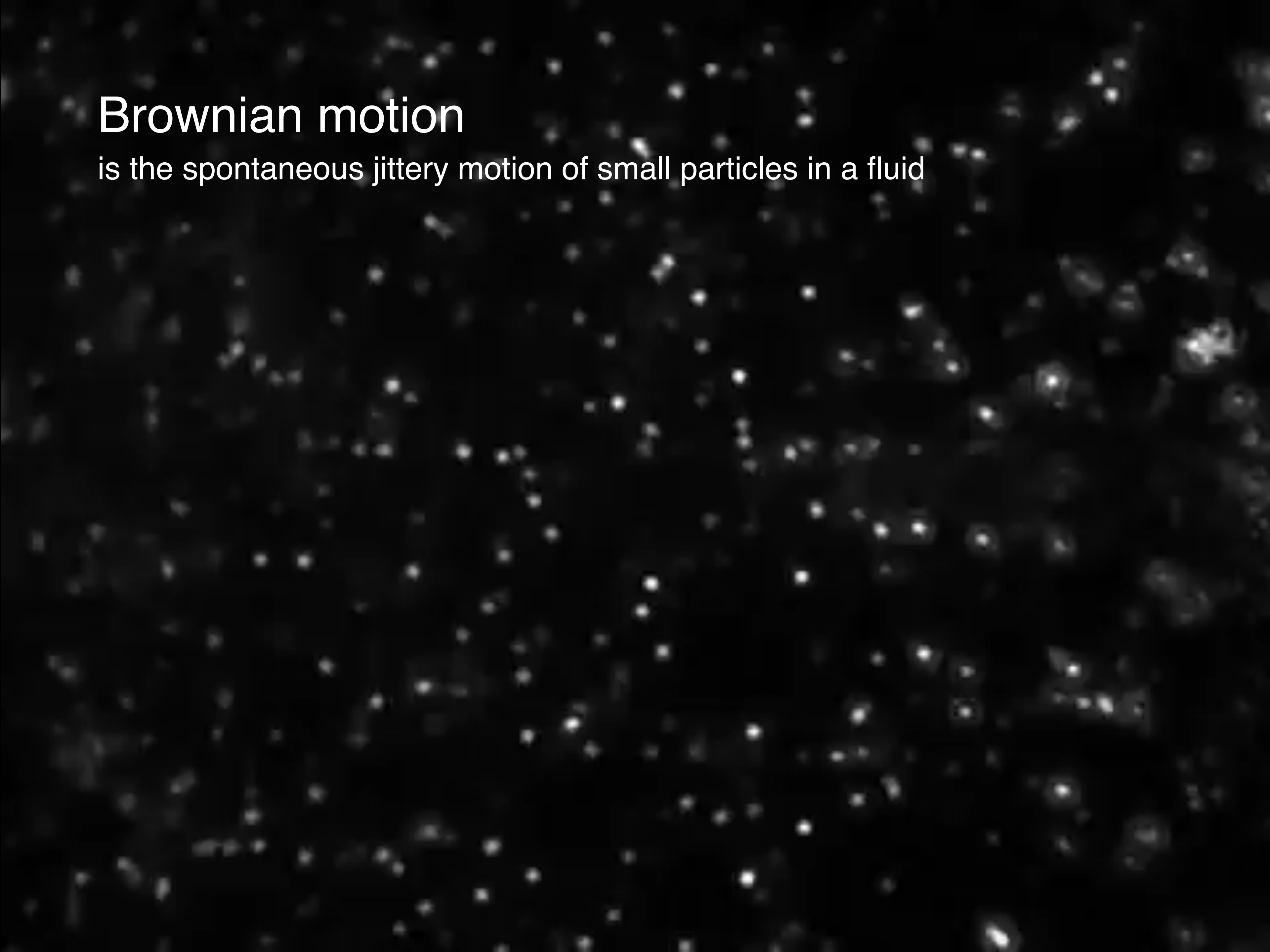
Brownian motion

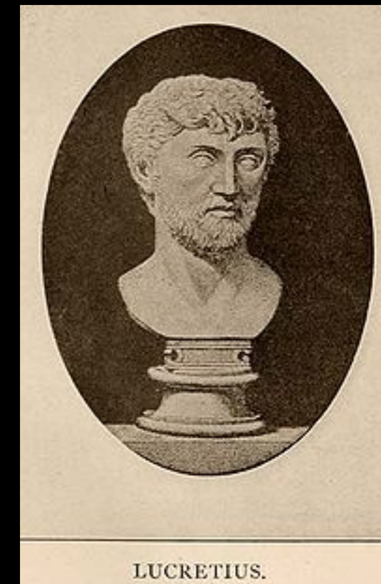
is the spontaneous jittery motion of small particles in a fluid



Brownian motion

On his scientific poem *“De Rerum Natura"* (c. 60BC) Lucretius makes a remarkable description of the (Brownian) motion of dust particles.

He uses this observation as a proof for the **existence of atoms**



Lucretius
roman philosopher
(ca.99 BC ca.55 BC)

“Observe what happens when sunbeams are admitted into a building and shed light on its shadowy places. You will see a multitude of tiny particles mingling in a multitude of ways... ***their dancing is an actual indication of underlying movements of matter that are hidden from our sight****…* ***It originates with the atoms which move of themselves****. Then those small compound bodies that are least removed from the impetus of the atoms* ***are set in motion by the impact*** *of their invisible blows and in turn cannon against slightly larger bodies. So the movement mounts up from the atoms and gradually emerges to the level of our senses, so that those bodies that we see in sunbeams are in motion, moved by blows that remain invisible.”*

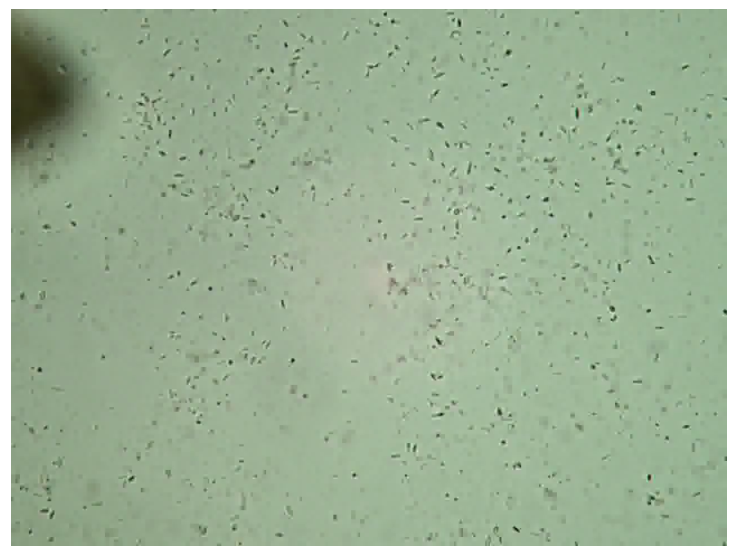
Lucretius (c. 60 BC) *“De Rerum Natura"*

Brownian motion

Robert Brown (Scottish botanist, 1773 -1858)

In 1827, while examining pollen grains suspended in water under a microscope, Brown observed the particles expelled when the pollen grains burst, now known to be amyloplasts (starch organelles) and spherosomes (lipid organelles). These **small particles** were "**executing a continuous jittery motion**".

Clarkia pulchella pollen bursting (the grain's diameter is around 50μm)



Brownian motion of the contents of *Clarkia pulchella* pollen

Brownian motion

Robert Brown (Scottish botanist, 1773 -1858)

In 1827, while examining pollen grains suspended in water under a microscope, Brown observed the particles expelled when the pollen grains burst, now known to be amyloplasts (starch organelles) and spherosomes (lipid organelles). These **small particles** were “**executing a continuous jittery motion**”.

Are these particles moving because they are “alive”?

Brown observed the same motion in particles of **inorganic matter**, enabling him to **rule out the hypothesis that the effect was life-related**.

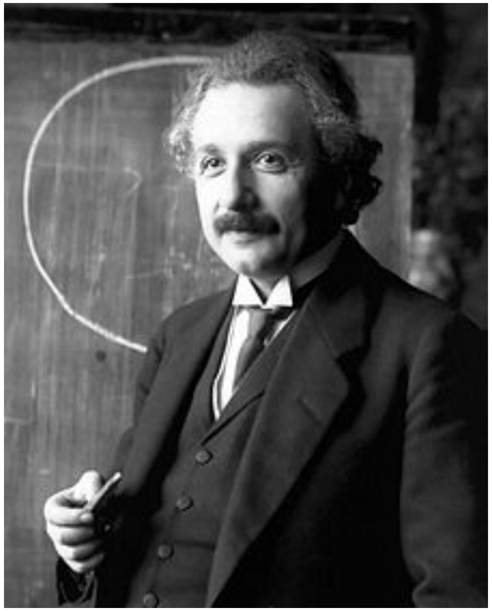
The motion doesn’t arise from a “vital force”, it’s a purely physical phenomenon, common to both living and non-living things.

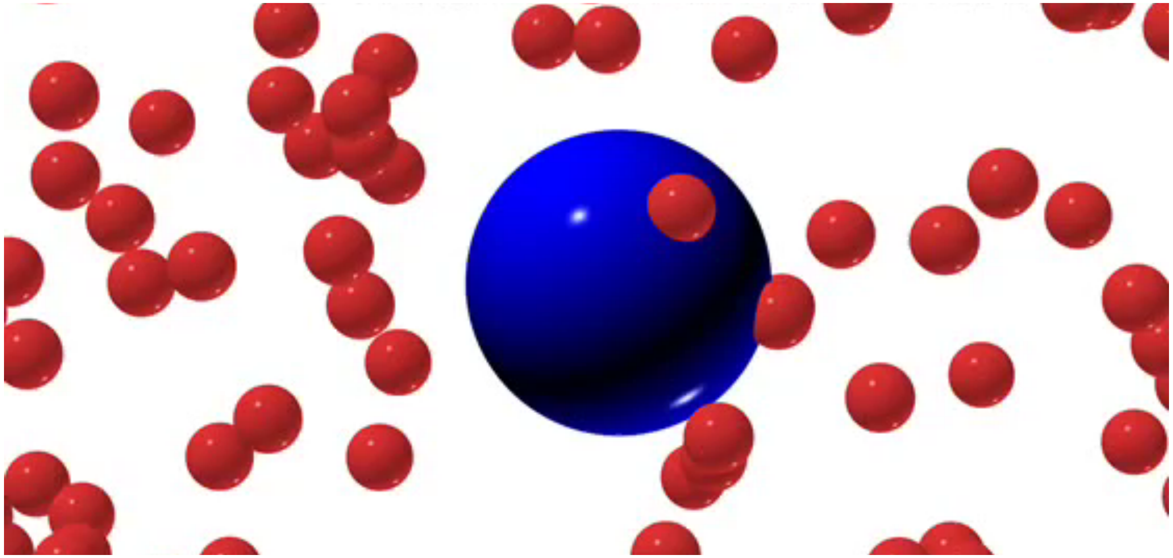
Brownian motion

Albert Einstein (1879 - 1955)

In 1905, Einstein proposes that the small particles are pushed around by collisions with water molecules moving randomly in all directions.

In the light of this hypothesis, Brown's observations would be a way to indirectly confirm the existence of atoms and molecules.



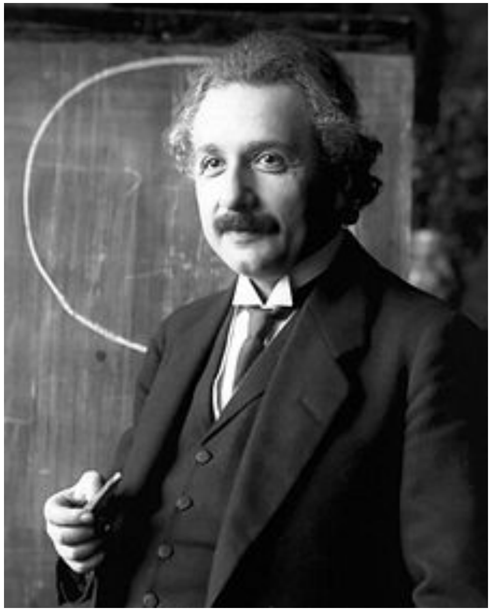


Brownian motion

Albert Einstein (1879 - 1955)

In 1905, Einstein proposes that the small particles are pushed around by collisions with water molecules moving randomly in all directions.

