CELL MECHANICS

LECTURE 3

2. Physical principles

2.1. Forces at molecular and cell level

- Physical forces and their magnitudes at the single-molecule level
- Modeling complex mechanical devices as protein machines by using three elements: Spring, Dashpot, Mass; example: Mass, Stiffness and Damping of Proteins

2.2. Thermal forces, diffusion, and chemical forces

- Boltzmann Distribution Law and the Principle of Equipartition of Energy
- Diffusion equation - Einstein relation – Stokes law
- Autocorrelation function and Power Spectrum
- The effect of force on the equilibria and rate of chemical reactions
- Example of single molecule force spectroscopy experiments – unbinding, unfolding

Reference: Book_Howard_Ch_4

2.2. Thermal forces, diffusion, and chemical forces

In addition to mechanical forces, proteins and cells are subject to **thermal forces**, arising from collisions with water and other molecules in the surrounding fluid

Thermal forces → thermal energy → thermal / Brownian motion

The magnitude of thermal energy is in the range of the energies of chemical reactions driving biological processes, which are just a little bit higher than thermal energy → thermal fluctuations are necessary for proteins to reach their transition states

Molecular machines operate in diffusive environment, differently from macroscopic machines of our everyday world

Boltzmann Distribution Law

describes how the probability of a molecule having a certain energy depends on the surrounding temperature

Principle of Equipartition of Energy

states how much thermal energy a molecule has at a certain temperature

Boltzmann distribution Law:

if a particle (or a group of particles) is in **thermal equilibrium,** the **probability p_i** of finding the particle in the state **i** , characterized by **energy U_i** is:

$$p_i = \frac{1}{Z} exp\left[-\frac{U_i}{kT}\right]$$

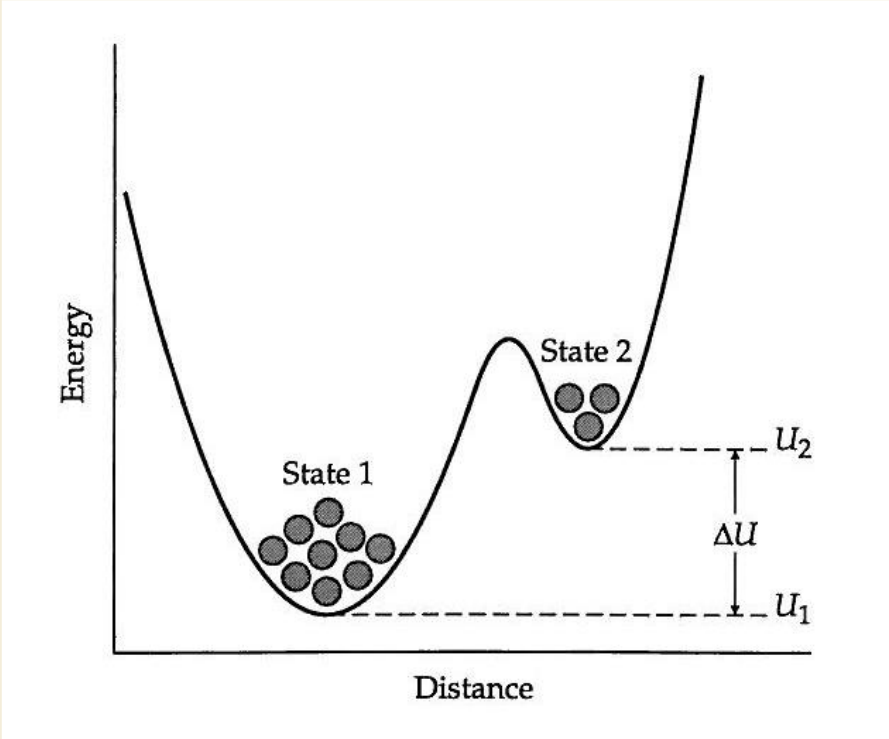
where:

$$Z = ct = \sum_i exp\left[-\frac{U_i}{kT}\right]$$

is the **partition function** to guarantee that $\sum p_i = 1$.

K is the Boltzmann constant, ***K*** = 1.381 x 10^{-23} [J K^{-1}]

T is the absolute temperature.



Boltzmann's Law *<= > Boltzmann's distribution, equation or formula*

For T= 298.15 K (Tc= 25 C) the energy KT = 4.116 x 10^{-21} [J] → ***1 KT ≈ 4.1 [pN nm]***

Thermal energy KT is a convenient energy unit for processes at molecular and cellular level

Comparison with other biologically relevant energies:

Energy values	Formula	Value (10^{-21} J)	
Thermal energy (25°C)	kT	4.1	= 1 ***KT***
Photon (green, $\lambda = 500$ nm)	$h\nu = hc/\lambda$	397	≈ 100 ***KT***
ATP hydrolysis in the cell	ΔG	100	≈ 25 ***KT***

Planck constant ***h= 6.6 x 10^{-34} [J s]***

Boltzmann's law is very general

The energy could correspond to the particle's potential energy (gravitational, elastic, or electrical) its kinetic energy, or energy associated with its phase, or electronic or chemical state.

The state of a particle (or group of particles) is specified by the position and velocity of the constituent atoms as well their electronic states.

Boltzmann's law is fundamental: we can use it to define **equilibrium** and **temperature:**

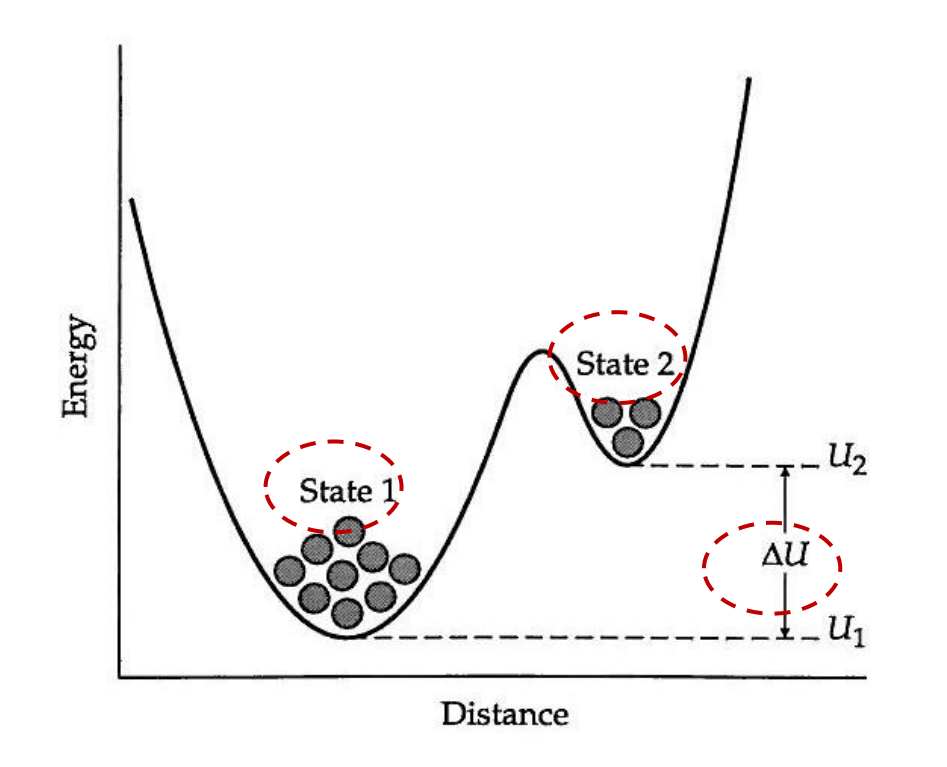
A system is at **equilibrium** if Boltzmann's law holds.

The **temperature** is defined as the corresponding constant in the exponent of the Boltzmann's law formula.

Boltzmann's law is a very important physical law in biology and chemistry.

