c), and nanoparticles are injected into the vitreous (d). Trajectories characterizing the thermal motion of the nanoparticles in the vitreous humor (e) are obtained by optical microscopy. To see this figure in color, go online.

- Fibrillar structure present might “slow down” diffusion...
Possible to change permeability by changing the charge structure?
Basic idea is create some sort if irregular (but controlled) “jungle gym” for bacteria to swim around in and see how such affects their dynamics.
Depending upon the “structure” you make, bacteria swim differently.

**Figure 1** Trajectories of motile bacteria in isotropic and anisotropic solutions. (A) *E. coli* swimming tracks in isotropic media at 0 wt % DSCG and (B) in anisotropic media at 12 wt % DSCG (at 22.5 ± 0.5°C). In (B), the x axis is parallel to the rubbing direction of the chamber. To see this figure in color, go online.

**Figure 2** Characterization of the motility of bacteria in DSCG solutions. (A) Bacterial speed and (B) standard deviation of the orientation of the bacterial body as a function of the DSCG concentration. The standard deviation (SD) was used as the error bars. All experiments were made at 22.5 ± 0.5°C. The number of data acquired for each concentration is shown in Table S3 (1808 individual bacteria in total, and more than 83,500 positions). The gray hatched zone represents the DSCG concentration range where both phases coexist (isotropic and anisotropic). The gradient shaded zone represents the DSCG concentration range where the pretransition phenomena are observed (see main text for details). To see this figure in color, go online.
Bacterial Motility Reveals Unknown Molecular Organization

FIGURE 3  Diffusion of beads and nonmotile bacteria in DSCG solutions and anchoring of the DSCG molecules on their surfaces. (A) Trajectories of the diffusion of 0.75 μm diameter microspheres in an isotropic solution with 0 wt % DSCG and (B) in an anisotropic solution with 13.2 wt % DSCG. (C) Trajectories of the diffusion of paralyzed bacteria (without flagellum) in a solution with 13.2 wt % DSCG. (D) Image of a 3 μm polystyrene microsphere taken in brightfield with crossed polarizers and (E) without polarizers. (F) Image of three bacteria taken between crossed polarizers and (G) schematic representation of the perturbation of \( \mathbf{n} \) around a polystyrene microsphere (circle) and a bacterium (ellipse). All experiments were made at 22.5 ± 0.5°C. The white bar in (F) measures 10 μm. To see this figure in color, go online.

\[ f_{\text{sphere}} = 6\pi \eta a \]
Basic idea is that the collective swarm dynamics allow for appreciable forces such that biofilms dynamically “shape” themselves (e.g., grow).
**Bacillus subtilis** Bacteria Generate an Internal Mechanical Force within a Biofilm

**FIGURE 1** Direct measurement of the compressive force. (A and B) Schematic oblique (A) and top (B) views of the setup. We studied the force generated by a floating pellicle located between a mobile plate and the opposite edge. As the pellicle covered the whole air-liquid surface, we successively cut different parts of the pellicle to keep only one rectangular piece intact. The views in (A) and (B) illustrate the state of the pellicle at cutting step 2. A negative force corresponded to the case in which the plate moved away from the opposite edge. (C) Top views of the cutting steps. For clarity, a well-marked hatched rectangle is superimposed on the mobile plate and the green dashed lines show the successive cuts. Step 1: in the initial state, the pellicle covered the whole liquid surface and closely surrounded the mobile plate. During its formation, it attached to the vertical walls of the dish’s edges and the mobile plate. Step 2: part of the pellicle located behind the plate was cut and removed. Step 3: the pellicle sides were removed and a pellicle band of dimensions $L$ and $W$ stood between the mobile plate and the opposite edge. Step 4: in the final state, the biofilm was detached and released by moving the plate away from the opposite edge (scale bars = 5 mm). (D) Force measurements. At each cutting step, we measured the forces acting on the mobile plate (blue, step 1; black, step 2; green, step 3; red, step 4). To see this figure in color, go online.
**Bacillus subtilis** Bacteria Generate an Internal Mechanical Force within a Biofilm

FIGURE 2  Force generated by the bacterial biofilm during its growth. At the beginning of the incubation period, no force was measured. As the biofilm developed, the force suddenly became compressive and remained constant regardless of the degree of maturation. This suggests the existence of a critical step for biofilm development (scale bar = 5 mm). The continuous red lines are just visual guidelines. To see this figure in color, go online.
Related: “flying spaghetti monster,”

The Flying Spaghetti Monster Lives

The deeply weird creatures oil workers spot near deep-water rigs.

By Jim Festante

“Although a siphonophore appears to be a single organism, each specimen is actually a colony composed of many individual animals”

wikipedia (Siphonophorae, flocking)