In the light of this hypothesis, Brown's observations would be a way to indirectly confirm the existence of atoms and molecules.

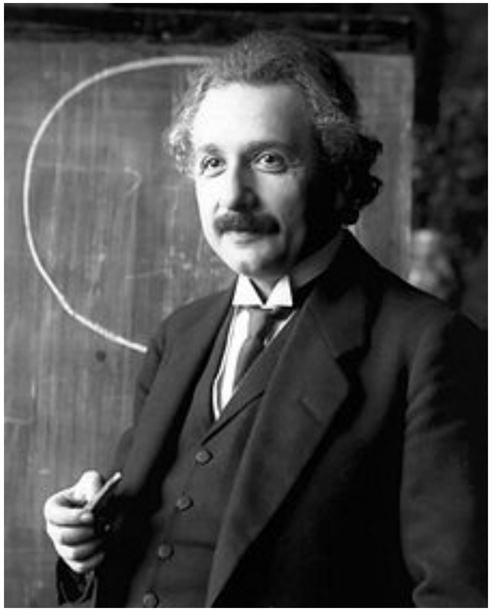


If this is true, then:

- the motion should obey the Newton's laws of motion (inertia, force=mass×acceleration, action-reaction)
- the forces acting on the particle movement should be random
- the diffusion coefficient of the particles could be calculated and measured
- the particles moving in a fluid would also be affected by frictional forces (Stokes formula)

Brownian motion

Albert Einstein (1879 - 1955)



In 1905, Einstein proposes that the small particles are pushed around by collisions with water molecules moving randomly in all directions.

In the light of this hypothesis, Brown's observations would be a way to indirectly confirm the existence of atoms and molecules.

Taking all these effects together, we can calculate the particles' kinetic energy (the amount of agitation) and relate it to the temperature of the liquid.

These are the bases for the molecular kinetic theory of heat, where Einstein **relates Newton mechanics to thermodynamics**, and the Brownian motion to temperature and diffusion.

This framework provides a theoretical explanation for Brown's observations, but lacks the experimental proof.

ON THE MOVEMENT OF SMALL PARTICLES SUSPENDED IN STATIONARY LIQUIDS REQUIRED BY THE MOLECULAR-KINETIC THEORY OF HEAT

by A. Einstein

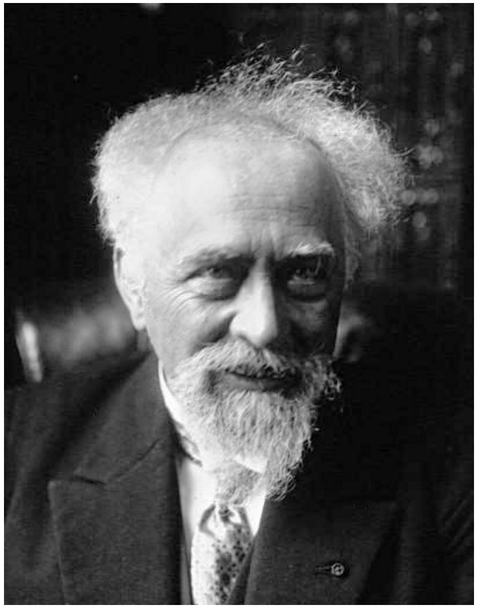
[*Annalen der Physik* 17 (1905): 549-560]

It will be shown in this paper that, according to the molecular-kinetic theory of heat, bodies of microscopically visible size suspended in liquids must, as a result of thermal molecular motions, perform motions of such magnitude that these motions can easily be detected by a microscope. It is possible that the motions to be discussed here are identical with the so-called "Brownian molecular motion"; however, the data available to me on the latter are so imprecise that I could not form a definite opinion on this matter.

If it is really possible to observe the motion to be discussed here, along with the laws it is expected to obey, then classical thermodynamics can no longer be viewed as strictly valid even for microscopically distinguishable spaces, and an exact determination of the real size of atoms becomes possible. Conversely, if the prediction of this motion were to be proved wrong, this fact would provide a weighty argument against the molecular-kinetic conception of heat.

Brownian motion

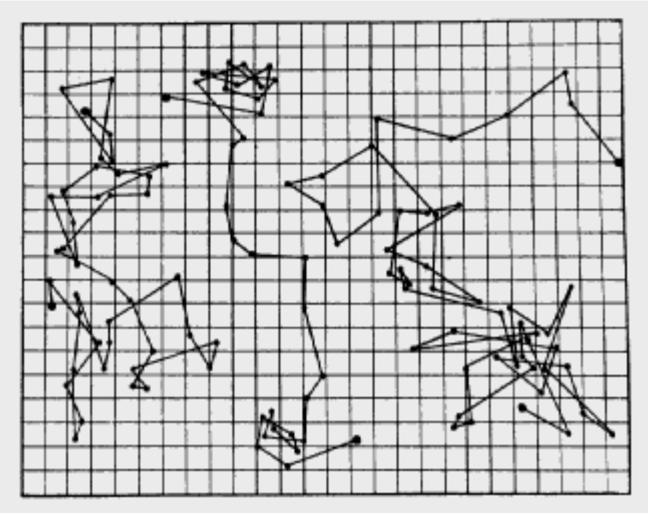
Jean Perrin (1870 - 1942)



Einstein's statement that **thermal molecular motions** should be easily observed under a microscope stimulated Jean Perrin to make quantitative measurements

"I did not believe that it was possible to study the Brownian motion with such a precision."

(letter from Albert Einstein to Jean Perrin, 1909)

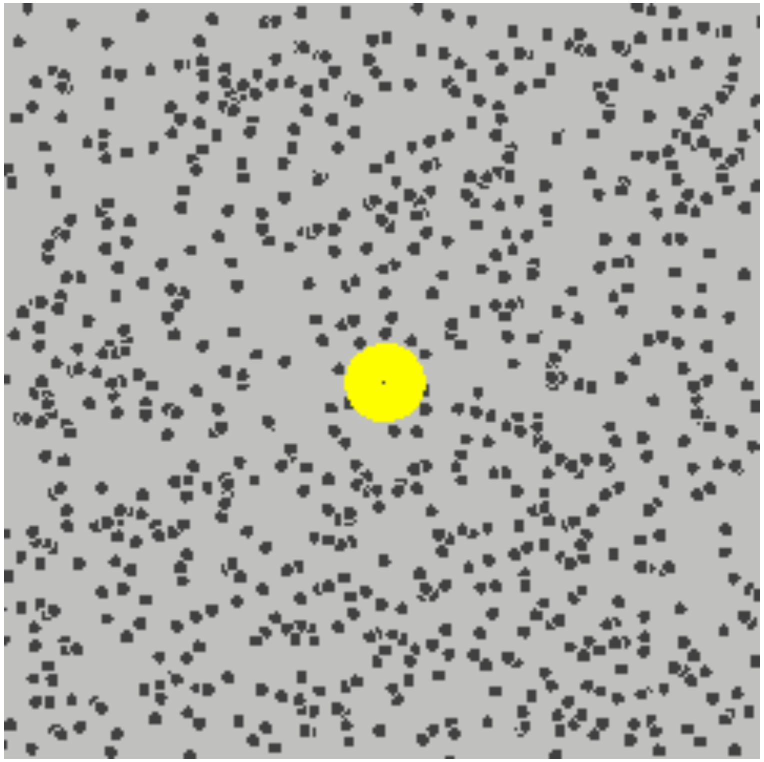


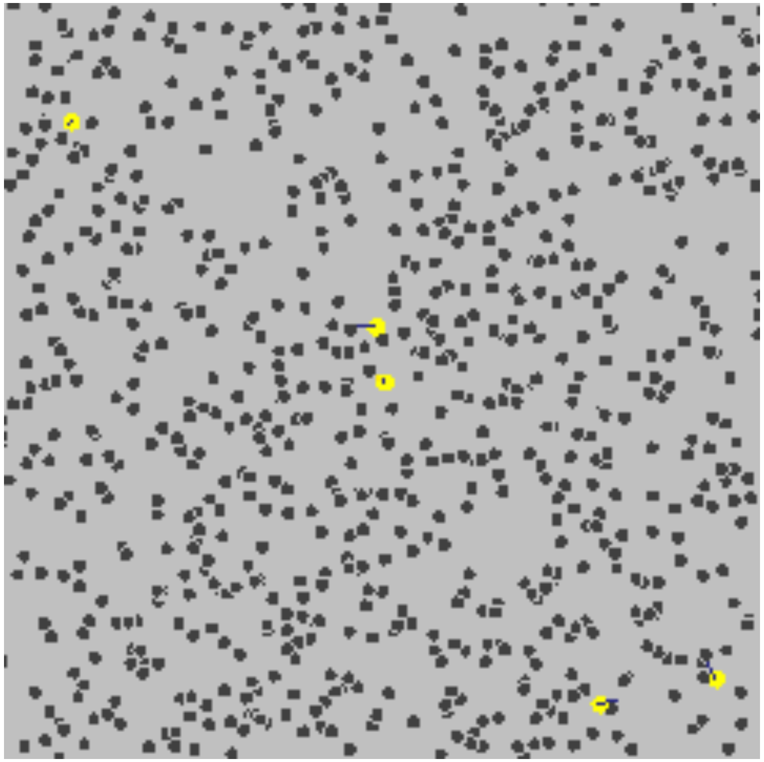
Tracings of the motion of 3 colloidal particles of radius 0.53 μm, as seen under the microscope. Successive positions every 30 seconds are joined by straight line segments (the mesh size is 3.2 μm).

Perrin JB (1909) *"Mouvement brownien et réalité moléculaire"*, Ann. de Chimie et de Physique (VIII) 18: 5-114 & Perrin JB (1909), *"Les Atomes"*