Energy landscape

Molecules in a two-state energy landscape:



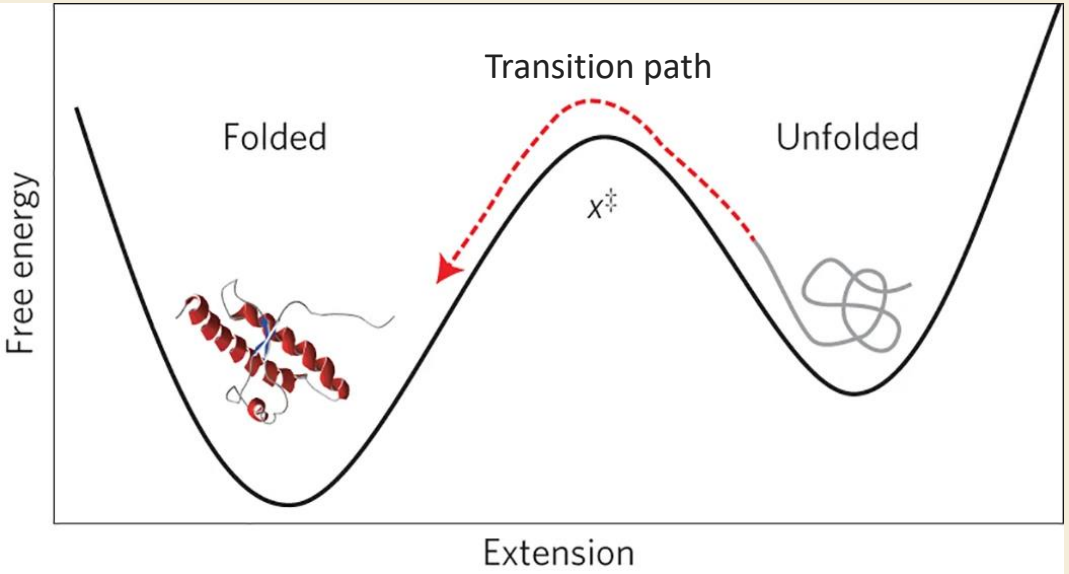
Considering the Boltzmann's equation, the probability of finding a molecule in state 2 relative to state 1 is:

$$\frac{p_2}{p_1} = exp\left[-\frac{\Delta U}{kT}\right]$$

Boltzmann distribution allows to calculate the probability of observing a system at finite temperature in any particular microstate.

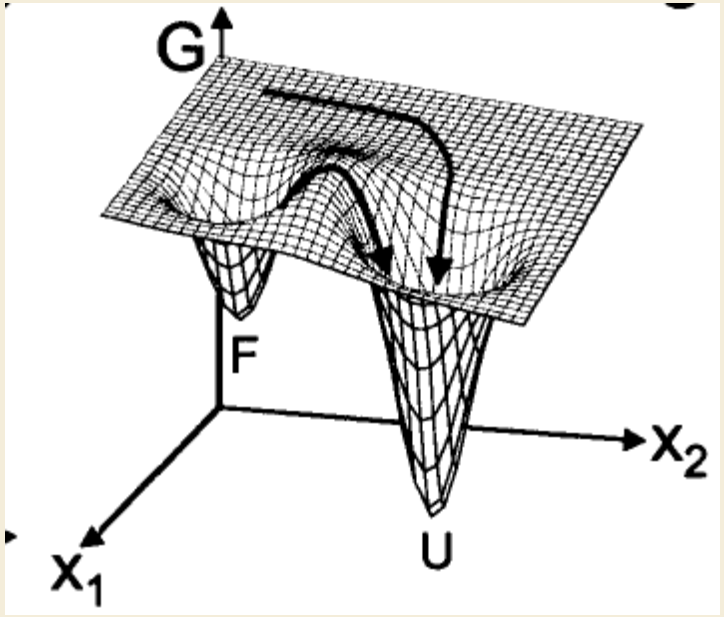
The probability only depends on the energy (free energy) of the state.

Protein unfolding – free energy landscape



A one-dimensional free energy diagram allowing for single unfolding pathway – transition path.

The extension x represents the unfolding reaction coordinates



A two-dimensional free energy diagram allowing for multiple unfolding pathways.

x1 and x2 represent generalized unfolding reaction coordinates.

$$p_i = \frac{1}{Z} exp\left[-\frac{U_i}{kT}\right]$$

1. Earth's athmosphere

Knowing that the density of molecules in a gravitational field falls exponentially with the height,
estimate the Earth's atmosphere scale height, SH.

SH **:** the height for which the density falls by 1/e (= 37%)
Consider the gravitational potential energy: U = mgh, of a particle of mass m, at a height h above the Earth's surface.
Molecular mass for an oxygen molecule MM=32 g/mol.
A: SH ~ 8 km

2. Settling of beads

Same problem, considering glass microspheres of diameter d= 200 nm, (mass density of glass: 2 g/cm^3)
A: SH ~ 100 µm

Homework

3. Analytic centrifugation

Measuring the mass m of a protein with the analytic centrifuge.

$U= (m-m_w)a_c h$ - potential energy;

$m-m_w$ – additional mass over that of the displaced solvent (water);

h – height above the bottom of the centrifuge tube; a_c – centrifuge acceleration.

One measures the height SH10 for which the density of protein falls by 1/e^{10} (exp term vanishes)

→ $U_0 \approx 10\ kT$ → $m = m_w + 10\ kT/(a_c\ SH)$

Exp values: ac ~ 10^3 g ; SH10 ~ 10 mm → **m= ?**

4. Nernst equation

Considering a set of molecules with charge *q* that are free to equilibrate between two compartments at electrical potential 0 and V volts,

Find the ratio of the concentration of molecules in the two compartments.

A:

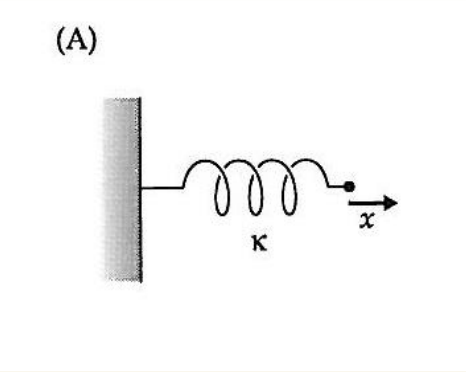
$$\frac{C_V}{C_0} = \frac{p_V}{p_0} = exp\left[-\frac{U}{kT}\right] = exp\left[-\frac{qV}{kT}\right]$$

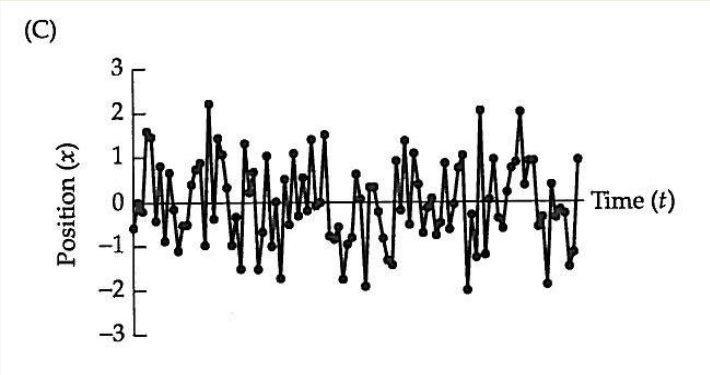
q= 1.6 x 10^{-19} C

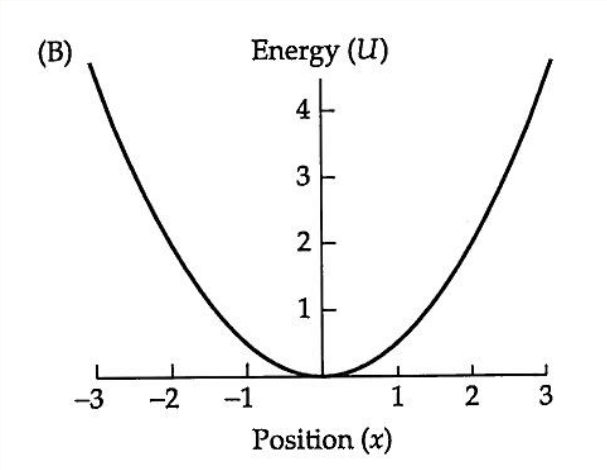
At room temperature K= 300 K, kT/q = 25.6 mV

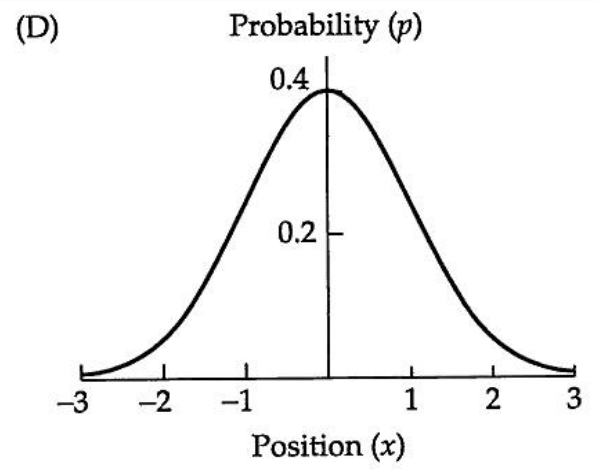
- -> for each 25.6 mV increase in voltage, the concentration of monovalent cations decreases *e*-fold.

