Biological space

Cosmic scale

$$F = \frac{m_0}{\sqrt{1 - \frac{v^2}{c^2}}} a$$

Macroscale

$$F = ma$$

Bio-nano-scale

$$\zeta \frac{dx}{dt} = -\frac{\partial \varphi(x,t)}{\partial t} + f_B(t)$$

Quantum Mechanics

$$i\hbar \frac{\partial}{\partial t} \Psi = \hat{H} \Psi$$

Time-dependent Schrödinger equation *(general)*

The micro world

- ***Diffusion***
- ***Thermal fluctuations***
- ***Low Reynold's number***

The radius of a water molecule is about 0.1 nm.

Protein radius is in the range 2 - 10 nm.

→ *Fluid can be considered as a continuum*

Transport Phenomena

A system is not in equilibrium when the macroscopic parameters (***T***, ***P***, etc.) are not constant throughout the system.

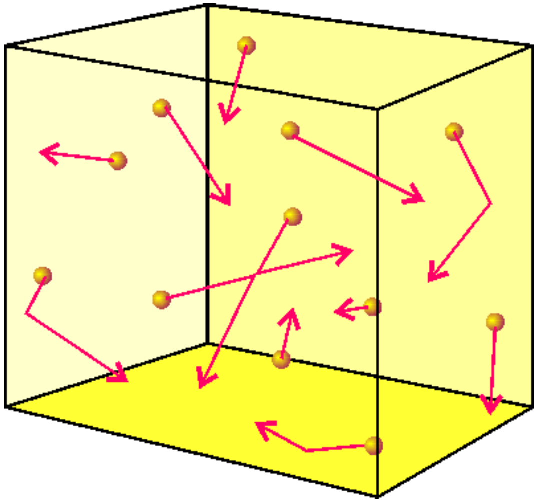
To approach equilibrium, these non-uniformities have to be dissipated through **the transport of energy, momentum, and mass**.

The mechanism of transport is molecular movement.

$$\frac{3}{2}\boldsymbol{kT} = \frac{1}{2}\boldsymbol{M}\langle \boldsymbol{v} \rangle^2$$

$$\langle \boldsymbol{v} \rangle = \left(\frac{3\boldsymbol{kT}}{\boldsymbol{M}} \right)^{\frac{1}{2}}$$

Molecular speed



For T = 300 K

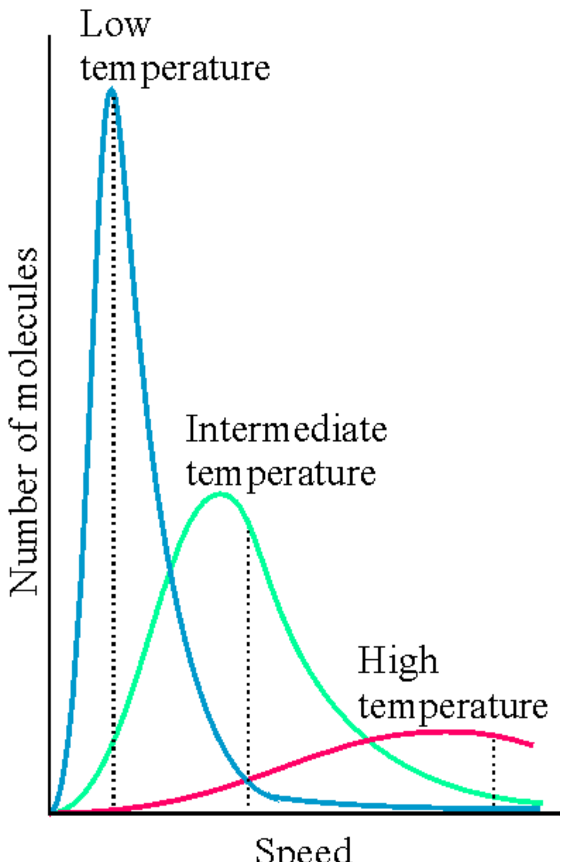
500 Da (ATP) – v = 70 m/s

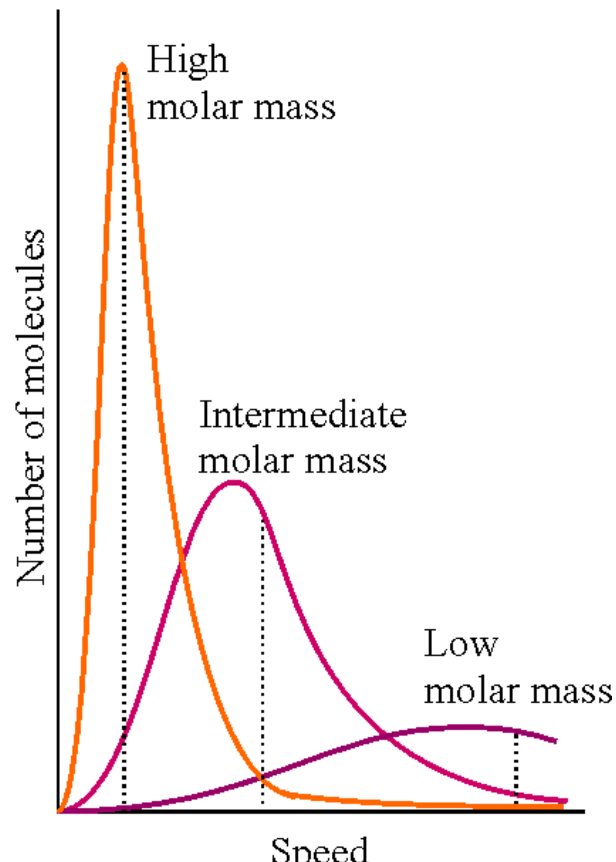
50 000 Da (protein) – v = 7 m/s

6.25 GDa (200 nm diameter vesicle) – v = 600 µm/s

Actual velocity ⇒ Maxwell's distribution

$$f(v) = 4\pi\left(\frac{M}{2\pi RT}\right)^{3/2} v^2 e^{-\frac{Mv^2}{2RT}}$$





dS=0 defines thermal, mechanical and chemical equilibria

$$\boxed{dS = \left(\frac{\partial S}{\partial U}\right)_{V,N} dU + \left(\frac{\partial S}{\partial V}\right)_{U,N} dV + \sum_{j=1}^{M} \left(\frac{\partial S}{\partial N_j}\right)_{U,V,N_{i \neq j}} dN_j}$$

$$\boxed{dS = \left(\frac{1}{T}\right) dU + \left(\frac{p}{T}\right) dV - \sum_{j=1}^{M} \left(\frac{\mu_j}{T}\right) dN_j}$$