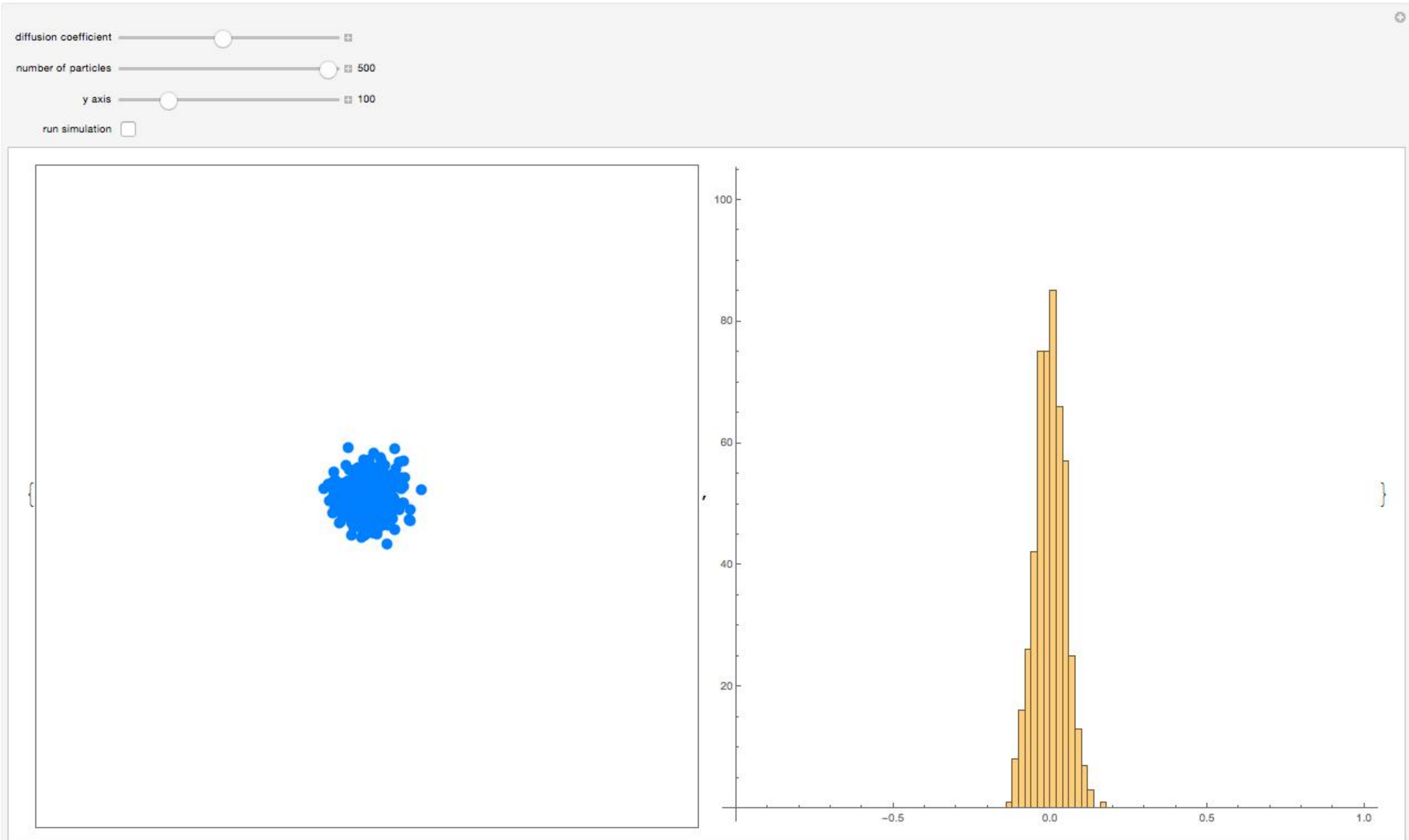
Brownian motion and random walks

Smaller particles move faster and travel more than big ones

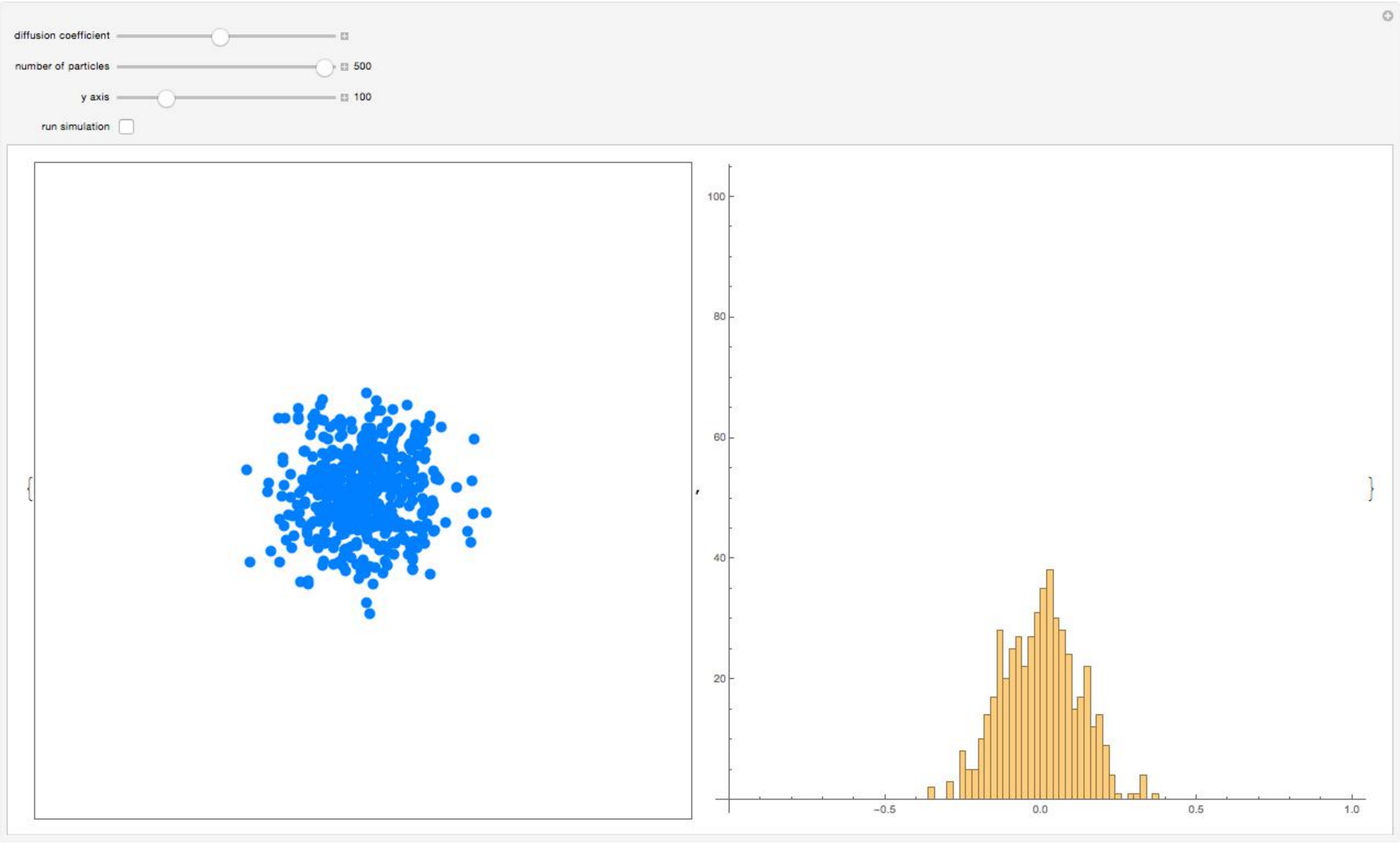




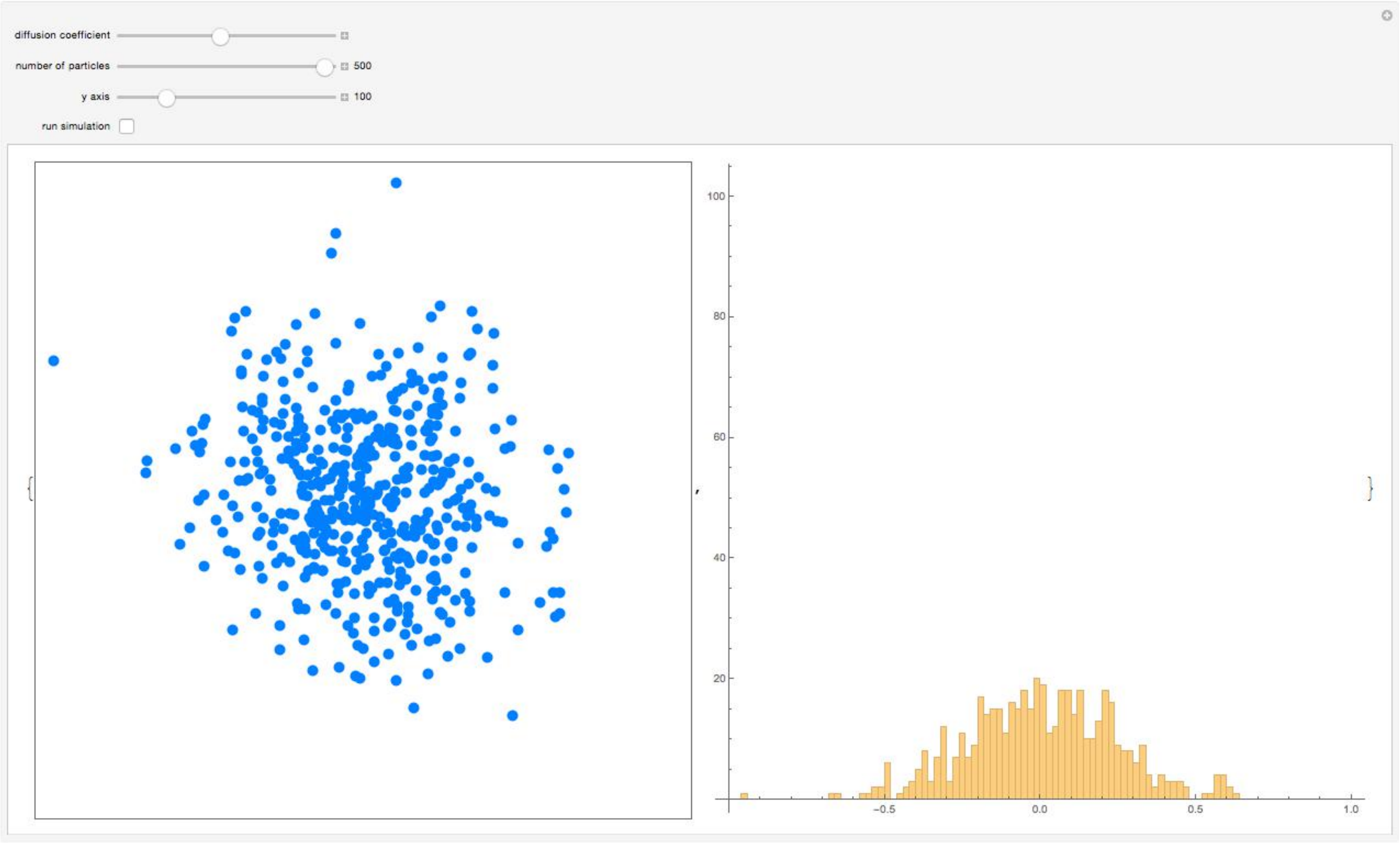
Brownian motion and random walks



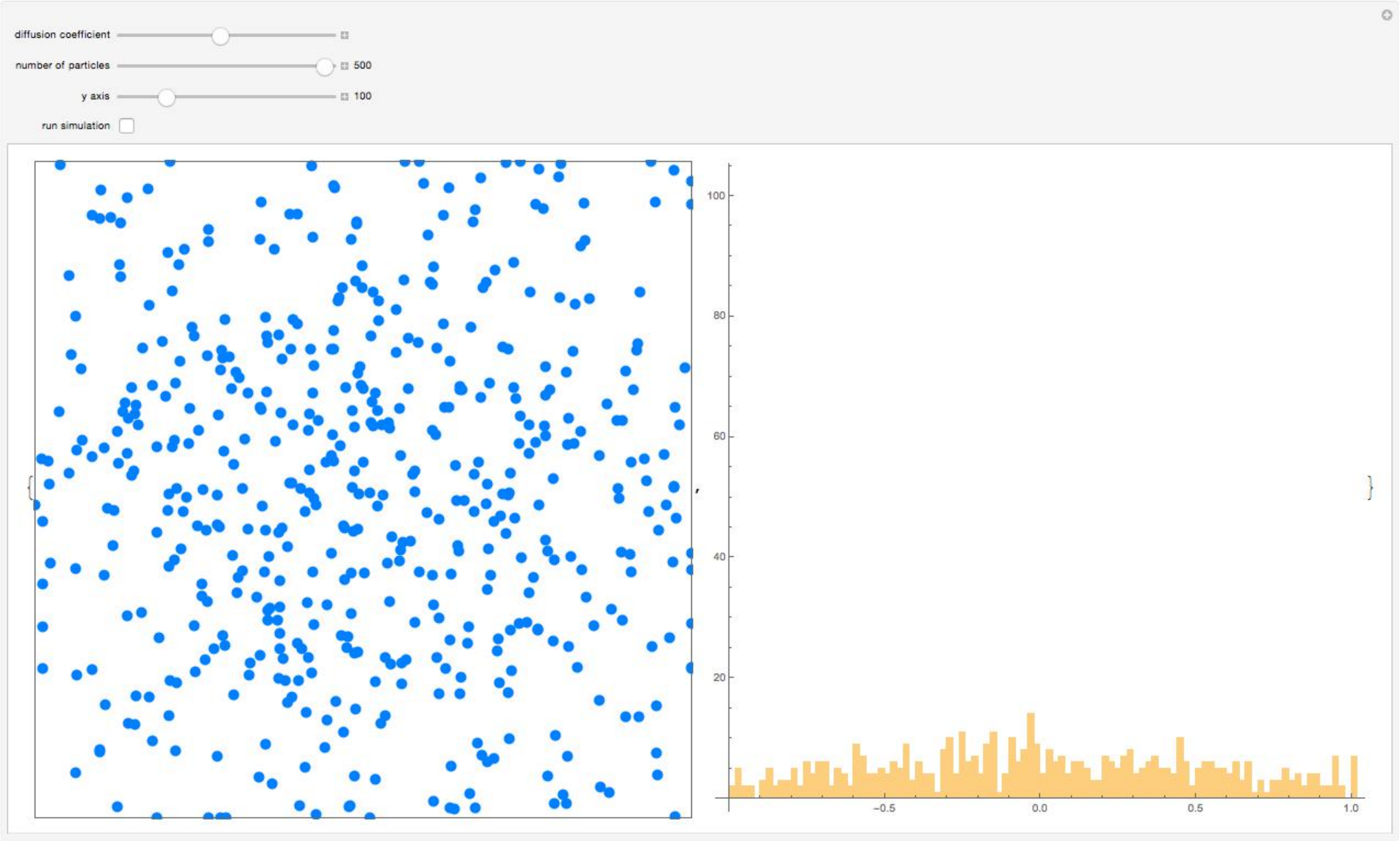
Brownian motion and random walks



Brownian motion and random walks



Brownian motion and random walks



Brownian motion and diffusion

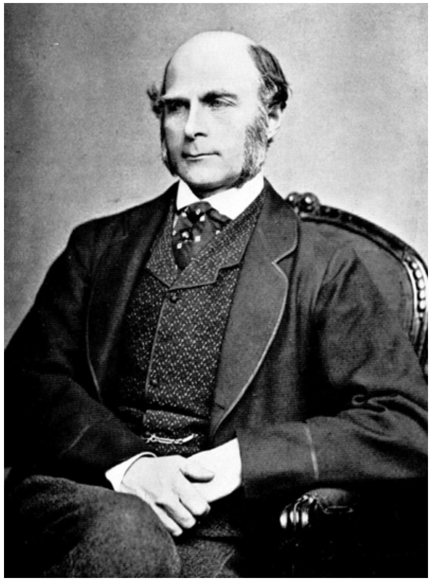
- Why do the particles “spread”?
- What is the shape of their distribution during the first time steps?
- How does this distribution vary with time?
- What is the shape of the particle distribution at equilibrium?
- Why are the particles normally distributed in space?

The Central Limit Theorem

The central limit theorem (CLT) states that the mean of a sufficiently large number of independent random variables, identically distributed and each with finite mean and variance, will be approximately normally distributed.

Let $\mathbf{X_1, X_2, X_3, ..., X_n}$ be identical and independently distributed random variables with mean $\mathbf{m}$ and variance $\mathbf{s^2}$.
Let $\sum\mathbf{X}$ be the sum of the values of the $\mathbf{n}$ variables.
When $\mathbf{n}$ is very large $\sum\mathbf{X}$ follows approximately a Normal distribution with mean $\mathbf{n \cdot m}$ and variance $\mathbf{n \cdot s^2}$

The Central Limit Theorem



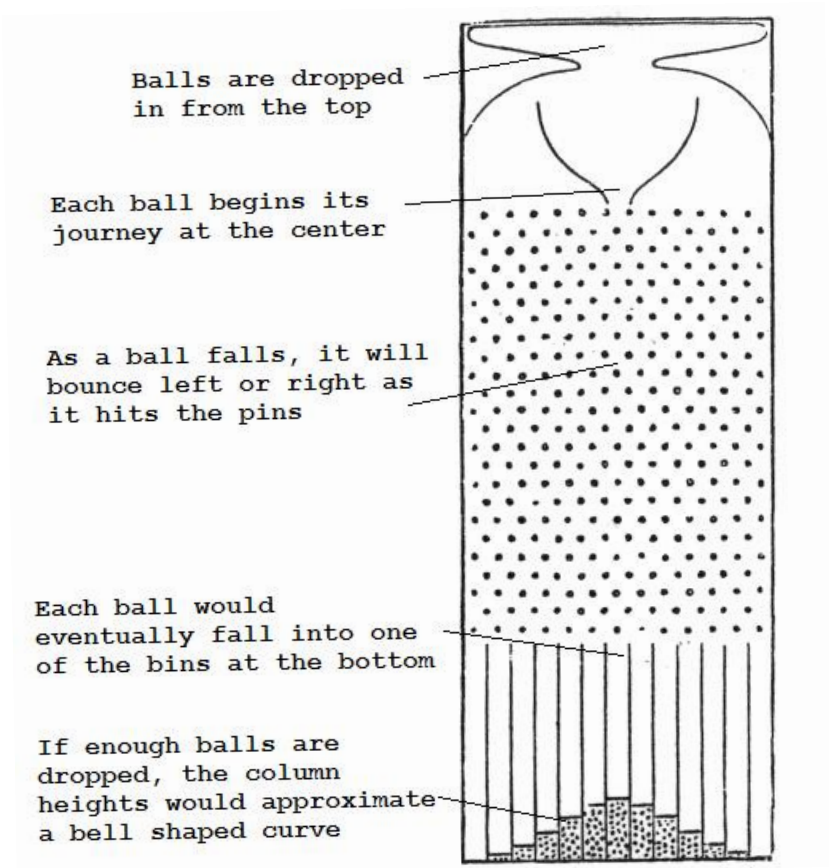
Sir Francis Galton (1822 -1911)

As described by Galton:

I know of scarcely anything so apt to impress the imagination as the wonderful form of cosmic order expressed by the "Law of Frequency of Error". The law would have been personified by the Greeks and deified, if they had known of it. It reigns with serenity and in complete self-effacement, amidst the wildest confusion. The huger the mob, and the greater the apparent anarchy, the more perfect is its sway. It is the supreme law of Unreason. Whenever a large sample of chaotic elements are taken in hand and marshalled in the order of their magnitude, an unsuspected and most beautiful form of regularity proves to have been latent all along.

Galton F. (1889) Natural Inheritance

The Galton board
(aka the quincunx or the bean machine)



The Galton board
(aka the quincunx or the bean machine)

Diffusion coefficient and mean square displacement

When a particle diffuses, its mean displacement is zero because diffusion is an isotropic process (it is uniform in all directions).