Boltzmann's law allows to calculate the average **thermal energy of a molecule** (or system of molecules).









Example

Suppose a molecule is at equilibrium in an **energy landscape *U(x)***, that varies with position ***x***, but not with time; e.g. the molecule could be connected to a spring with potential energy:

$$U(x) = \tfrac{1}{2} k x^2$$

Due to thermal agitation, the molecule is constantly changing position.

Aim:

Calculate the statistical properties of the molecule's position:

mean, mean squared, variance

The statistical properties of the molecule's position, such as its mean or its variance can be calculated in two ways:

1. Follow the molecule over a long period of time T, and measure its time-averaged **mean** position or **mean-squared** position :

mean $\langle x \rangle_T \equiv \frac{1}{T}\int_0^T x(t)\cdot dx$ **mean-squared** $\langle x^2 \rangle_T \equiv \frac{1}{T}\int_0^T x^2(t)\cdot dx$ **variance** $\sigma_x^2 = \langle (x - \langle x \rangle)^2 \rangle = \langle x^2 \rangle - \langle x \rangle^2$

2. Use the Boltzmann's law to calculate **the probability p(x)** of finding the molecule at **position x** and then calculate the expected **values E(x)** of the position or position squared according to:

$$E(x) \equiv \int_{-\infty}^{\infty} xp(x)\cdot dx \qquad E(x^2) \equiv \int_{-\infty}^{\infty} x^2 p(x)\cdot dx$$

If we measure for a long enough time, then the estimates of the average position should agree:

$$\langle x \rangle \equiv \langle x \rangle_\infty = E(x) \qquad \langle x^2 \rangle \equiv \langle x^2 \rangle_\infty = E(x^2)$$

In this way we can **relate measurements** (time averages) **to** the **expectations**, based on Boltzmann's law.

The Equation above is the link between experiments and theory!

It holds generally for any function of x : E[f(x)]=<f(x)>. In particular it holds for the variance of x, σ_x^2.

This approach can be used to calculate the average energy of a molecule.

For instance, for the molecule attached to a spring, the average energy is:

$$\langle U \rangle = \tfrac{1}{2}\kappa\langle x^2 \rangle = \tfrac{1}{2}\kappa \int_{-\infty}^{\infty} x^2 p(x) \cdot dx = \tfrac{1}{2} kT$$

(appendix 4.1. Book Howard)

using Boltzmann's law for p(x):

$$p(x) = \frac{1}{Z} exp\left[-\frac{U(x)}{kT}\right]$$

The result above is remarkable because the average energy <U> does not depend on the stiffness of the spring !

It only depends on the temperature *T* !

This is a special case of a general theorem known as **the Principle of Equipartition of Energy** which states that **if the energy of a molecule depends on the square of a parameter** such as position or speed,

then the mean energy associated with the degree of fredom measured by the parameter is:

$$\boldsymbol{\langle U \rangle = \frac{1}{2} KT}$$

Another example of the principle is **that the average kinetic energy** of a molecule (in one direction) with mass m is:

$$K.E. = \frac{1}{2}m\langle v^2 \rangle = \frac{1}{2}KT$$

If there are more degrees of freedom, that are independent, then each degree of freedom contains ½ KT of energy.

E.g. : the velocities of a molecule in x, y, z directions are independent for 3 degrees of freedom.

Thus, the **total kinetic energy** is: **3/2 kT**.

The **root mean-square speed, v_{rms},** of a molecule in three dimensions is therefore:

$$v_{rms} = \sqrt{\langle v^2 \rangle} = \sqrt{\frac{3KT}{m}}$$

Examples of v_{rms} at 25 C , for:

- Water molecule, v_{rms}= 640 m/s
- Protein, 100 kDa, v_{rms}= 8.6 m/s
- Bacterium of volume 1 μm^3= 3.5 mm/s

The Principle of Equipartition of Energy is generally true only if the energy dependence is quadratric.

If, for instance, U(x) ~ x → <U> = KT (and not 1/2 KT)

It breaks down also if *KT* is small compared to energy levels between different quantum states.

For proteins at room temperature thermal energy is large compared to the vibrational energy levels because proteins are relatively soft materials

(appendix 4.1 for details)

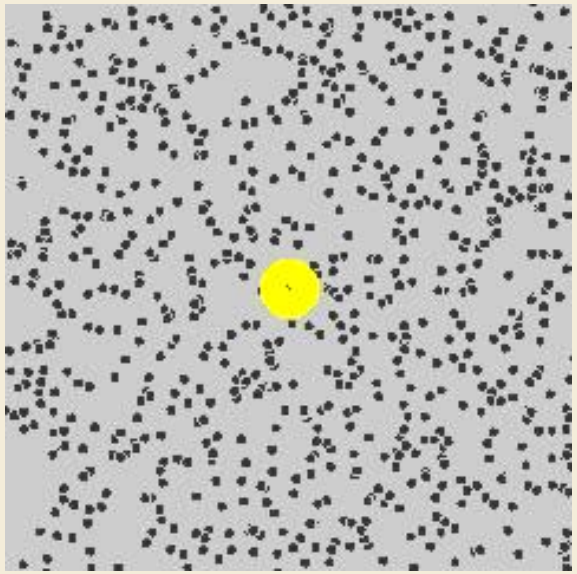
Thermal energy KT ~ 4 x 10^{-21} J while vibrational energy hfrequency h ν ~ 6.6 x 10^{-22} J (ν ~10^{12} Hz , h ~ 6.6 10^{-34} m^2kg/s)

→ **hν << KT**

→ **the principle of equipartition of energy applies to elastic deformation of proteins**

Molecular collisions cause **Brownian motion** and **diffusion**.

These are forms of random motion that are characterized by frequent, abrupt changes in direction.



In **Brownian motion**, a particle **does not have a specific direction** to travel. Therefore, it will move in all directions.

In **diffusion** the particles will travel from a high concentration to a low concentration. Therefore, **they have a direction**.

However, the particle movement is random in both scenarios.

Diffusion plays a crucial role in many physical and chemical processes at microscopic scales.

- Einstein – Nobel prize award for 'elucidating the molecular mechanism of Brownian motion'.
- Perin and Svedberg – Nobel prize – measurements of the diffusion of micron-sized particles, confirmed Einstein's theory and allowed the measurement of Boltzmann's constant K and the determination of the Avogadro number N_A.
- Brownian motion confirmed the atomic theory of gases and liquids and bridged the gap between visible objects and invisible molecules.

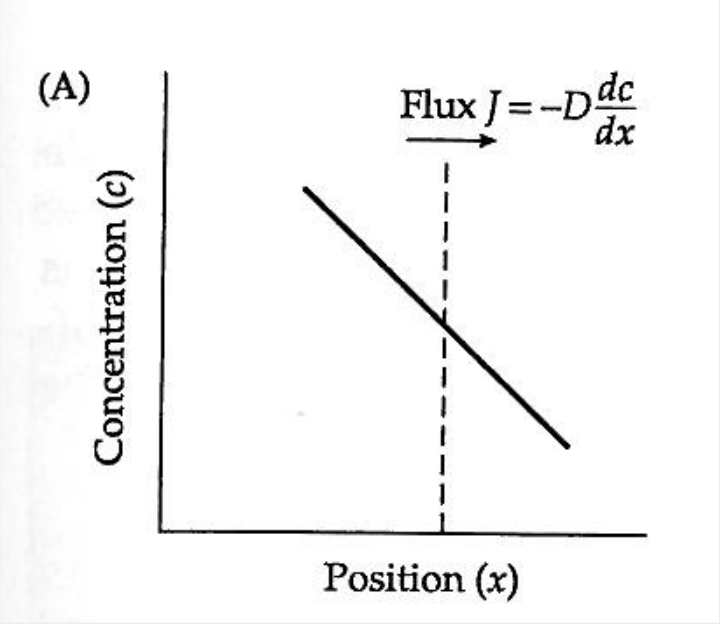
In the presence of **a concentration gradient**, the molecules moving in random directions tend to move, in average, **from areas of high concentration to areas of low concentration**.