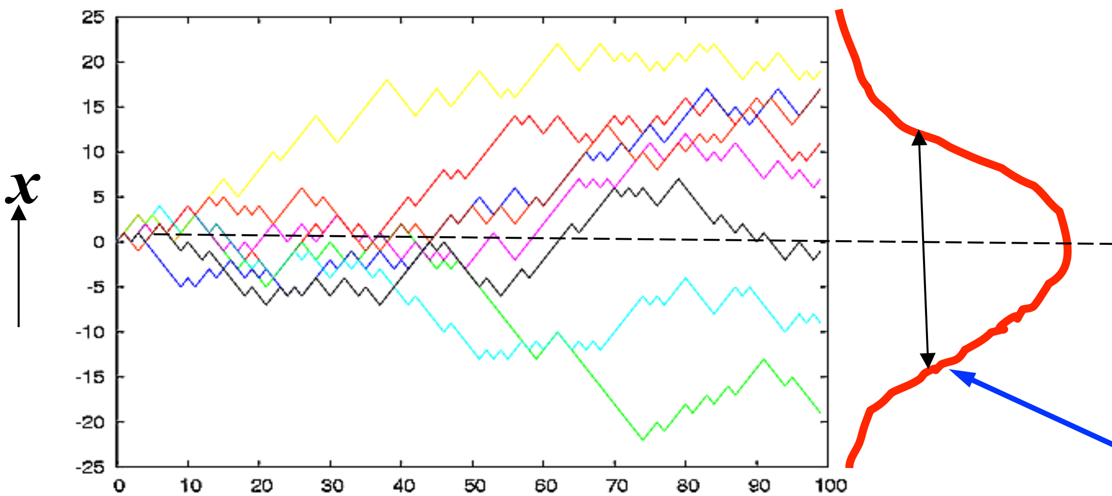
The tendency to maximize multiplicity predicts that when there is inequity in a given quantity (e.g. concentration of particles), there will be a net movement of this quantity from areas of higher concentration to areas of lower concentration until equilibrium is reached = **diffusion**

μ/T is a measure of system's tendency for particle exchange

Diffusion – the flow of randomly moving particles caused by variations of the *concentration* of particles.

$$J \propto \frac{d(potential)}{dx} = -Force$$

The random walk of a large number of particles results with deterministic flow of particles.



a 1D random walk of a drunk

Gaussian distribution

$$n(x,t) = \frac{k}{\sqrt{Dt}} \exp\left(-\frac{x^2}{4Dt}\right)$$

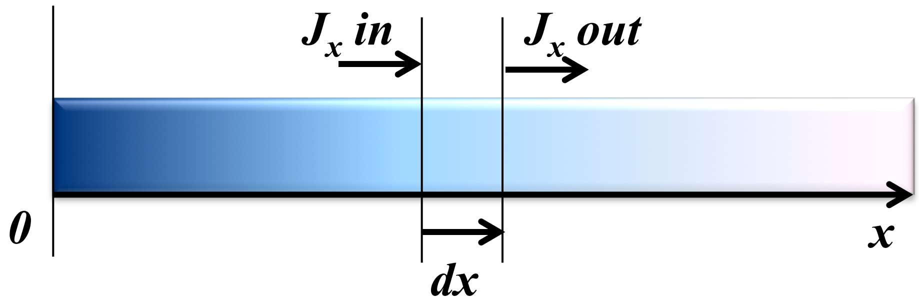
$$\boxed{\sqrt{\left\langle x^2 \right\rangle_{\Delta t}} = \sqrt{D\Delta t}}$$

the *rms* displacement

Macroscopic theory of diffusion:

Assumptions:

1. *conservation of mater*
2. *the relation between gradient and flux is linear*



Adolf Eugen Fick
(1829-1901)

Fick's 1st law: $$J_x = -D\frac{\partial C}{\partial x}$$

From the conservation of mater: $$\frac{\partial C}{\partial t} = -\frac{\partial J}{\partial x}$$

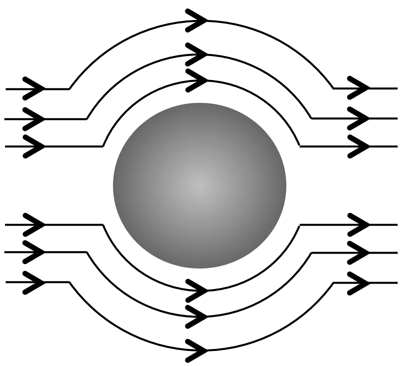
$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial^2 x}$$

Fick's 2nd law:

In thermodynamic terms, we're watching the increase in entropy within a small, isolated system without an input of energy.

Diffusion coefficient

Diffusion coefficient depends on the velocity of diffusing particles and hence on ***size*** of the particles, ***temperature***, and on the ***viscosity*** of the media



$$D = \frac{RT}{N_A} * \frac{1}{F_{friction}}$$

$$F_{friction} = 6\pi\eta r$$

its units $m^2\,s^{-1}$

$$\boxed{D = \frac{RT}{6\pi\eta r N_A} = \frac{k_B T}{6\pi\eta r}}$$

Stokes-Einstein relation

Diffusion coefficient

Calculate diffusion coefficient for a typical globular protein (100 kDa; r ~ 2nm) in aqueous media

$$\boxed{D = \frac{k_B T}{6\pi\eta r}}$$

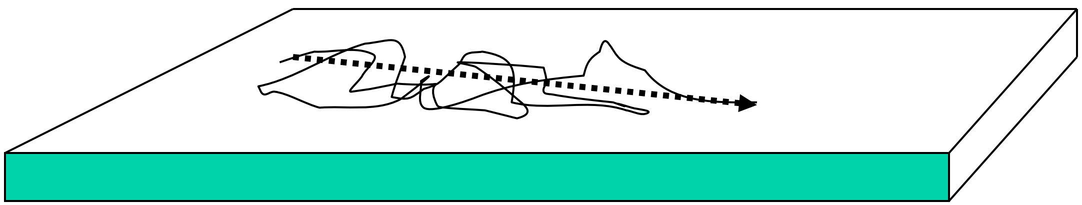
Stokes-Einstein relation

$$\underbrace{\begin{array}{l} k_B = 1.38 * 10^{-23}\ JK^{-1} \qquad 1\ J = 1kg*m^{2*}s^{-2} = 10^3\ g*m^{2*}s^{-2} \\ \eta_{H2O} = 1cP = 1\ g*m^{-1*}s^{-1} \\ T \approx 300K \\ r \approx 2\ nm = 2*10^9\ m \end{array}}$$

$$\boxed{D \approx 10^{-10}\ m^2 s^{-1}}$$

1D

$$\langle l^2 \rangle = 2Dt$$

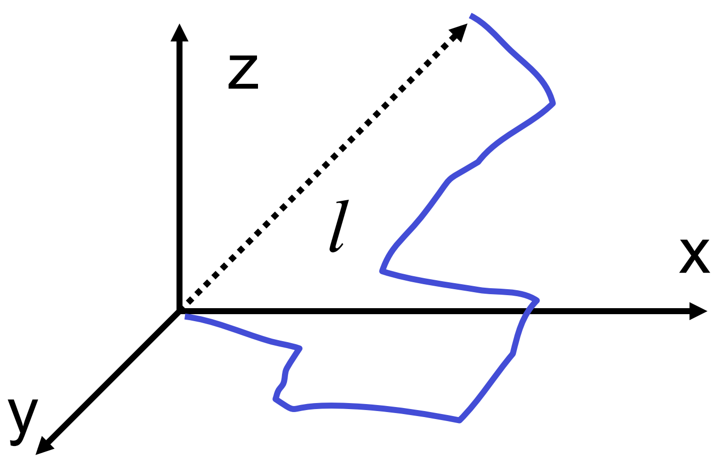


2D

$$l^2 = x^2 + y^2$$

$$\langle l^2 \rangle = 4Dt$$

3D



$$l^2 = x^2 + y^2 + z^2$$

$$\langle l^2 \rangle = 6Dt$$

In three dimensions:

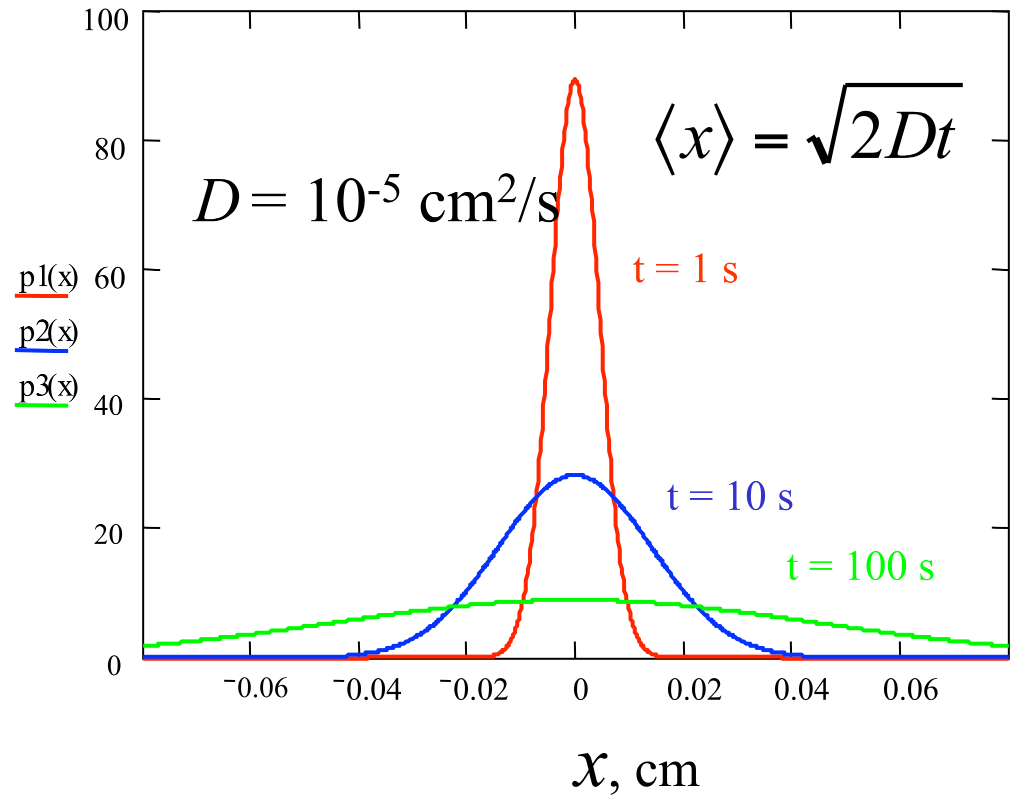
$$\vec{J} = -D\nabla C \quad and \quad \frac{\partial C}{\partial t} = D\nabla^2 C$$

$$\left.\frac{dc(x,y,z)}{dt}\right|_{x,y,z} = D\left.\left(\frac{d^2C}{dx^2} + \frac{d^2C}{dy^2} + \frac{d^2C}{dz^2}\right)\right|_t$$

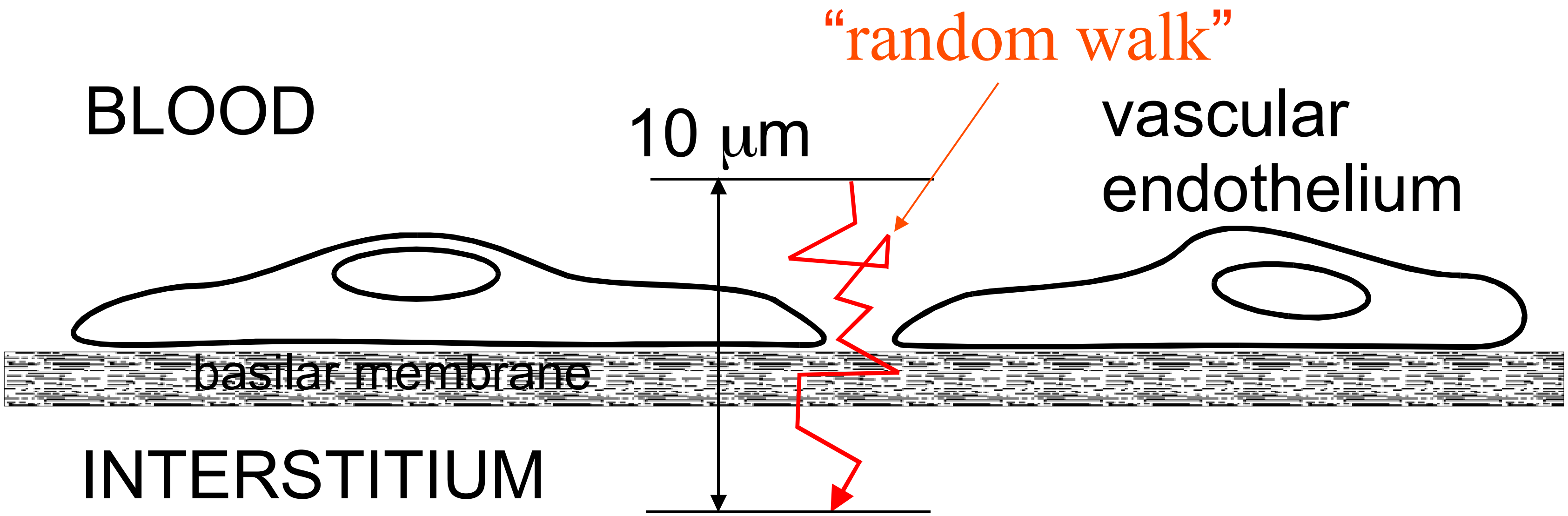
The ***rms*** displacement of particles:

$$\langle x \rangle = 0$$

$$\boxed{\sqrt{\langle x^2 \rangle} \approx \sqrt{Dt}}$$



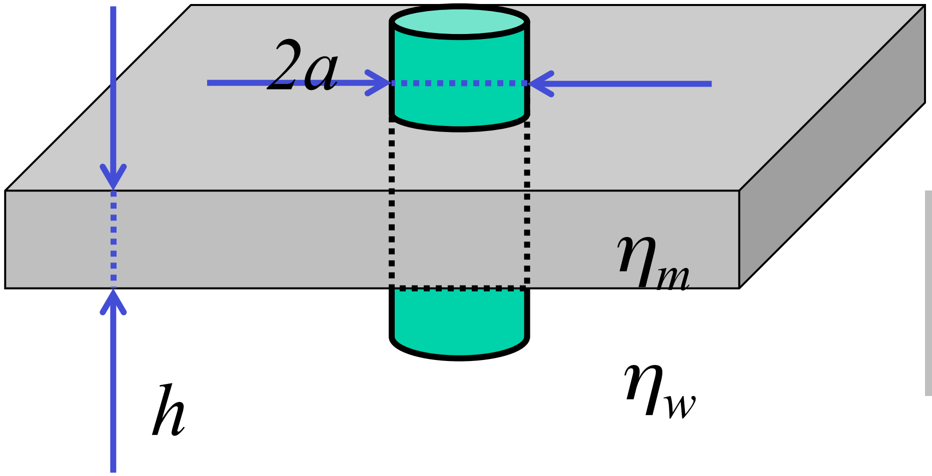
Diffusion across exchange epithelium



Einstein eqn: $$< x^2 > = 2Dt$$

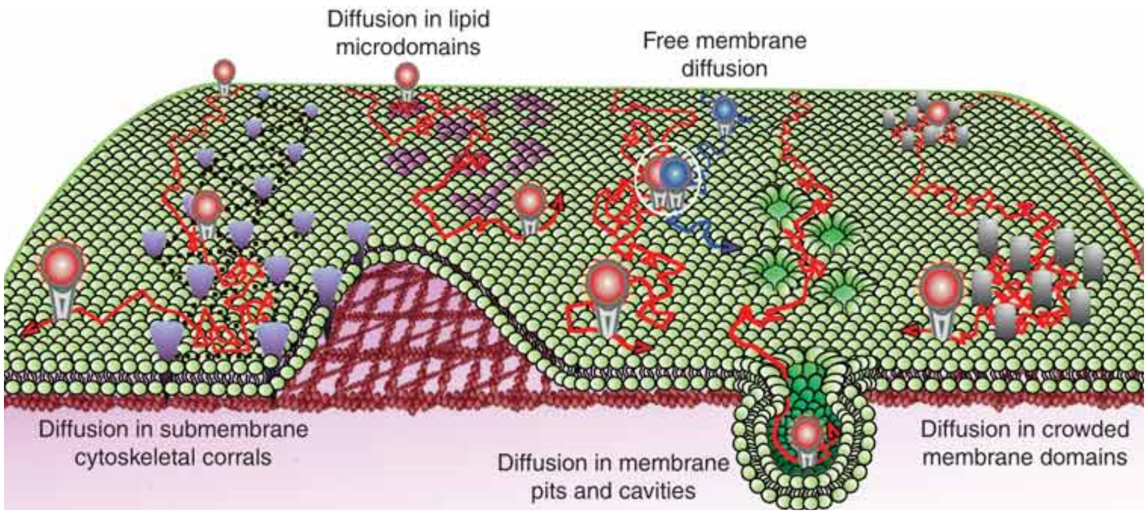
$<x^2>$ - mean square distance (cm^2)
D – diffusion coefficient (cm^2/s)
t – time interval (s)

Lateral Diffusion

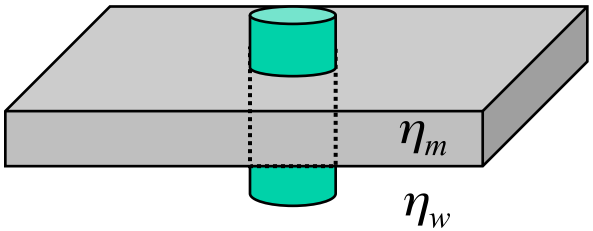


$$D_L = \frac{k_B T}{4\pi\eta_m h}\left(\ln\frac{\eta_m h}{\eta_w a} - 0.5772\right)$$

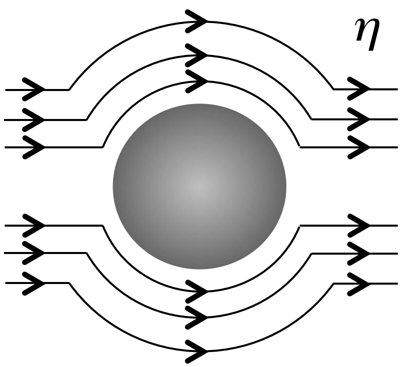
Saffman – Delbrück equation



3D vs. Lateral Diffusion



$$D_L = \frac{k_B T}{4\pi\eta_m h}\left(\ln\frac{\eta_m h}{\eta_w a} - 0.5772\right)$$



$$D = \frac{RT}{6\pi\eta r N_A} = \frac{k_B T}{6\pi\eta r}$$

$D \sim 10^{-5}$ for most small molecules in water

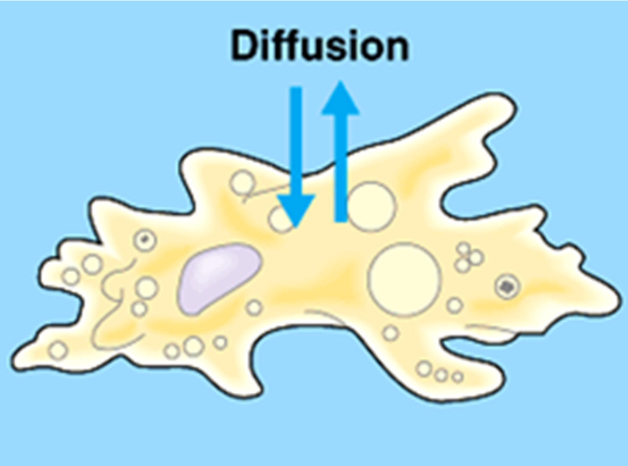
Distance	**Ave. Diffusion Time**	**Significance**
100 angstroms	0.0000001 sec	Cell membrane thickness
1 micron	0.001 sec	Size of most bacteria or mitochondria
10 microns	0.1 sec	Diameter of small eukaryotic cells
100 microns	10 sec	Diameter of large eukaryotic cells
250 microns	1 min	Radius of giant squid axon
2 millimeters	1 hr	Thickness of frog sartorius muscle, half thickness of lens of eye
5 millimeters	7 hr	Radius of mature ovarian follicle
2 centimeters	5 days	Thickness of ventricular myocardium
10 centimeters	120 days	Diameter of sea urchins & other small animals
1 meter	32 yrs	Half height of human