However, its mean square displacement, which characterises the spread of the particle's position, is a linear function of time. The coefficient of proportionality is called the diffusion coefficient, and describes how easily a particle moves in a concentration gradient.

The diffusion of particles in one dimension is given by

$$< \Delta X^2 > = 2\ D\ t$$

Where $< \Delta X^2 >$ is the average displacement squared, **D** is the diffusion coefficient and **t** is the elapsed time.

The diffusion coefficient (D) is given for a pair of molecule types (e.g. a solute in water), in the units area/time (usually cm^2/s).
Depends on several properties of the molecules, such as size, charge, mobility and viscosity, and changes with pressure and temperature.

Diffusion coefficient and mean square displacement

$$< \Delta X^2 > = 2\ D\ t$$

A larger diffusion coefficient reflects a greater spread in position during a given time interval.

An important aspect of diffusion that is evident from this equation is that the average distance travelled by a small particle subjected to random collisions increases with the square root of time.

$$x : \sqrt{t}$$

In contrast, the displacement of a particle moving in a straight line, without collisions or any other forces acting on it, would changes linearly with time, according to Newton's first law of motion (law of inertia).

$$x : t$$

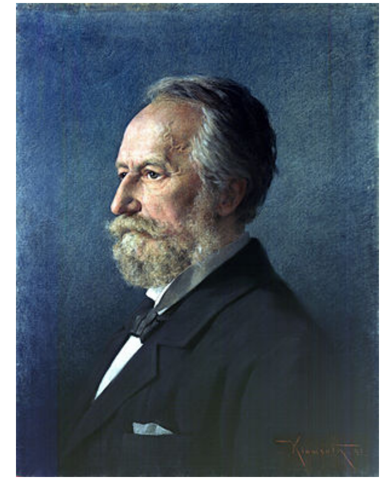
→ How long will a protein with a diffusion coefficient of 10μm^2/s take to move 10μm?

→ A protein with a diffusion coefficient of 10μm^2/s takes, on average, 5 seconds to move 10μm, and 500 seconds to move 100μm.

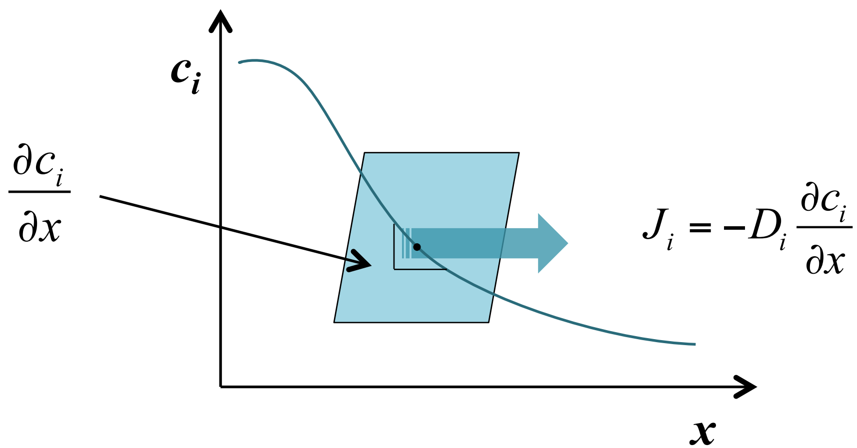
Steady state diffusion: Fick's first law

$$J_i = -D_i \frac{\partial c_i}{\partial x}$$

The diffusive flux of a molecule ***i*** along the direction ***x*** is proportional to its concentration gradient (in this case, the flux doesn't change with time)
(in number of molecules per unit area per unit time)



Adolf Fick (1829-1901)



Flux of molecules across a plane with area = 1
(the minus sign in the equation means that diffusion is down the concentration gradient)

Non-steady state diffusion: Fick's second law

$$\frac{\partial c_i}{\partial t} = D_i \frac{\partial^2 c_i}{\partial x^2}$$

In most real situations the concentration profile and the concentration gradient are changing with time. The changes of the concentration profile is given in this case by this differential equation

Adolf Fick (1829-1901)

$$\frac{\partial c_i}{\partial t} = D_i \left(\frac{\partial^2 c_i}{\partial x^2} + \frac{\partial^2 c_i}{\partial y^2} \right)$$