The prediction, confirmed experimentally, is that the **concentration flux *J(x)***, which is the rate of movement of molecules per unit area, **is proportional to the concentration gradient *dc/dx***:

$$J(x) = -D\frac{dc(x)}{dx}$$

Fick's law

***D* – diffusion coefficient**



To derive the diffusion equation we need to **relate the flux** back **to the concentration**.

The change in concentration over time at any point **equals** the negative of **the flux gradient** at that point**:**

$$\frac{\partial c(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial t}$$

If the system is in steady – state (***dc/dt=0***), then the concentration flux is the same everywhere in the solution (***dJ/dx=0***). Conversely, if the flux does not change from one position to another, then the concentration does not change with time.

Substituting equation above into Fick's law one gets:

$$J(x) = -D\,\frac{dc(x)}{dx}$$

$$\frac{\partial c(x,t)}{\partial t} = D\,\frac{\partial^2 c(x,t)}{\partial x^2}$$ **Diffusion equation**

Usually, we are thinking about single molecules and we want to know the probability ***p(x,t)*** of finding a molecule at position *x* at time *t,* rather than the concentration ***c(x,t)*** of a large number of molecules.
Because **the probability is proportional to the concentration** (it is the concentration divided by the total number of molecules) and because **differentiation is a linear operator**, it follows that also the **probability *p (x,t)* satisfies the diffusion equation**.

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p(x,t)}{\partial x^2}$$

Boltzmann's law allows to derive an expression that relates the diffusion coefficient to the drag coefficient
(Einstein relation)

Suppose that an external force, ***F(x)***, acts on a diffusing molecule. The force will cause the molecule to move with a *velocity* ***v(x)= F(x) / γ .***This 'drift' velocity is an average speed superimposed on the diffusive motion. The external force increases the flux by ***v(x) c (x,t)*** or by ***v(x) p(x,t),*** if we are thinking of the **probability flux, *j(x)***:

$$J(x) = -D\frac{dc(x)}{dx} \quad \Rightarrow \quad j(x) = -D\frac{dp(x)}{dx} + \frac{F(x)}{\gamma}p(x)$$

Thus, in the presence of a force, the probability satisfies the equation (derived from diffusion equation):

$$\frac{\partial p}{\partial t}(x,t) = D\frac{\partial^2 p}{\partial x^2}(x,t) - \frac{\partial}{\partial x}\left[\frac{F(x)}{\gamma}p(x,t)\right]$$

This equation is known as the **forward diffusion equation** or the **Fokker-Planck equation** and describes diffusion with drift.

If the system is in equilibrium, the probability does not change with time and the **F-P equation** can be resolved in ***p(x)***. (See Appendix 4.2)

Comparing the solution to the Boltzmann's law, it is found that the flux must be equal to zero everywhere, and that the diffusion coefficient is related to the drag coefficient by:

$$D = \frac{KT}{\gamma}$$ **Einstein relation**

Einstein relation relates the diffusion coefficient of a molecule to its drag coefficient

$$D = \frac{KT}{6\pi\eta r}$$

Einstein relation allows to estimate the **diffusion coefficient** from the **size** of the particle and the **viscosity** of the solution.

Conversely, knowledge of the viscosity and the diffusion coefficient permits an estimate of the size of the particle.

Example: Diffusion of ions. Consider sodium ion Na+ in water.

The diffusion coefficient for an ion at room temperature (25 C) is D= 1.33 x 10^{-9} m^2/s.

From the Einstein relation it results an apparent radius r= 1.8 Å , which is about two times the ionic radius of 0.95 Å measured in crystals.

A useful rule of thumb is that a diffusion coefficient D= 10^{-9} m^2/s corresponds to 1$\mu m^2/ms$,
so a small ion diffuses about 1 µm in 1 ms.

Note:

We considered that there is no chance of the molecule being destroyed. If polymerization of cytoskeletal filaments and movement of motor proteins are considered, this condition is relaxed, allowing chemical reactions to convert one type of molecule into another, or to destroy or create molecules.

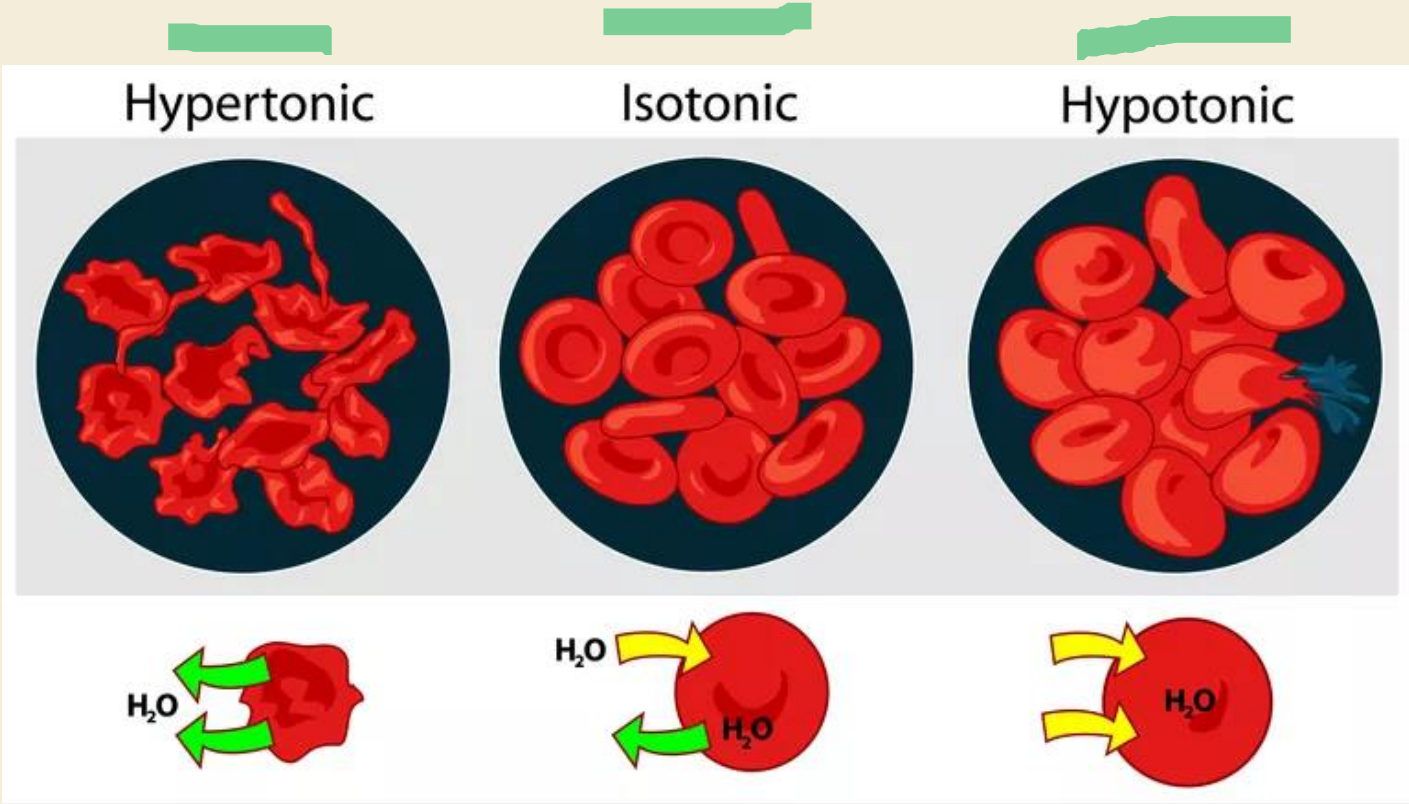
When these reactions also depend on position, the motion becomes very rich and is described by the reaction-diffusion equation:

$$\frac{\partial p_i}{\partial t}(x,t) = D\frac{\partial^2 p_i}{\partial x^2}(x,t) - \frac{\partial}{\partial x}\left[\frac{F(x)}{\gamma}p_i(x,t)\right] + \sum_j \left[k_{ji}(x)\cdot p_j(x,t) - k_{ij}(x)\cdot p_i(x,t)\right]$$

where *pi*, *pj*, are the probabilities of the molecule being in various chemical states, *kij* is the rate constant for the transitions between the *i* and *j* states.