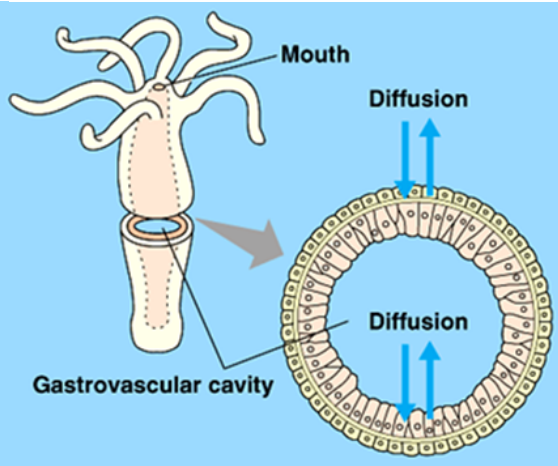
Diffusive transport in biology

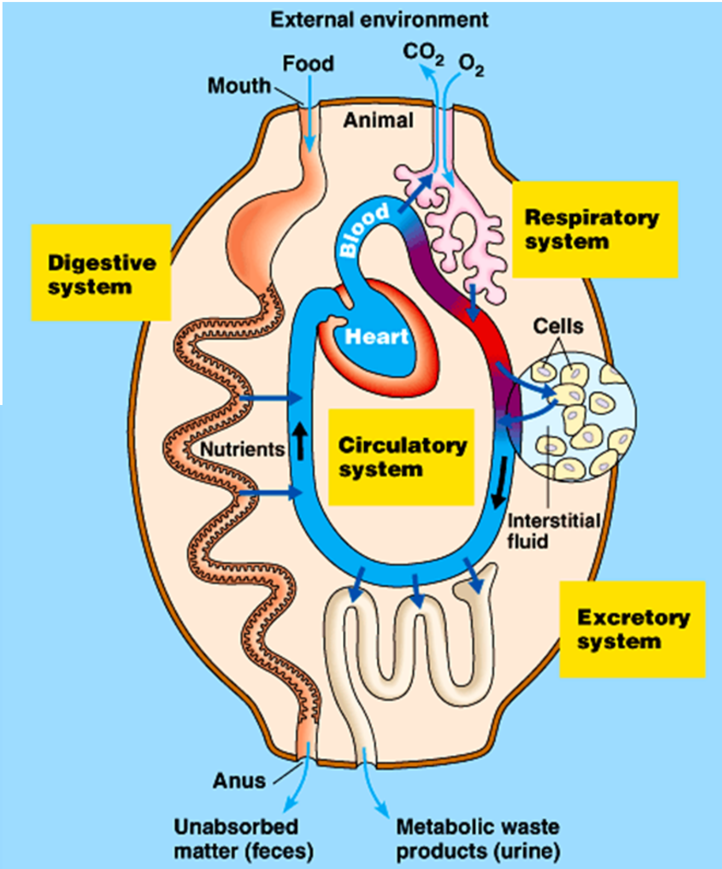
$$J_x = -D\frac{dC}{dx}$$

- ***A concentration penalty*** – diffusive transport requires a concentration gradient.
- ***No directional specificity***
- ***The time penalty*** – diffusive transport time scales as the square of the distance or $\langle X^2 \rangle = 4Dt$

There is a time when its surface area is insufficient to meet the demands of cells.







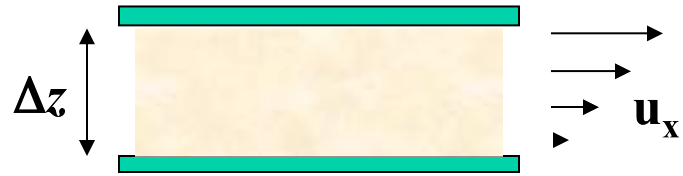
Characteristics of Fluids

(1) Fluids have density (ρ), and thus moving fluids have momentum (requires a force to start or stop them).

(2) Fluids have viscosity
   (1) Viscosity changes with temperature and salinity
   (2) When fluids contact a solid, there is a thin layer that sticks very tightly to the solid surface. = "No-slip condition"

Momentum Transfer, Viscosity

Drag – transfer of the momentum in the direction perpendicular to velocity.



Laminar flow between two surfaces moving with respect to each other.

$$\frac{\Delta p_x}{\Delta t} \equiv F_x \propto \frac{A \cdot \left(u_{x,\mathrm{top}} - u_{x,\mathrm{bottom}}\right)}{\Delta z}$$

$$\boxed{\frac{F_x}{A} = \eta \frac{d\, u_x}{\Delta z}}$$

F_x – the viscous drag force, ***η*** - the coefficient of viscosity
F_x/A – shear stress

Shear viscosity η is the proportionality between the velocity gradient and the force required, per area, to keep the plates moving at constant velocity.

	η(kg/m•sec at 20º C)
Water	*10^{-3}*
Olive oil	*0.084*
Glycerine	*1.34*
Glucose	*10^{13}*

The Langevin approach – dissipative force

Averageing over a large number of particles

Forces acting on a particle due to the solvent:

(i) Stochastic thermal (Langevin) force:

- changes direction and magnitude
- averages to zero over time

$$\langle \xi(t) \rangle = 0$$

(ii) a viscous drag force that always slows the motions.

$$f = -\zeta v$$

friction (damping) coeff.

$$\zeta = 6\pi\eta R$$

Stokes law

viscosity

The thermal forces

$$f \approx 4.5nN$$

The gravitational force

$$F_g \approx 10^{-14} nN << f$$

Newton's law for the protein motion in a one-dimensional domain of length L, x(t):

$$\boxed{\frac{dx}{dt} = v, \quad m\frac{dv}{dt} = -\zeta v + f_B(t) \quad 0 \le x(t) \le L}$$

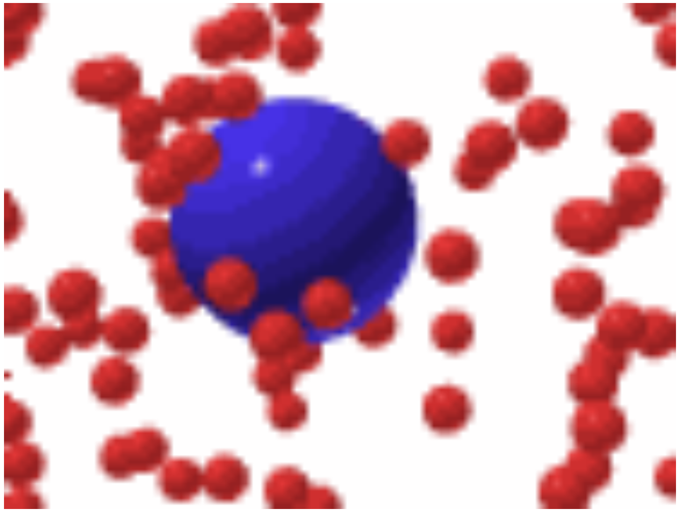
$$\boxed{\frac{m}{2}\frac{d^2(x^2)}{dt^2} - mv^2 = -\frac{\zeta}{2}\frac{d(x^2)}{dt} + xf_B(t)}$$

The average over a large number of proteins

$$\boxed{\frac{m}{2}\frac{d^2\left\langle x^2\right\rangle}{dt^2} - \left\langle mv^2\right\rangle = -\frac{\zeta}{2}\frac{d\left\langle x^2\right\rangle}{dt} + \left\langle xf_B(t)\right\rangle}$$