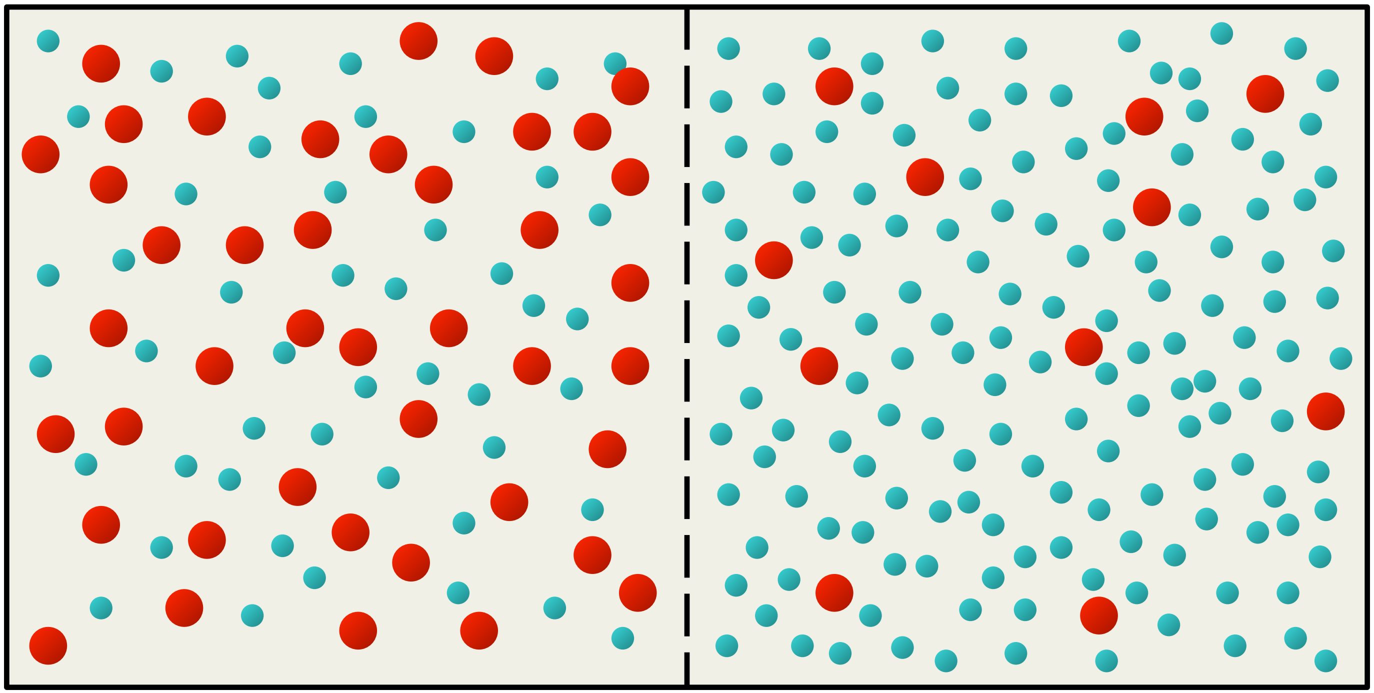
In two dimensions

$$\frac{\partial c_i}{\partial t} = D_i \left(\frac{\partial^2 c_i}{\partial x^2} + \frac{\partial^2 c_i}{\partial y^2} + \frac{\partial^2 c_i}{\partial z^2} \right)$$

In three dimensions

Diffusion and Osmosis

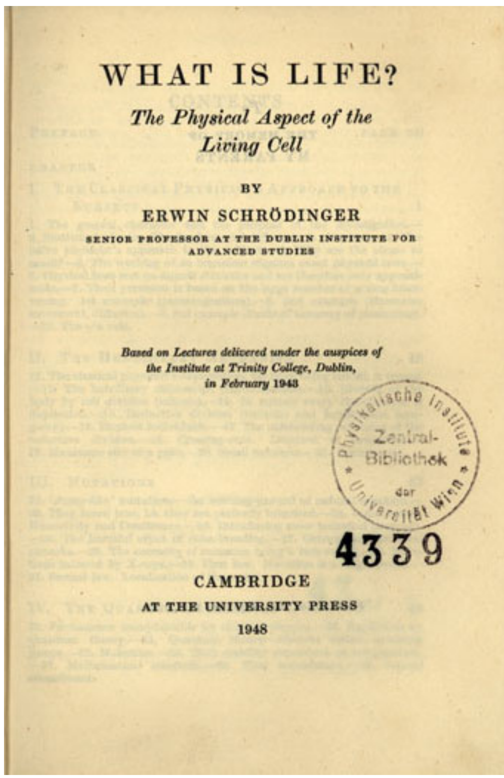
Osmosis is the **net movement** of solvent molecules through a partially permeable membrane into a region of higher solute concentration



When are the diffusion equations valid?

Most physical laws are statistical

Diffusion can only be understood as a deterministic process if we consider a large number of particles



WHAT IS LIFE?

The Physical Aspect of the Living Cell

BY

ERWIN SCHRÖDINGER

SENIOR PROFESSOR AT THE DUBLIN INSTITUTE FOR ADVANCED STUDIES

Based on Lectures delivered under the auspices of the Institute at Trinity College, Dublin, in February 1943

CAMBRIDGE

AT THE UNIVERSITY PRESS

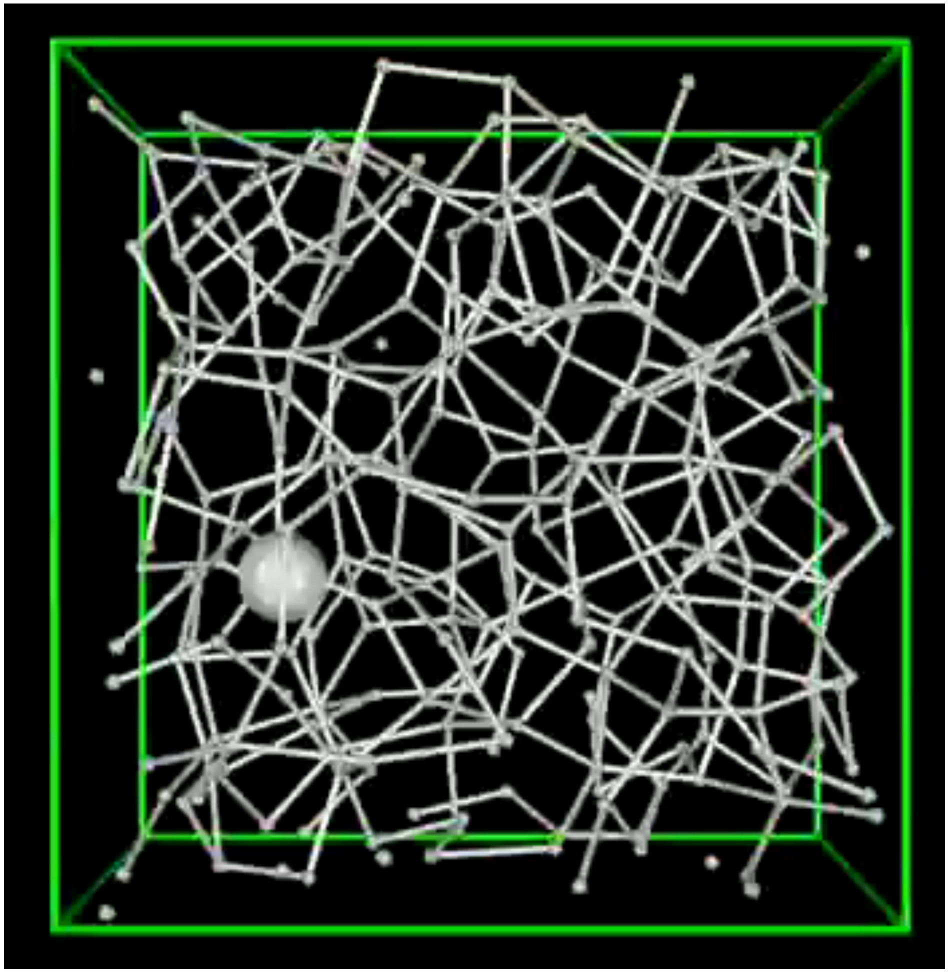
1948

Erwin Schrödinger
(1887-1961)

In chapter I, Schrödinger explains that most physical laws on a large scale are due to chaos on a small scale. He calls this principle "order-from-disorder." As an example he mentions diffusion, which can be modeled as a highly ordered process, but which is caused by random movement of atoms or molecules. If the number of atoms is reduced, the behaviour of a system becomes more and more random.

Ideal diffusion doesn't exist in biology

A small non-charged particle (H atom) moving in water



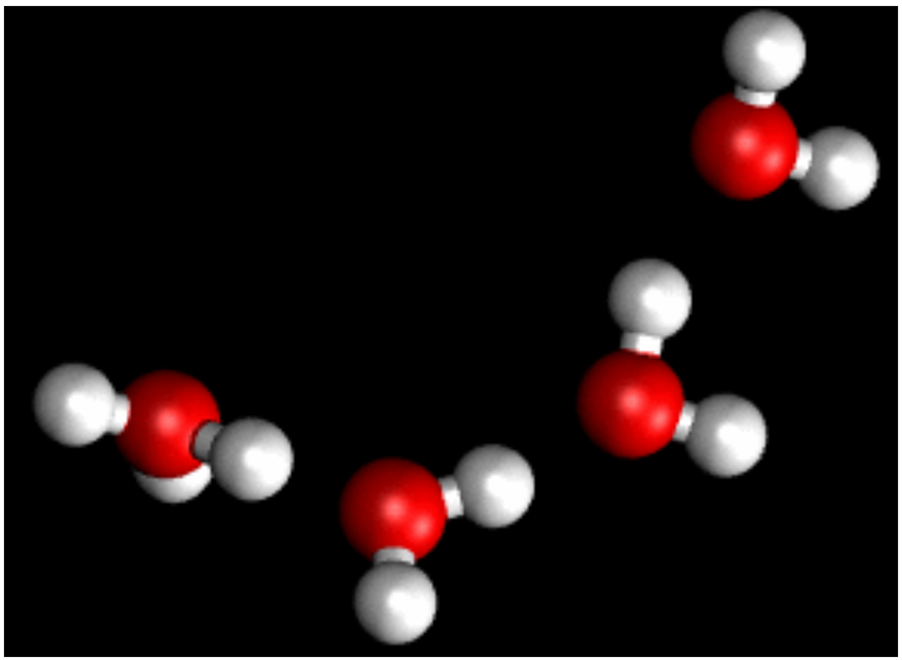
The movie captures 5 picoseconds of a molecular dynamics simulation of a metastable "hydrophobic" hydrogen atom dissolved in liquid water at 300 K and ambient pressure conditions. Shown is the fluctuating hydrogen bond network of water embedding the H-particle. The oxygen atoms of the water molecules represent the vertices of the network. Note that the small H particle is quickly exploring the accessible free volume left over by the water molecules. The "open" water network structure permits the H-particle to adopt a diffusion coefficient being about three to four times larger than the diffusion coefficient of water itself.

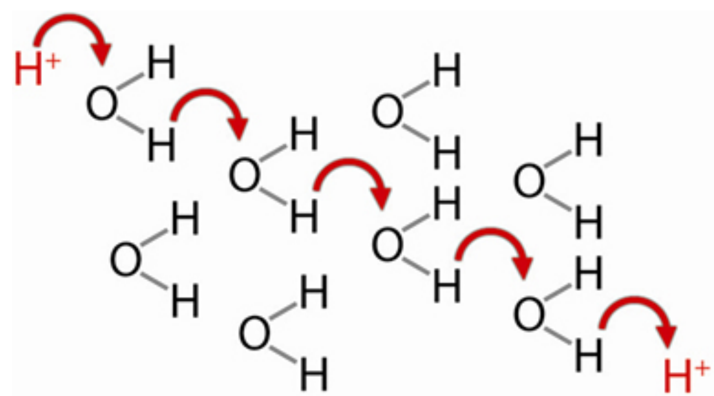
$D \approx 4.5 \times 10^3\ \mu m^2/s$ (at 26.85°C)

Proton hopping in water

Protons (H^+) move much faster than Hydrogen atoms!