Diffusion is the movement of **particles** from an area of higher concentration to lower concentration. The overall effect is to equalize concentration throughout the medium.

Osmosis is the movement of solvent particles across a semipermeable membrane from a dilute solution into a concentrated solution. The **solvent** moves to dilute the concentrated solution and equalize the concentration on both sides of the membrane.



The utility of the diffusion equation is that it allows one to calculate how quickly, on average, it takes for a molecule to diffuse through a certain distance.

This information can be used to evaluate **the efficiency of diffusion as a transport process within cells.**

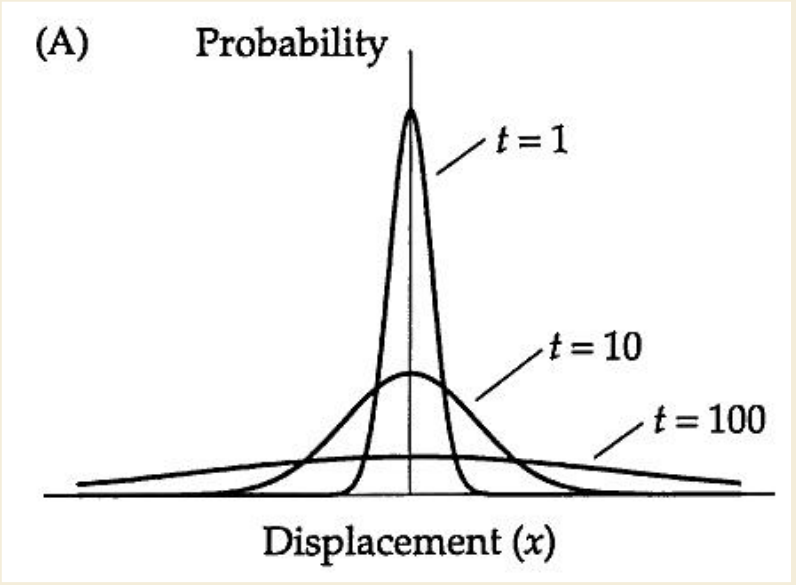
Furthermore, with the aid of the Fokker-Planck equation, we can calculate the time that it takes for a molecule to diffuse against an applied force. One can then gain insight into how forces affect chemical rates.

Solutions of the diffusion equation for some particular cases that are relevant to cellular and molecular mechanics.

The diffusion from a point source

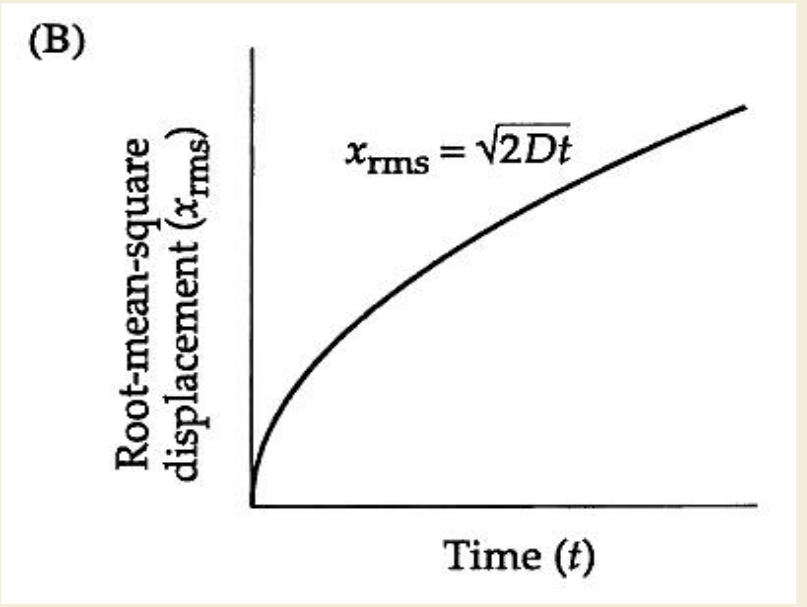
If a molecule is released at the origin and allowed to diffuse in one dimension, then the probability of finding it at position x at time t is:

$$p(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-\frac{x^2}{4Dt}\right] \qquad t>0$$



Q: how far, on average, does a molecule diffuse in a given time ?

root-mean-square displacement: $x_{rms} = \sqrt{2Dt}$



Another, relevant, question is: how long on average, does it take a molecule to diffuse through a given distance ?

first-passage time: $t = \frac{x_0^2}{2D}$

First passage time is relevant because it allows to calculate the rate of a process that is limited by diffusion.

The **diffusion-limited rate**, k_{dl} is the reciprocal of the **first-passage time, t:** $k_{dl} = 1/t$.

In the **absence of an external force**, the first-passage time for one-dimensional diffusion through a distance x_0 is:

$$t = \frac{x_0^2}{2D} \longleftrightarrow x_{rms} = \sqrt{2Dt}$$

The first-passage time can be calculated by solving the diffusion equation for the particular geometry of the problem.

Case study: Evaluate if diffusion might be a feasible mechanism to transport molecules and organelles in the cell.

Let us consider a globular protein, a potassium ion K+ , and an organelle (mitochondrion).
How long it takes for these three particles to propagate different distances in the cell ? Size of cell: max 100 µm.

$$t = \frac{x_0^2}{2D} \qquad D = \frac{KT}{6\pi\eta r}$$

	Distance diffused			
Object (particle)	**1 µm**	**100 µm**	**10 mm**	**1 m**
Protein (r = 3nm, D ~ 100 µm²/s)	5 ms	~ 1 min	6 days	150 years
K+ (r ~ 0.1 nm, D ~ 2000 µm²/s)	0.25 ms	2.5 ms	7 hrs	8 years
Organelle (r ~ 500 nm, D ~ 0.5 µm²/s)	1 s	3 hrs	3 years	30 millenia

Size of a cell: 100 µm

Protein and ion diffusion are efficient, the organelle diffusion is very slow.

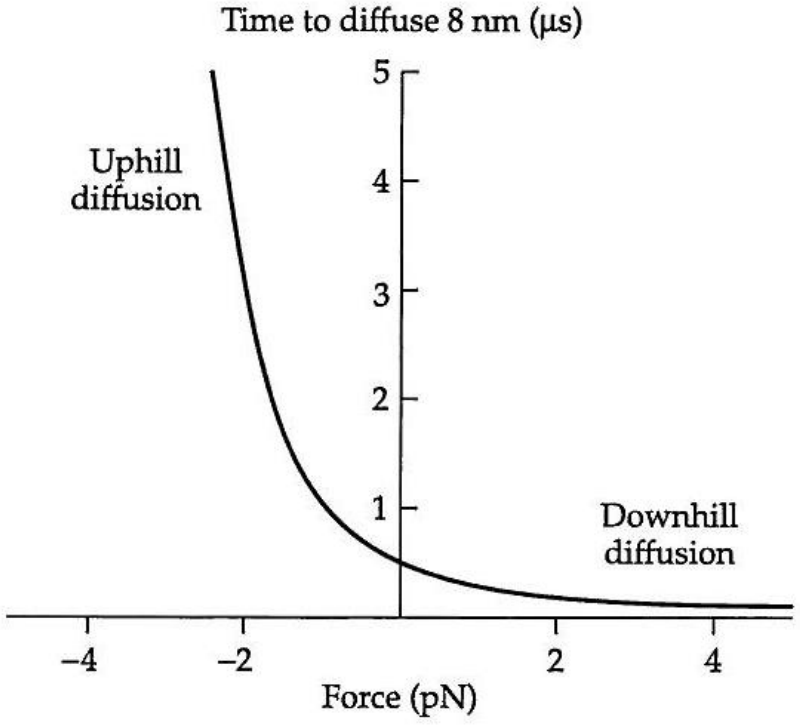
Actually, the organelle diffusion is even slower, because the cytoplasm is like a gel with mesh size of about 50 nm. Organelles larger than 50 nm are almost immobile.

Motor proteins are required to move organelles from one place to another.

On the other side, the low mobility of the organelles is benefic: large organelles stay where they are, and the internal structure of the cell will be reasonable stable.