The mass, m, of a typical protein is about 10^{-21} kg

The random impulses from the water molecules are uncorrelated with position.



$$\boxed{\left\langle x(t)\cdot f_B(t)\right\rangle = 0}$$

Integrating twice between t = (0, t) with x(0) = 0:

$$\boxed{\frac{d\left\langle x^2\right\rangle}{dt} = \frac{2k_BT}{\zeta}\left(1-e^{-t/\tau}\right), \quad \left\langle x^2\right\rangle = \frac{2k_BT}{\zeta}\left[t-\tau\left(1-e^{-t/\tau}\right)\right]}$$

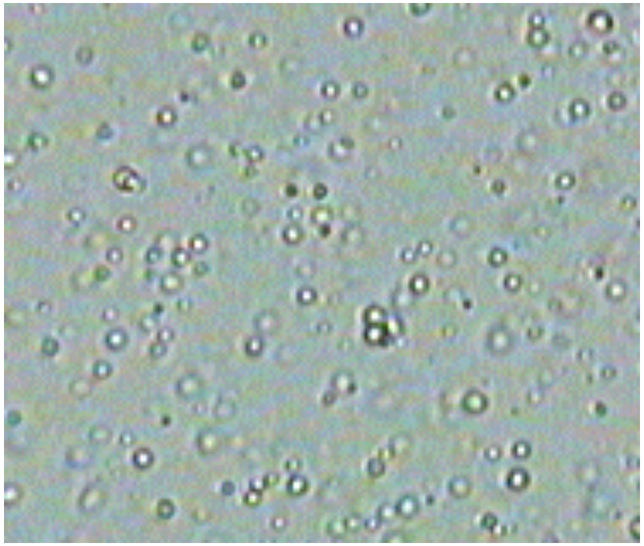
where $\tau = m/\zeta$.

Robert Brown and Brownian motion

Robert Brown

Brown (1827): observed irregular movement of pollens in water under microscope.

Major contribution of Brown: made sure non-organic particles also have Brownian motion, confirmed that Brownian motion is not a manifestation of life.



$$\langle x^2 \rangle = \frac{2k_BT}{\zeta}\left[t - \tau\left(1 - e^{-t/\tau}\right)\right]$$

For short times, $t \ll \tau$, the exponential can be expand to second order:

$$\langle x^2 \rangle = \frac{k_BT}{m}t^2 \qquad (t \ll \tau)$$

- The protein behaves as a ballistic particle moving with a velocity $v = (k_BT/m)^{1/2}$. For a protein with m = 10^{-21} kg, **v = 2 m/s.**

- In a fluid the protein moves at this velocity only for a time **$\tau \sim m/\zeta = 10^{-13}$ sec** – shorter than any motion of interest in a molecular motor.

- During this time the protein travels a distance **$v \cdot \tau \sim 0.01$ nm** before it collides with another molecule.

$$\boxed{\left\langle x^2 \right\rangle = \frac{2k_BT}{\zeta}\left[t - \tau\left(1 - e^{-t/\tau}\right)\right]}$$

When t >> τ, the exponential term disappears and:

$$\boxed{\left\langle x^2 \right\rangle = \frac{2k_BT}{\zeta}t \quad (t >> \tau)}$$

Because **$<x^2> = 2Dt$** (Einstein relation – 1905):

$$\boxed{D = \frac{k_BT}{\zeta}}$$

Friction is quantitatively related to diffusion

For protein typically D ~ 10^{-11} m^2/sec.

Einstein, Brownian motion, and atomic hypothesis

Albert Einstein, 1905

Albert Einstein published 4 papers in the *Annalen der Physik* in 1905.

- Photoelectric effect
- Brownian motion
- Special theory of relativity

- Drag force: $f = \gamma v$
- Diffusion due to random walk: $d^2 = 6Dt$
- To reach equilibrium: $D\gamma = kT$
- Random collisions (random walk) are related to the dissipation of kinetic energy to solvent molecules.

External forces acting on macromolecules

$$\zeta \cdot \frac{dx}{dt} = F(x,t) + f_B(t)$$

The inertial term is neglected.