The Grotthuss mechanism ("proton-hopping"), along with the relative lightness and small size of the proton, explains the unusually high diffusion coefficient of protons relative to other ions, for which the movement is due simply to random thermal motion (Brownian motion)





$D \approx 3.6 \times 10^5\ \mu m^2/s$

The cytoplasm **is not a homogeneous solution**

Eukaryotic cell and its organelles

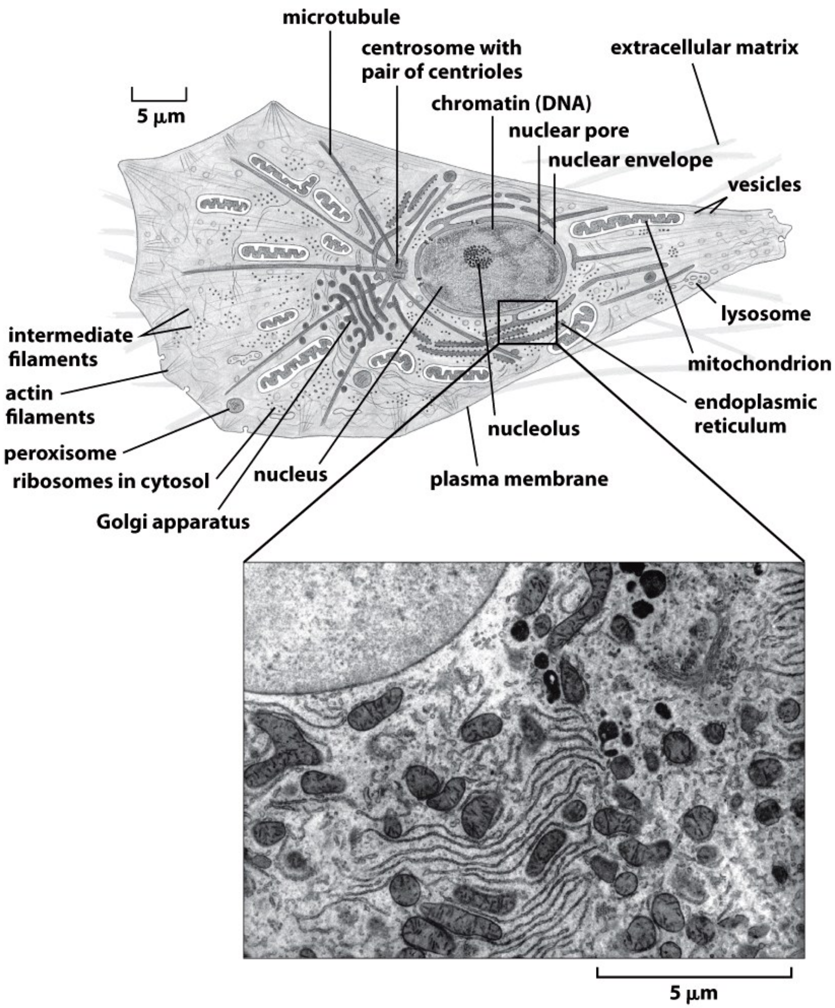
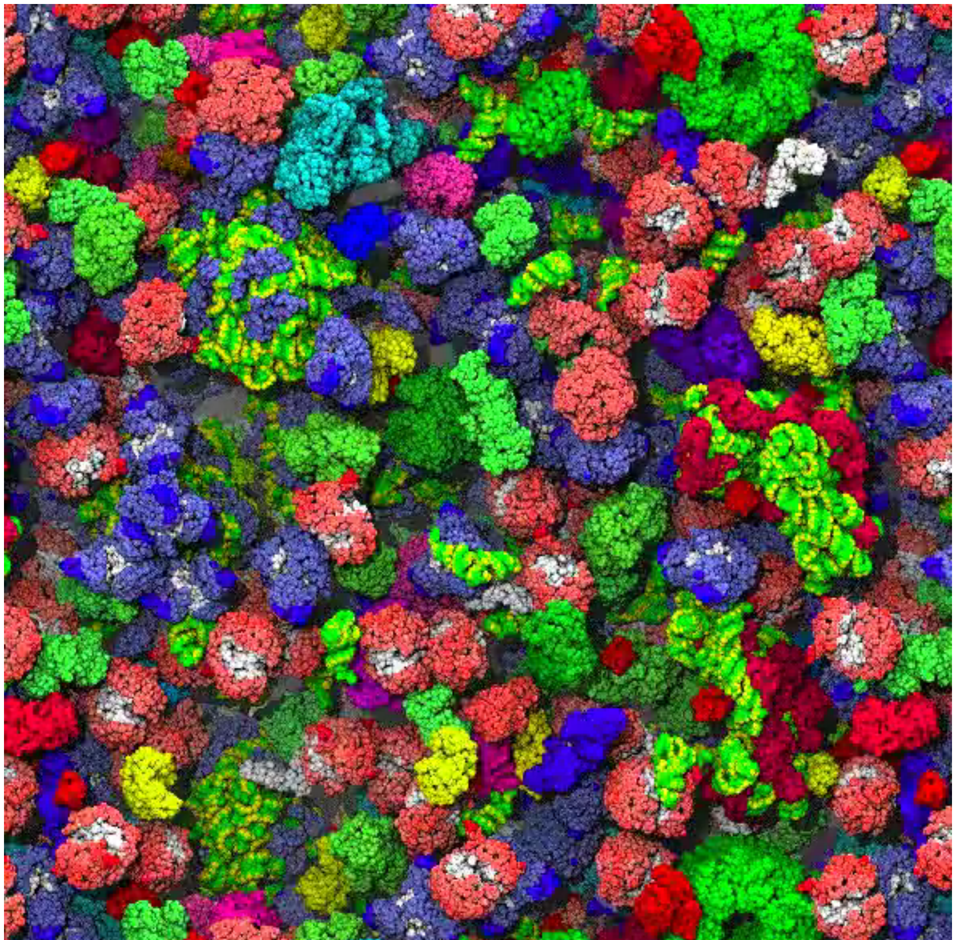


Figure 2.13 Physical Biology of the Cell (© Garland Science 2009)

The schematic shows a eukaryotic cell and a variety of membrane bound organelles. A thin-section electron microscopy image shows a portion of a rat liver cell approximately equivalent to the boxed area on the schematic. A portion of the nucleus can be seen in the upper left corner. The most prominent organelles visible in the image are mitochondria, lysosomes, the rough endoplasmic reticulum and the Golgi apparatus.
(adapted from Fawcett, 1966)

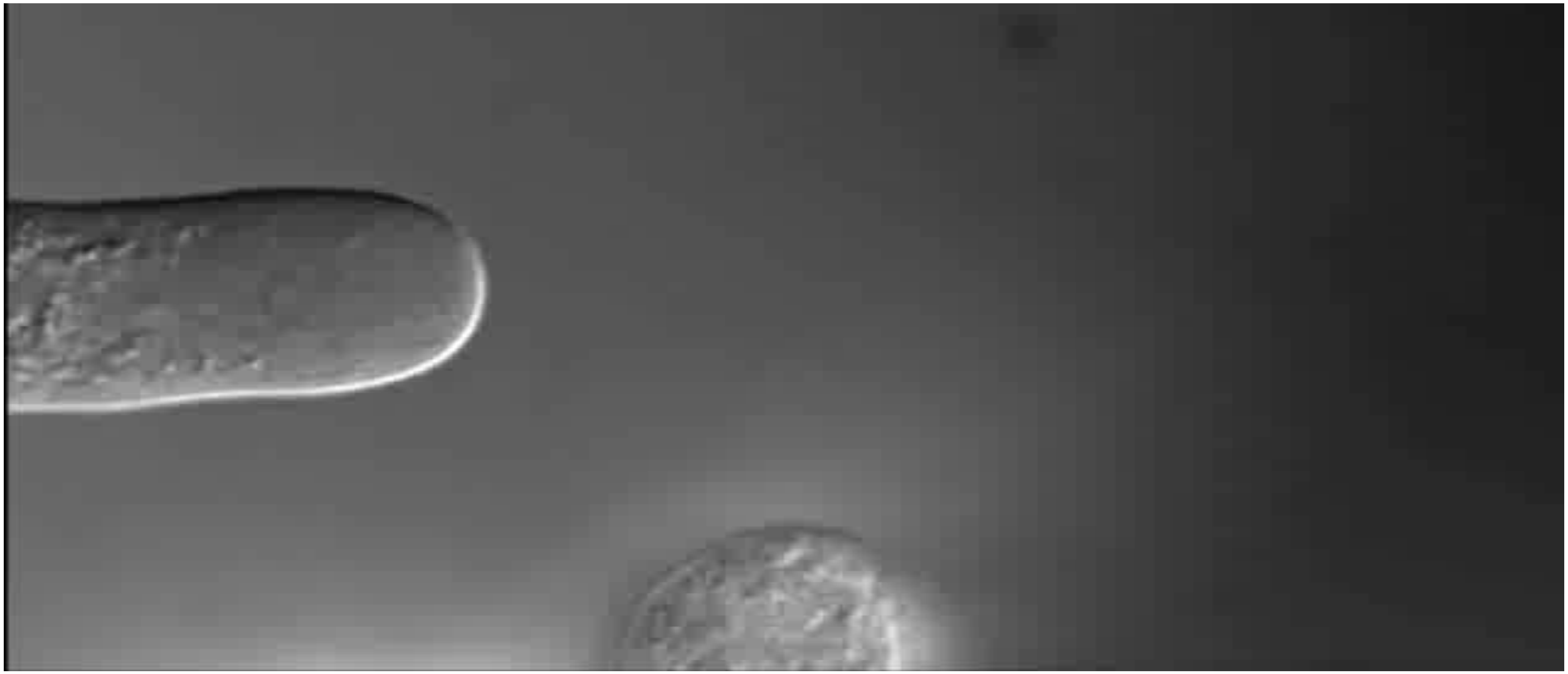
The cytoplasm is **crowded**

There are many physical barriers that restrict free particle movement (internal compartments, cytoskeleton, large proteins, organelles, etc)



This simulation shows a dynamic molecular model of the bacterial cytoplasm, giving us a spectacular glimpse of the crowded conditions of the interior of a cell over a brief 15 microsecond time span. The model includes 50 of the most abundant types of macromolecules reported in Escherichia coli, for a total concentration of 275g/L. This "full energy" simulation shows a model of macromolecular diffusion based on Brownian dynamics and intermolecular interactions including electrostatic and hydrophobic interactions.

Many molecules are **transported** by the cytoskeleton

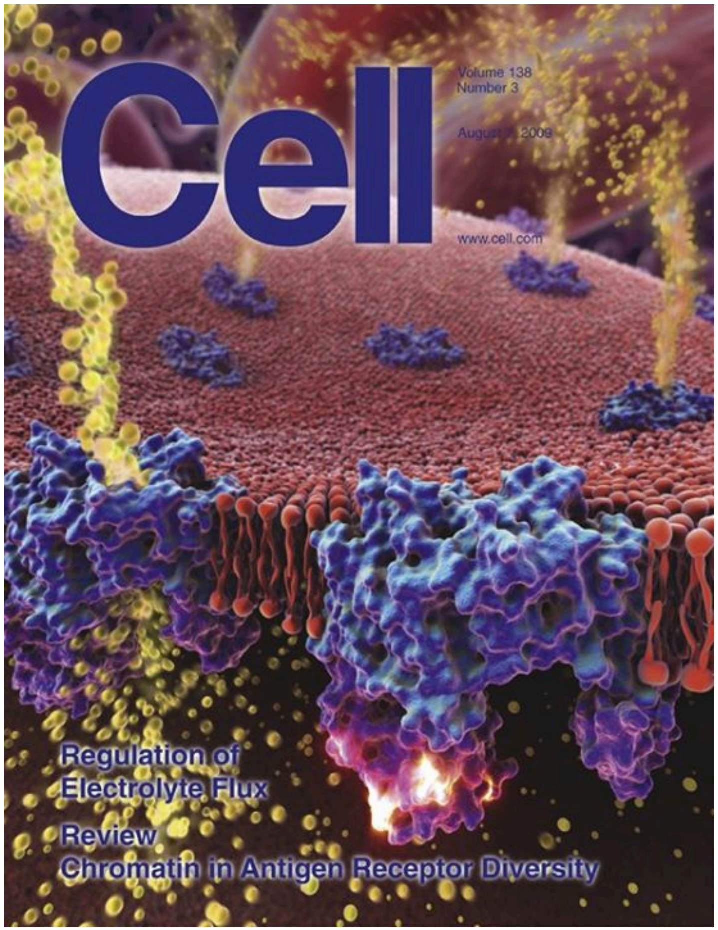


10 μm

Pollen tube growth in a germinating pollen grain (speed of growth can vary from μm/sec to μm/min, depending on the species)