More interesting from a biological point of view is when **diffusion is considered in the presence of an external force**. e.g. how long does it take for a molecule to diffuse over an energy barrier at $x = x_0$?

When the force is constant, the potential energy is $U(x) = -Fx$, and the **first-passage time**:



Time for a 100 kDa protein to diffuse 8 nm in presence of a constant force.

$$t = 2\left(\frac{x_0^2}{2D}\right)\left(\frac{kT}{Fx_0}\right)^2\left\{\exp\left(-\frac{Fx_0}{kT}\right) - 1 + \frac{Fx_0}{kT}\right\}$$

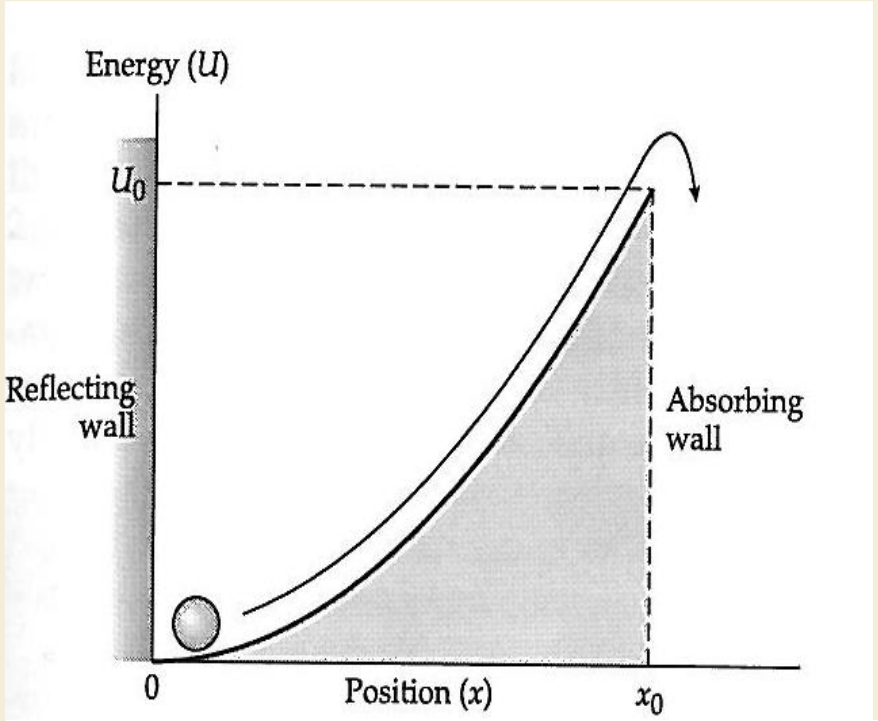
Uphill: against an opposing force the first-passage time t is long (and the corresponding diffusion-limited rate is small)

Downhill: in direction of the force, t is short.

The external force : *F= -k x* .

How long does it take for a molecule to diffuse over an energy barrier at ***x= x_0***?

When the force opposes the motion: ***F= -k x ,*** the potential energy is ***U(x)=- k x^2***, and the **first-passage time**:



Diffusion of a molecule out of a hemiparabolic energy well

$$t_K = \tau \sqrt{\frac{\pi}{4}} \sqrt{\frac{kT}{U_0}} \exp\left(\frac{U_0}{kT}\right)$$

t_K – Kramers time – basis of the Kramers rate theory, postulating that the rate of reactions is limited by diffusion over a high – energy transition rate.

τ= *γ/k* - time constant.

Assumption: The energy barrier is high: $U_0 = U(x_0) = 1/2\ k x_0^2 >> KT$.

Equation derived in Appendix 4.2.

So far, we have not needed details on the thermal forces that drive Brownian motion and diffusion.

We just needed to assume that the thermal forces were randomly directed to derive the diffusion equation: $\frac{\partial c(x,t)}{\partial t} = D\frac{\partial^2 c(x,t)}{\partial x^2}$

and relate the diffusion coefficient to the drag coefficient: $D = \frac{KT}{\gamma}$

The probability p(x,t) (to find the particle at position x, at time t), in presence of force F, satisfies the equation: (derived from diffusion equation):

$$\frac{\partial p}{\partial t}(x,t) = D\frac{\partial^2 p}{\partial x^2}(x,t) - \frac{\partial}{\partial x}\left[\frac{F(x)}{\gamma}p(x,t)\right]$$

Known as the **forward diffusion equation** or the **Fokker-Planck equation** and describes diffusion with drift.

If the system is in equilibrium, the **probability does not change with time** and the **F-P equation** can be resolved in ***p(x)***. (See Appendix 4.2) The solution has a similar form with Boltzmann's law, implying by comparison that the flux must be equal to zero everywhere, and that the diffusion coefficient is related to the drag coefficient by:

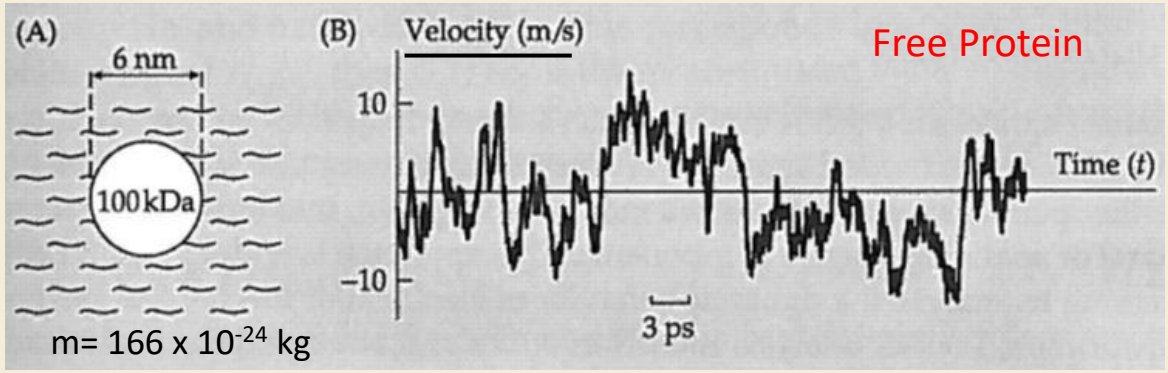
$$D = \frac{KT}{\gamma}$$ **Einstein relation**

Einstein relation relates the diffusion coefficient of a molecule to its drag coefficient

However, there are several **“microscopic” details of diffusive motion** that are important to answer questions as:

1. How long, on average, will a free molecule keep moving in one direction before thermal forces randomize its direction of motion ? i.e. which is the **persistence length** (or **correlation time**) of the velocity ?
2. How long, on average, will it take for a molecule in a potential to explore the different energy levels ?
   In particular, how long will the molecule spend at each energy level ? i.e. what is **the persistence time of the position** ?
3. What are the **amplitudes** and **statistical properties** of the thermal forces ?

Diffusion of a free protein vs diffusion of a tethered protein



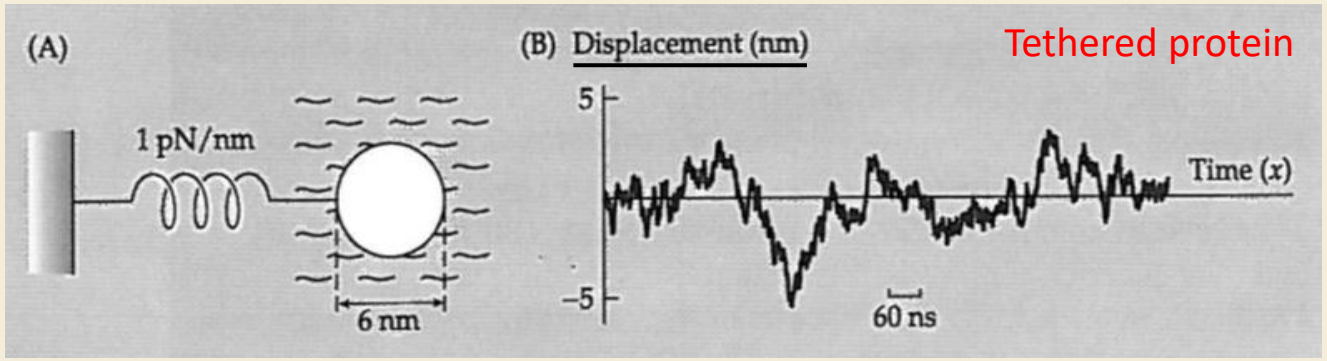
The root-mean-square velocity: $v_{rms} = \sqrt{\frac{3KT}{m}} \approx 8.6 \frac{m}{s}$;

The time constant $\tau_i = \frac{m}{\gamma} \approx 3\ ps$ (with $\gamma \cong 60\ pN \cdot s/m$)

is the **correlation time of the velocity**.