Forces acting on proteins can be characterized by a potential

$$F(x,t) = -\frac{\partial \varphi(x,t)}{\partial x}$$

$$\zeta \frac{dx}{dt} = -\frac{\partial \phi(x,t)}{\partial t} + f_B(t)$$

Langevin equation

The Reynolds Number

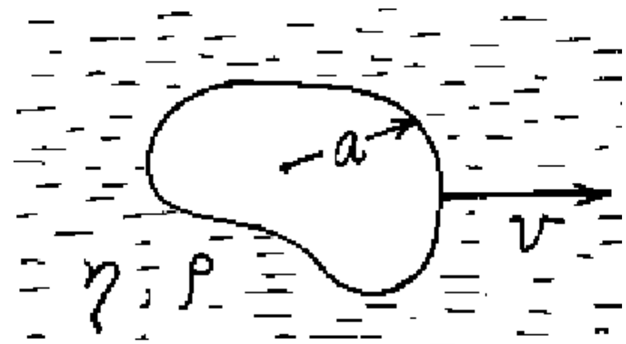
Dimensionless constant

$$R = \frac{inertial \quad term}{friction \quad term} = \frac{va\rho_m}{\eta}$$

a – radius of a particle

v – particle velocity

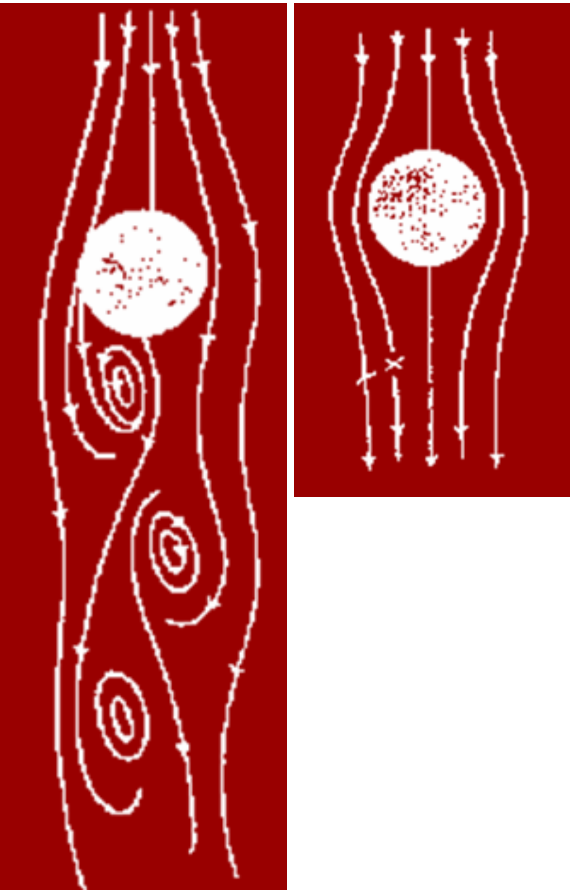
ρ_m – medium density



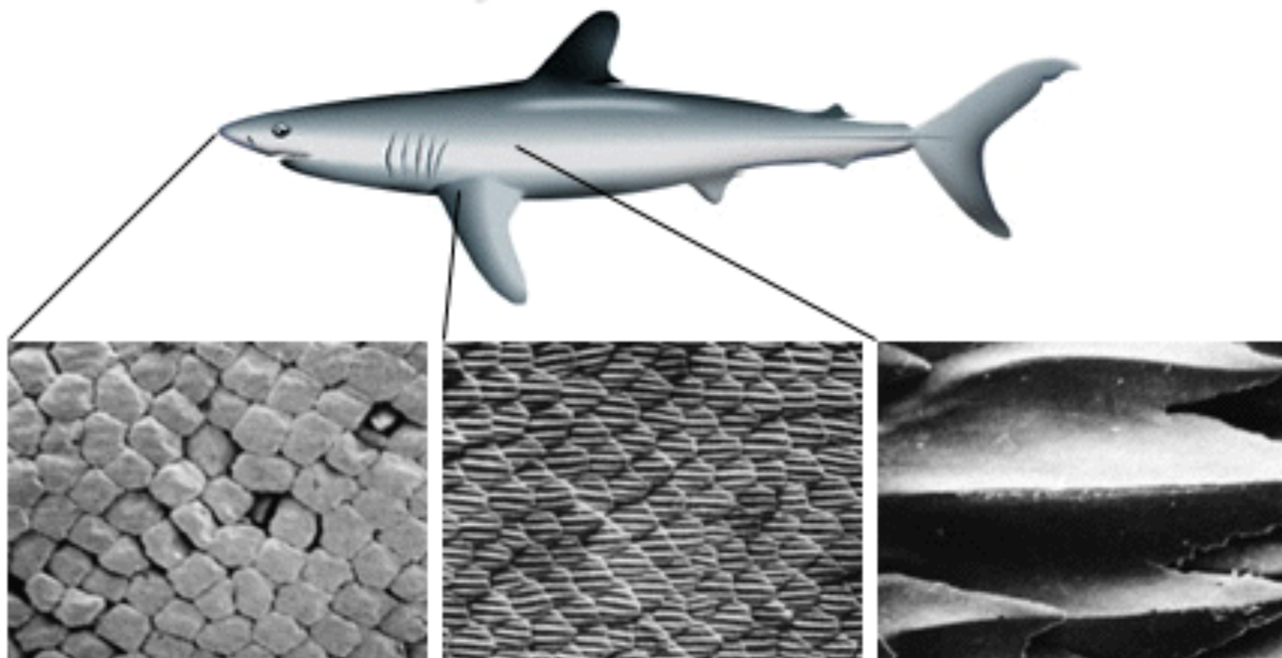
When the Reynolds number 'R' is small the viscous forces dominate.

		Mass [g]	Diffusion time	Swimming speed [cm/s]	Reynolds number
Bacterium	1 μm	10^{-12}	1 msec	10^{-3}	10^{-5}
Whale	10 m	10^{9}	10^{3} years	1000	10^{8}

Low Reynolds Number = Laminar Flow



Shark skin delays transition to turbulence



Advertisement of a new swim suit

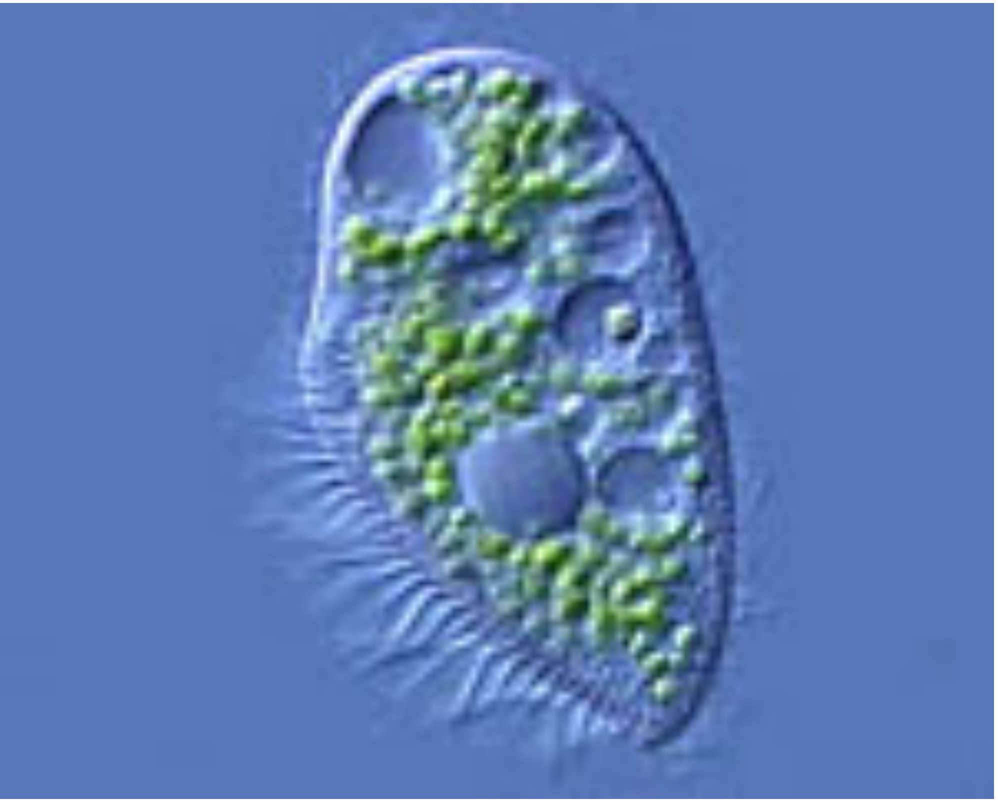
Mounting a riblet foil on the wing of an airbus