Nuno Moreno, Plant Development Lab, IGC

Some ions and molecules are transported across membranes by **active transport**, against their concentration gradient



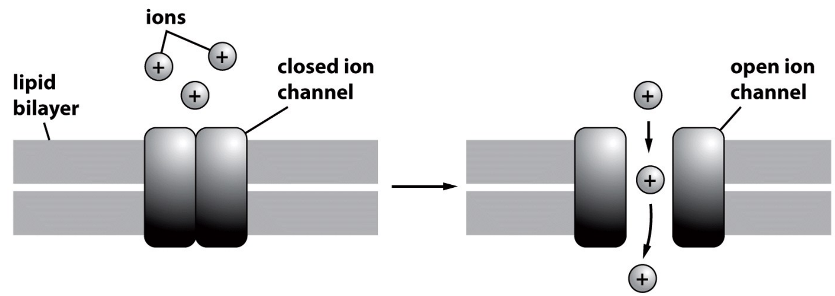


Figure 17.4 Physical Biology of the Cell (© Garland Science 2009)

K-Cl cotransporters (KCCs) control transmembrane electrolyte flux in a variety of physiologic settings, including the acute response to altered extracellular osmolarity. In this issue of Cell, Rinehart et al. (pp. 525–536) use targeted phosphoproteomics to reveal how phosphorylation at two conserved sites in KCCs controls their activity. The image depicts the activation of KCC3 in red blood cells in response to extracellular hypotonicity. KCC3 (blue) is shown embedded in the red blood cell membrane. Cotransporters that are phosphorylated at T991 and T1048 in the C terminus (highlighted in a white "flash") are inactive, while those that are dephosphorylated at these sites are active, allowing K-Cl efflux from the cell and preventing cell swelling due to influx of water. Image concept by E. Gulcicek, J. Rinehart, and R. Lifton. Design and artwork by Xvivo.

Dispersion of molecules can be equivalent to diffusion

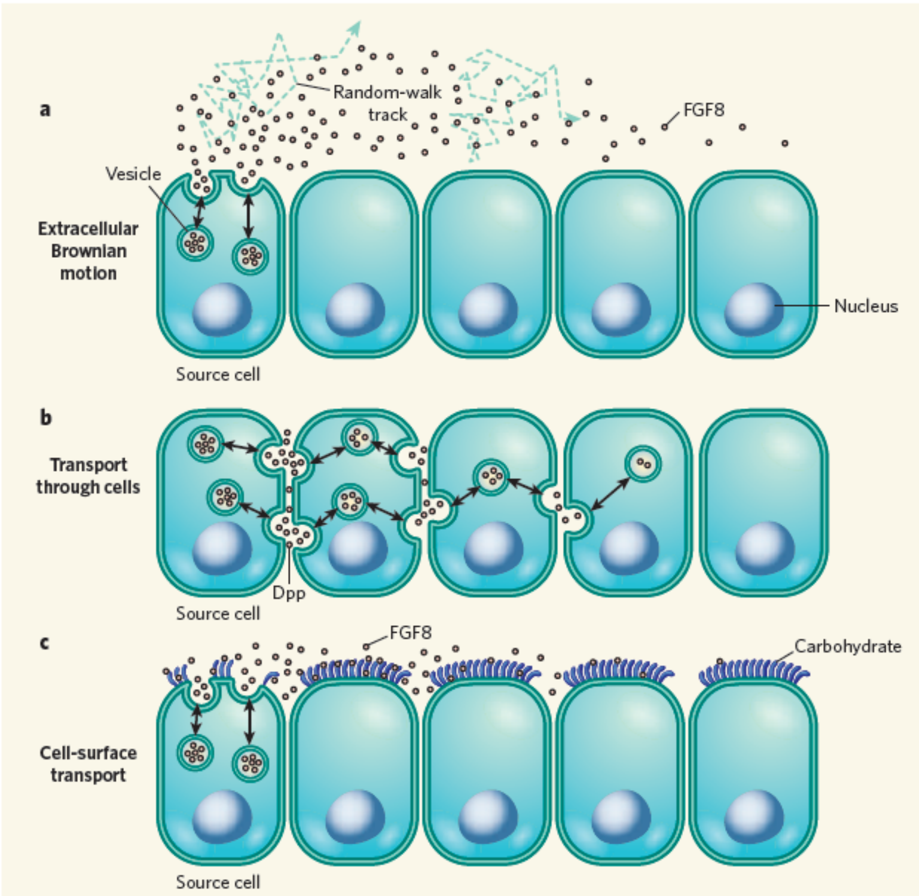


Figure 1 | Models of morphogen dispersal. Source cells harbour vesicles filled with morphogen molecules (red), which fuse with the cell membrane and release their contents. **a**, Yu *et al.*[2] propose that Brownian motion of molecules in the extracellular space leads to dispersal of the FGF8 morphogen. Two tracks of random walk by single FGF8 molecules are shown. **b**, Kicheva and colleagues[5] suggest that repeated release and uptake by cells (transcytosis) leads to dispersal of the morphogen Dpp in the fly wing. **c**, A few slowly diffusing FGF8 molecules are associated with carbohydrates at the cell surface[2]. This cell-surface pool may contribute to long-range dispersal of FGF8.

Several mechanisms can be reasonably approximated to diffusion, and described by the same type of equations.

Schier AF and Needleman D (2009). Rise of the source–sink model. Nature 461: 480-481

Yu SR et al.(2009) Nature 461:533–536

Sizes and numbers

Cells come in a wide variety of shapes and sizes and with a huge range of functions

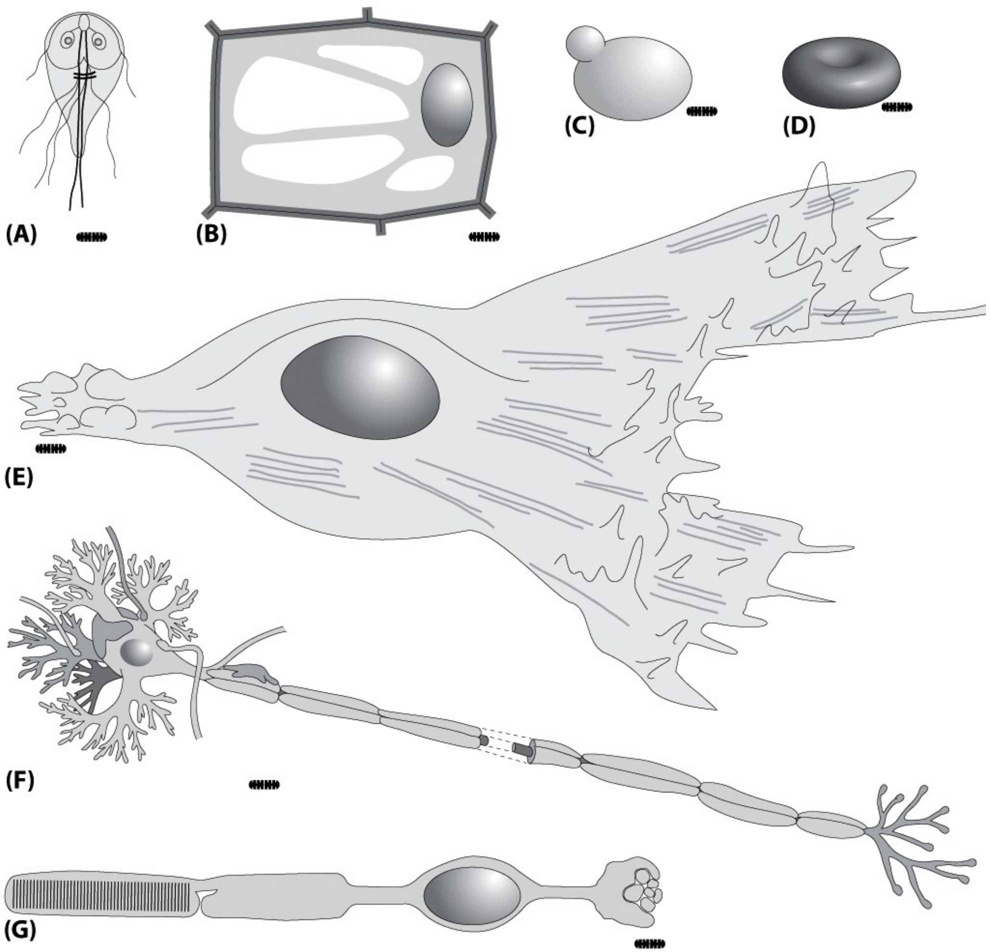


Figure 2.8 Physical Biology of the Cell (© Garland Science 2009)

Cartoons of several different types of cells all referenced to the standard *E. coli* ruler
(A) *Giardia lamblia* (protist)
(B) plant cell
(C) *Saccharomyces cerevisiae* (yeast cell)
(D) red blood cell
(E) fibroblast cell
(F) eukaryotic nerve cell
(G) rod cell

The bacterium *E. coli* as a standard ruler

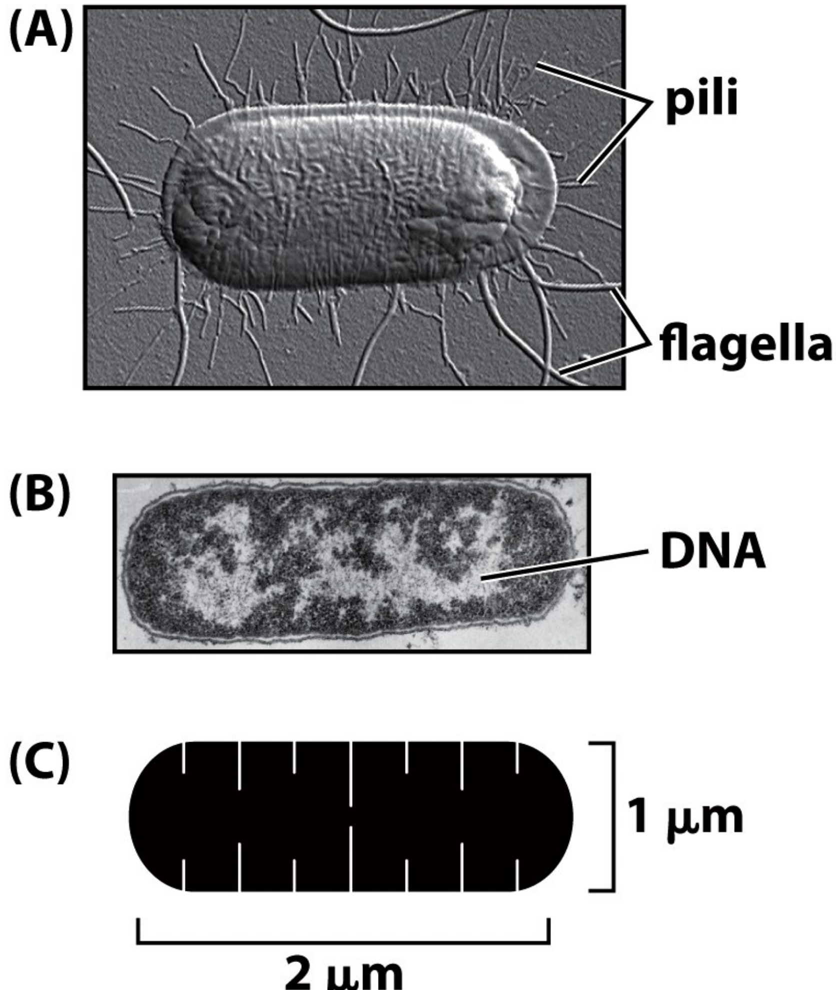


Figure 2.1 Physical Biology of the Cell (© Garland Science 2009)

E. coli as a standard ruler for characterizing spatial scales

Volume ≈ 1 µm3

Area ≈ 6 µm2

(A) Atomic force microscopy image of an *E. coli* cell (courtesy of C. T. Lim),

(B) Electron micrograph of *E. coli* bacterium,

(C) the *E. coli* ruler.