The corresponding **persistence length**: $l = v \cdot \tau = 0.24\ A$!

Even if the speed of molecule is large, the high damping it experiences in water opposes to inertia and after just a fraction of an Anstrom it changes direction.



Protein attached to a spring of stiffness *k= 1pN/nm*

The root-mean-square displacement (using Th Equipartition Energy)

$$x_{rms} = \sqrt{\langle x^2 \rangle} = \sqrt{\frac{KT}{k}} \approx 2\ nm\ ;$$

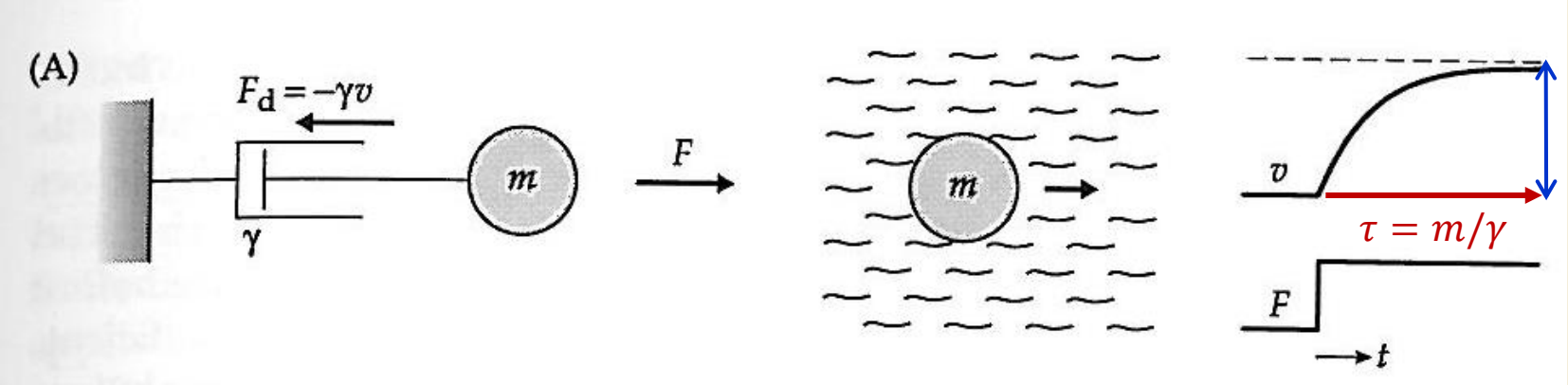
The time constant $\tau_p = \frac{\gamma}{k} \approx 60\ ns = \tau_i \cdot 2 \cdot 10^4$

This is the **correlation time of the protein's position**,
i.e. the time it takes to the protein to relax to a new position.

For times t< τ, the protein is quite near the same position; when t>>τ, the protein's position is uncorrelated and the probability of finding the protein in a certain position depends only on its potential energy and not on time.

RECONSIDERING the Motion of Combinations of Mechanical Elements in presence of thermal forces

A) DASHPOT and MASS. Model for the movement of a protein through a liquid



Eq of motion

$$m\frac{dv}{dt} + \gamma v = F$$

Solution (velocity)

$$v(t) = \frac{F}{\gamma}\left[1 - \exp\left(-\frac{t}{\tau}\right)\right]$$

Time constant

$$\tau = \frac{m}{\gamma}$$

10^{-12} s range

We considered **F= ct > 0**

We did not consider the thermal forces due to collisions of protein with water molecules.

What if F= 0 ?

J. Howard – Book, Ch. 2

What if $F = 0$?

Eq. of motion: $\frac{dv}{dt} = -\frac{\gamma}{m} v$; Solution: $v = e^{-\frac{t}{\tau}} \cdot v(0)$

$$m\frac{dv}{dt} + \gamma v = \cancel{F} 0$$

$\tau = \frac{m}{\gamma}$ 10^{-12} s range

$v \to 0$ for $t \to \infty$ can not be true, because the Equipartion Theorem says:

$v_{rms}^2 = \langle v^2 \rangle = \frac{3kT}{m}$ and $\langle v^2 \rangle \not\to 0$

At Equilibrium — our solution

A random force is necessary (thermal force). !!!

fluctuation

The force during an impact varies extremely rapidly over the time of observation.

Eq. of motion: $\frac{dv}{dt} = -\frac{\gamma}{m} v + \frac{1}{m}\xi(t)$ Langevin

Conditions for $\xi(t)$: $\langle \xi(t) \rangle = 0$ first moment; $\langle \xi(t_1)\,\xi(t_2) \rangle = q \cdot \delta(t_1 - t_2)$ second moment

$\delta(t)$ – delta function – indicates there is no correlation between impacts in any distinct time intervals dt_1 and dt_2 *correlation time is infinitely short*

q – is the amplitude of the fluctuation force,

$$q = 2kT\gamma$$

Fluctuation dissipation theorem FDT

$$g = 2kT\gamma$$

Fluctuation dissipation theorem FDT

- The amplitude of the thermal force depends only on the drag coefficient (friction dissipation).
- FDT expresses the balance between friction which tends to drive any system to a completely dead state and noise which tends to keep the system alive.
- This balance is required to have a thermal equilibrium state at long times.

Ref: Ch. 6 – Brownian Motion: Langevin Equation

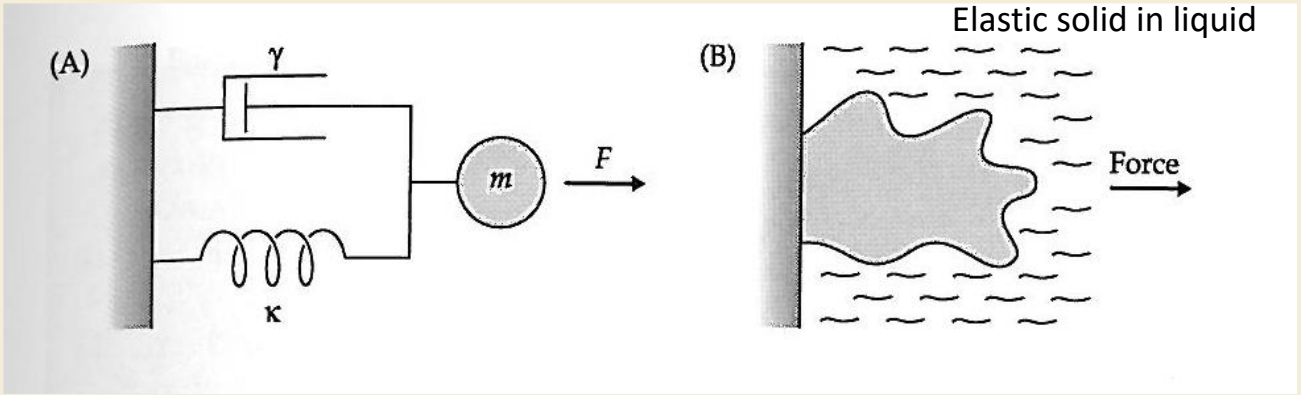
http://physics.gu.se/~frtbm/joomla/media/mydocs/LennartSjogren/kap6.pdf

https://web.stanford.edu/~peastman/statmech/friction.html

RECONSIDERING the Motion of Combinations of Mechanical Elements in presence of thermal forces

MASS and SPRING with DAMPING

Mechanical model of a protein undegoing a large scale conformational change that is damped by the surrounding fluid, and possibly by internal viscosity.



Elastic solid in liquid

$$m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + kx = F$$

Overdamped: $\frac{\gamma^2}{4mk} > 1$

$F = \phi$, $m\frac{d^2x}{dt^2} + \gamma\frac{dx}{dt} + kx = \xi(t)$

$\xi(t)$ - stochastic $\Rightarrow$ x can be described only by its statistical properties:

e.g. $\langle x \rangle$, $\langle x^2 \rangle$

Autocorrelation function, WHY ?