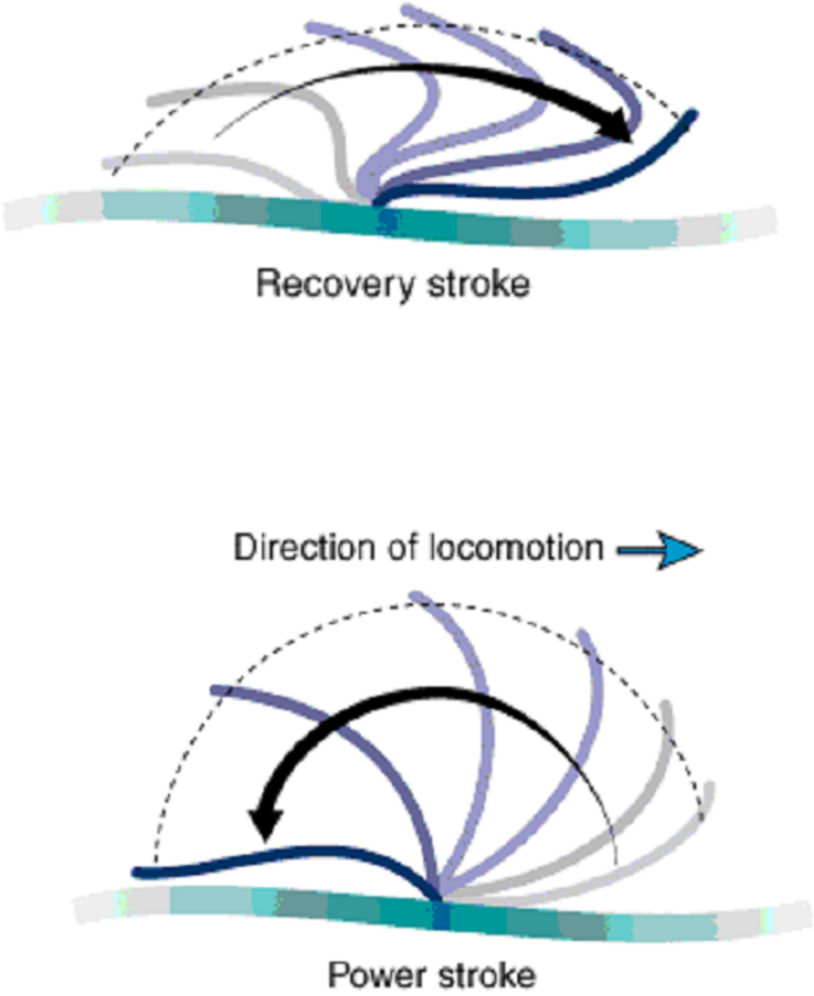
Small objects experience a large air viscosity.

If the animal tries to move by a reciprocal motion in low R number condition, it can't go anywhere.

There is a minimum size for insects that are able to fly.

The smallest flying insect is a parasitic wasp (*Dicopomorpha Echmepterygis*), which is about 1/10 of a mm long.



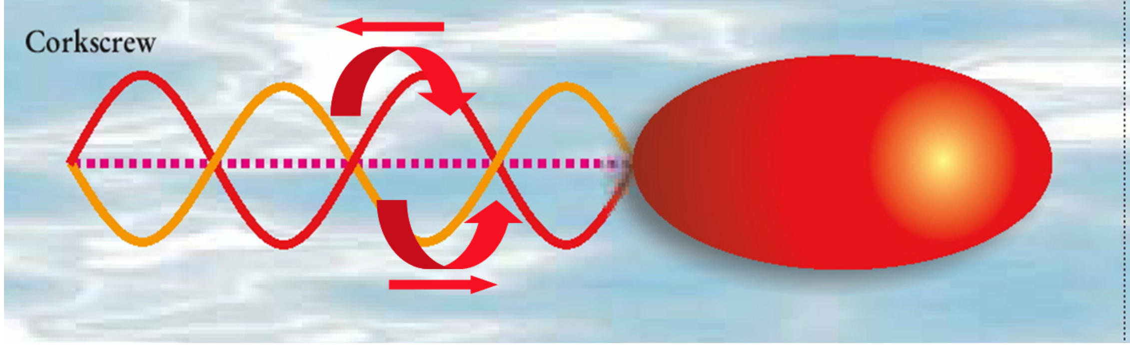


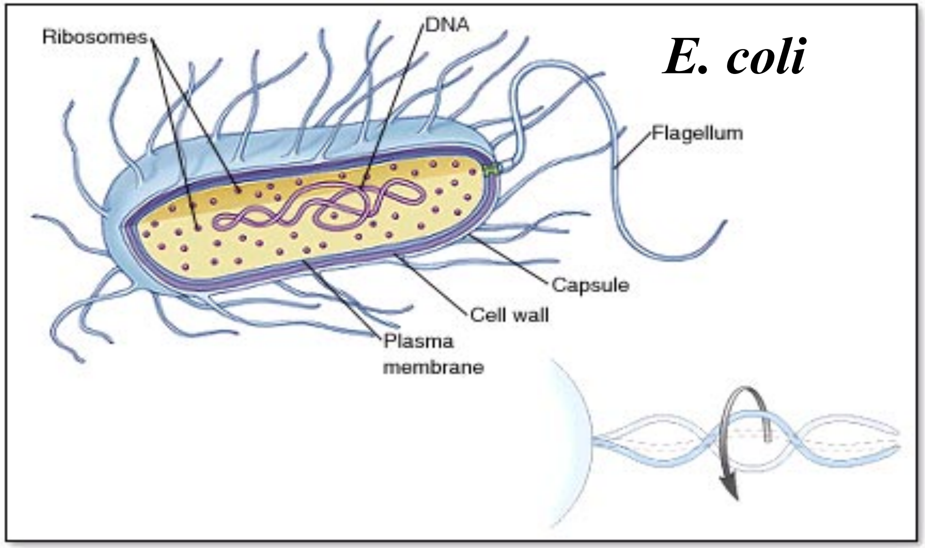
In addition the viscous friction coefficient can be anizotropic.

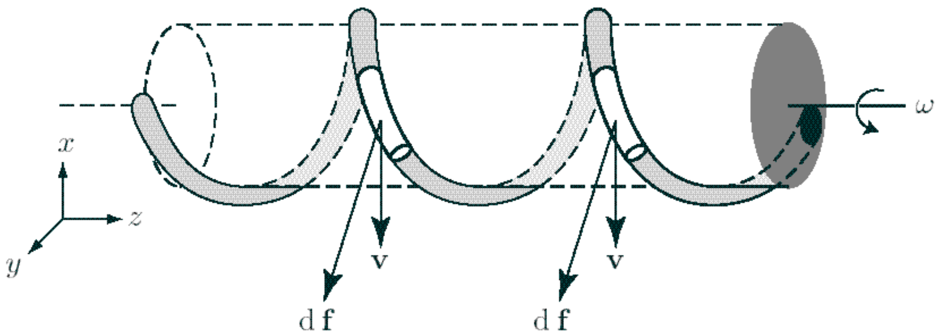
$$\eta_{II} < \eta_{\perp}$$

A „corkscrew”
(flagella)

It is a rigid, helical object.







All the components in the xy plane are canceled but df_z does not concel.

At low Reynolds number you can't shake off your environment.

Stirring vs. diffusion

Time for transport by stirring:

$$t_{stirring} = \frac{l}{v}$$

Time for tranport by diffusion:

$$t_{diffusion} = \frac{l^2}{D}$$

Stirring works if

$$a = \frac{t_{diffusion}}{t_{stirring}} = \frac{lv}{D} > 1$$

For a bacteria

$$S \approx 10^{-3}$$

Stirring number

$$S = \frac{lv}{D}$$

$D = 10^{-5}\ cm^2/s$

Reynolds number

$$R = \frac{lv}{\eta}$$

$\eta = 10^{-2}\ cm^2/s$

It can't do anything by stirring its local surroundings. It might as well wait for things to diffuse.