Molecular contents of the bacterium *E. coli*

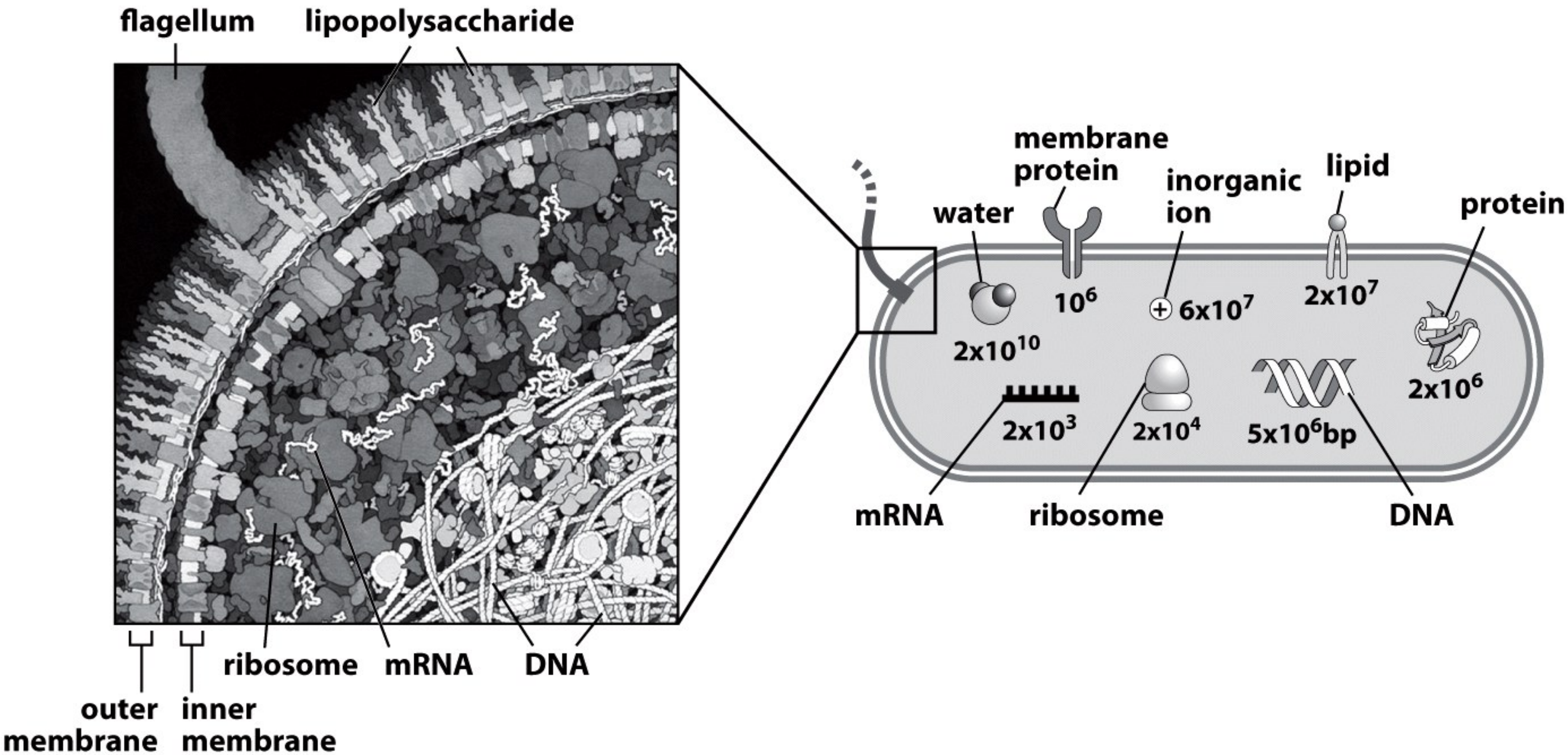


Figure 2.2 Physical Biology of the Cell (© Garland Science 2009)

The cartoon on the left shows the crowded cytoplasm of the bacterial cell.
The cartoon on the right shows an order-of-magnitude molecular census of the E. coli bacterium with the approximate number of different molecules in E. coli .

Molecular contents of the bacterium *E. coli*

Substance	% of total dry weight	Number of molecules
Macromolecule		
Protein	55.0	2.4×10^6
RNA	20.4	
23S RNA	10.6	19,000
16S RNA	5.5	19,000
5S RNA	0.4	19,000
Transfer RNA (4S)	2.9	200,000
Messenger RNA	0.8	1,400
Phospholipid	9.1	22×10^6
Lipopolysaccharide	3.4	1.2×10^6
DNA	3.1	2
Murein	2.5	1
Glycogen	2.5	4,360
Total macromolecules	**96.1**	
Small molecules		
Metabolites, building blocks, etc.	2.9	
Inorganic ions	1.0	
Total small molecules	**3.9**	

Table 2.1 Observed macromolecular census of an *E. coli* cell. (Data from F. C. Neidhardt et al., Physiology of the Bacterial Cell, Sunderland, Sinauer Associates Inc., 1990 and M. Schaechter et al., Microbe, Washington DC, ASM Press, 2006.)

Concentration in *E. coli* units

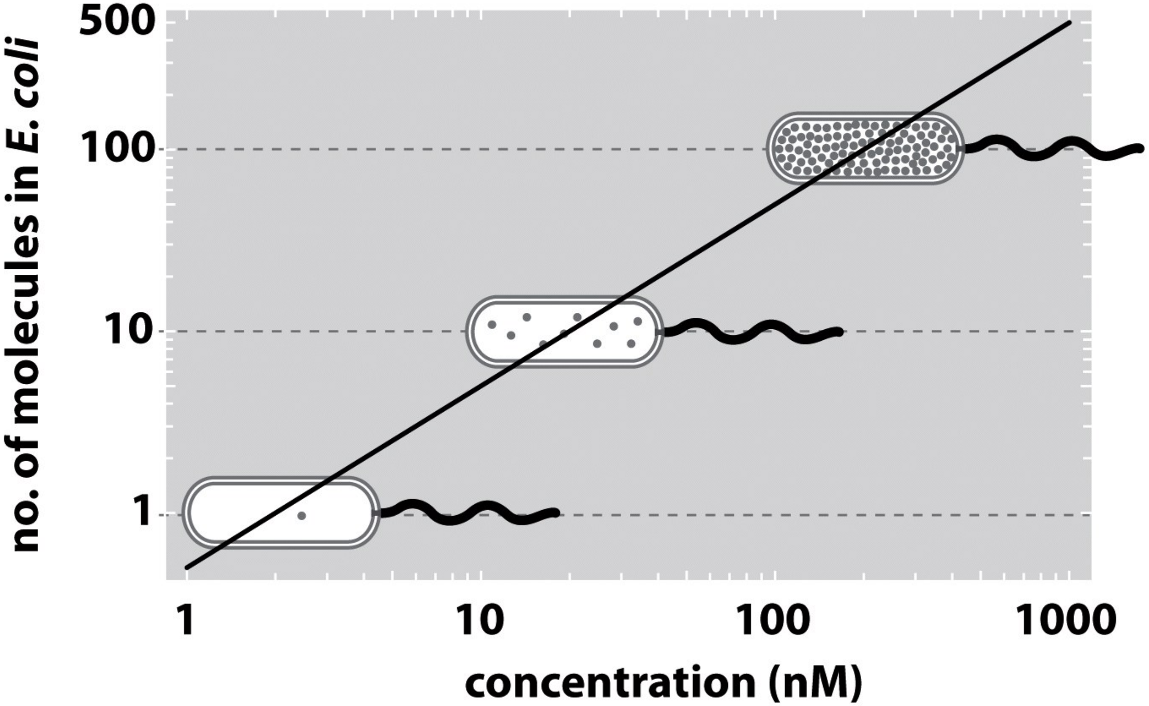


Figure 2.4a Physical Biology of the Cell (© Garland Science 2009)

Volume ≈ 1 μm3
Area ≈ 6 μm2

Number of copies of a given molecule in a volume the size of an E. coli cell as a function of the concentration

Powers of ten representation of biological length scales

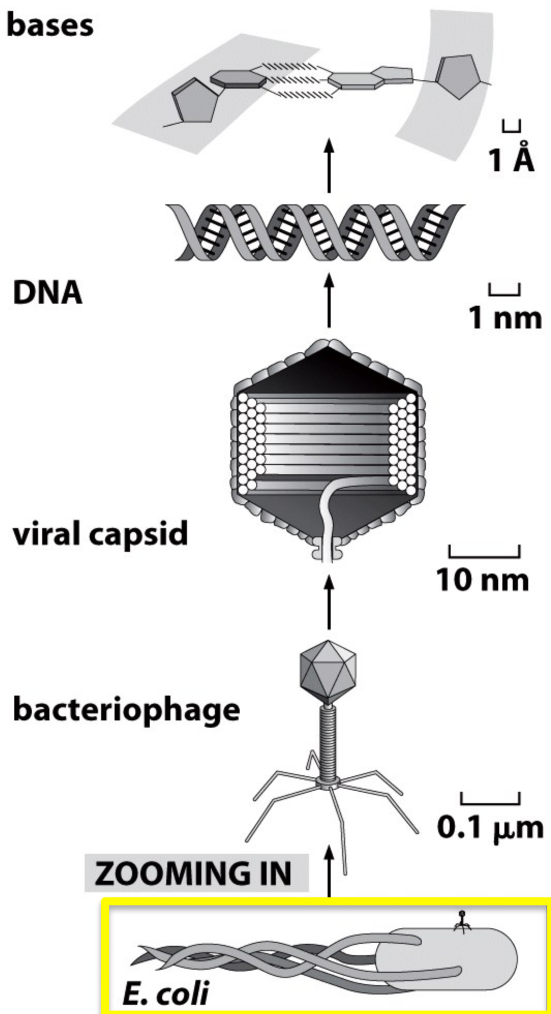


Figure 2.7 (part 1) Physical Biology of the Cell (© Garland Science 2009)

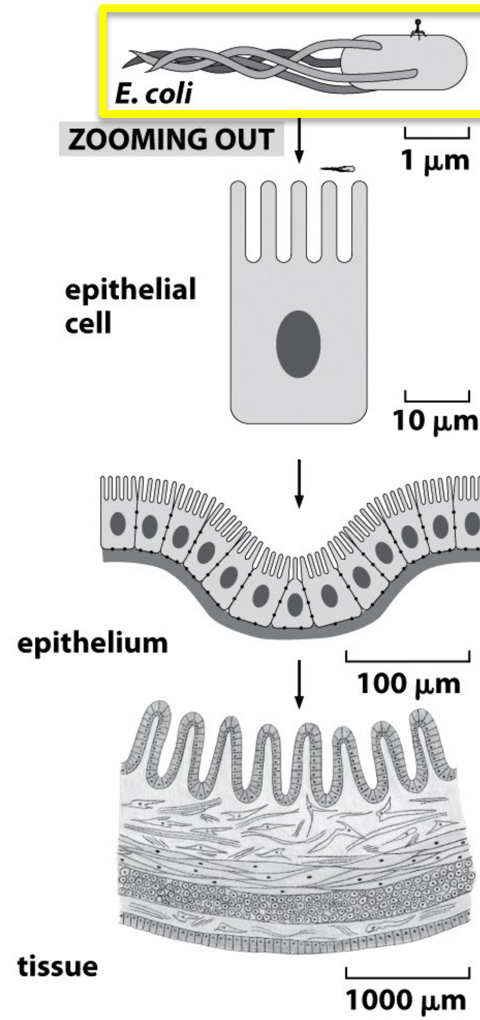


Figure 2.7 (part 2) Physical Biology of the Cell (© Garland Science 2009)