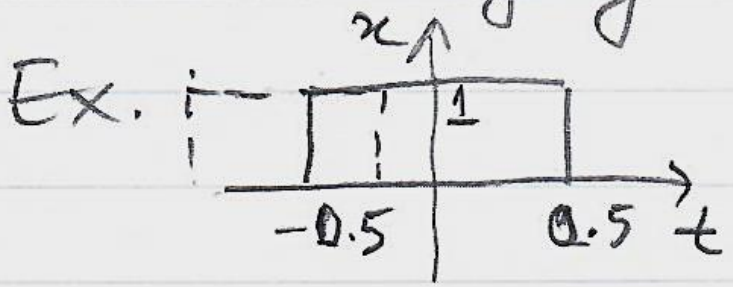
Using the autocorrelation function $R_x(\tau)$:

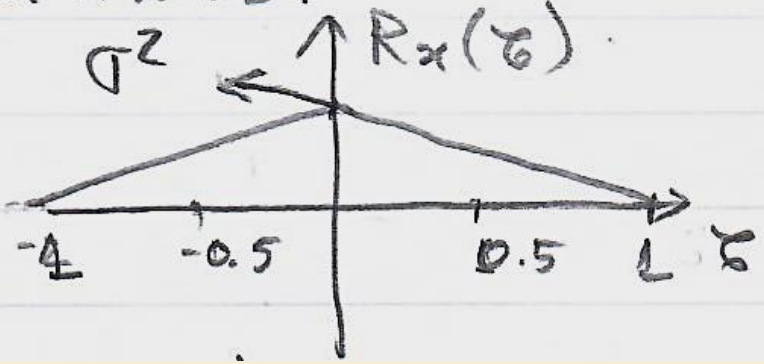
$$R_x(\tau) = x(t) * x(t) = \lim_{T\to\infty}\left\{\frac{1}{T}\int_{-\frac{T}{2}}^{\frac{T}{2}} x(t)\cdot x(t-\tau)\cdot dt\right\} =$$

$$= \langle x(t)\cdot x(t-\tau)\rangle$$

The autocorrelation at delay τ is calculated by multiplying the position at a given time by position at time τ earlier, and averaging over all times.

Ex.:





$R_x(0) = \sigma^2(x)$

variance

Autocorrelation function, WHY ?

Autocorrelation function (AF) satisfies the eq. of motion:

$$m\frac{d^2R_x}{dt^2} + \gamma\frac{dR_x}{dt} + kR_x = \phi$$

because $\langle F(t)\rangle = 0$

(appendix 4.3)

It means that AF has the same form as the response of the molecule to an impulsive external force.

Consequence: to estimate the molecule's molecular properties as mass, stiffness and damping we measure the thermal motion, calculate the AF and fit it to a predicted model, i.e. m, γ, k are fitting parameters.

OR

Use the Fourier analysis of the signal

Power Spectrum : PS

$PS = \mathcal{F}\{AF\}$ $\mathcal{F}$ - Fourier transform

So: - we measure the thermal motion of the molecule

- calculate the PS

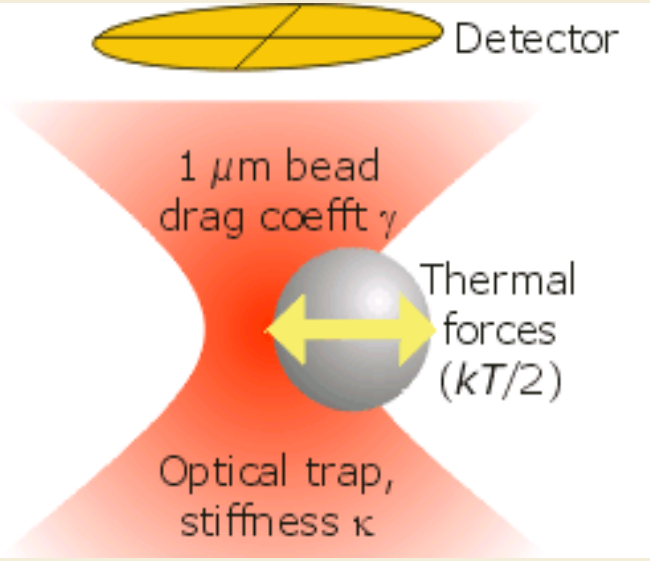
$$\underline{PS} = \mathcal{F}\{AF\} = \tilde{f}(x) \cdot \tilde{f}^{*}(x) = |\tilde{f}(x)|^2$$

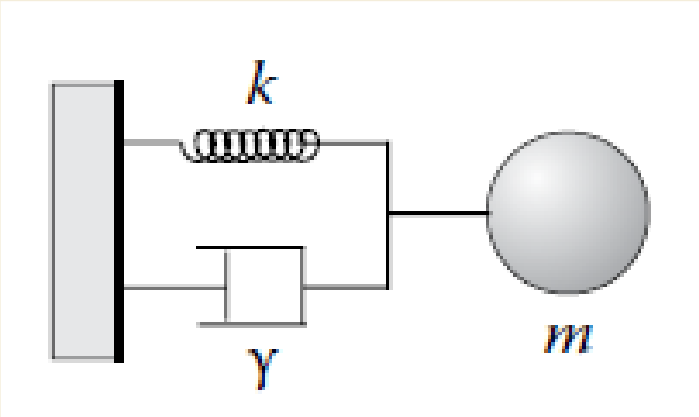
- compare PS with PS of a predicted model

deduce parameters as mass, damping, stiffness

Similar approach as in X-ray cristallography.

Schematic of a microbead in an optical trap

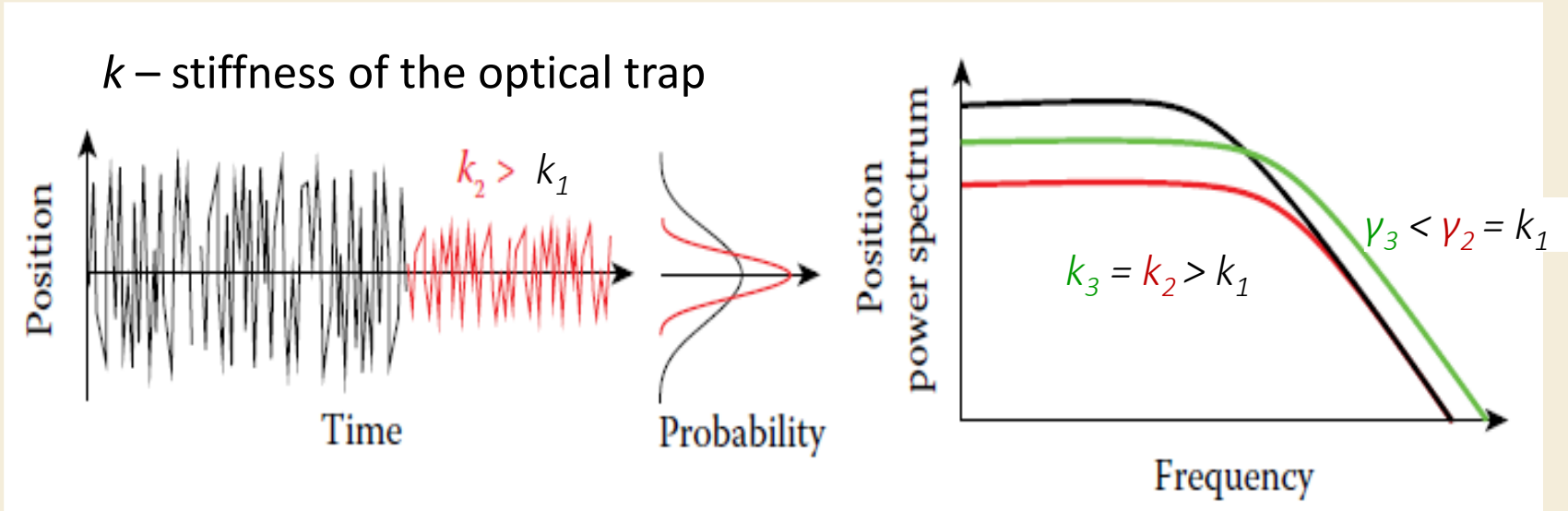




MASS and SPRING with DAMPING

Mechanical model also for a protein undegoing a large scale conformational change that is damped by the surrounding fluid, and possibly by internal viscosity.

k – stiffness of the optical trap



See the lesson on Optical Tweezers for a more detailed discussion