BB101 TSC: Physical Biology

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(Slides Courtesy: Jyotirmoy Roy)

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Thermal Energy

- Thermal Energy is given by , E=$k_B T$,

  where k_B=Boltzmann constant = 1.38064852 × 10^{-23} m^2 kg s^{-2} K^{-1}

- One of the primary forces responsible for protein folding and Brownian motions

QUESTION 1:

Hydrogen bonds are common in biological macromolecules such as proteins and DNA. Suppose that energy associated with hydrogen bond is 2 KJ/mol. Can thermal energy available at room temperature i.e. T=300 K can break a hydrogen bond?

MODEL ANSWER

$K_B T = 4.1 \times 10^{-21}$ pN nm at T = 300k

$= 4.1 \times 10^{-21}$ J

$E_{H\text{-}Bond} = \frac{2\,kJ}{mol} = \frac{2000}{6.023} \times 10^{-23}\,J = 332.06 \times 10^{-23}\,J$

$= 3.32 \times 10^{-21}\,J$

$\therefore E_{H\text{-}Bond} < K_B T$

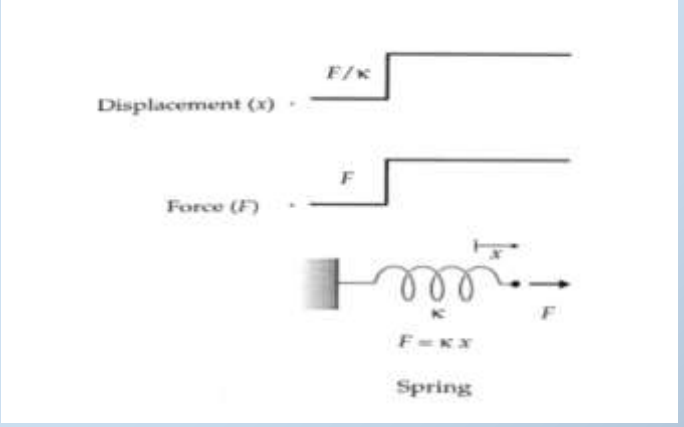
Hence, thermal energy can break this hydrogen bond.

Models to be considered

- Spring

i)Displacement directly proportional

to the force applied

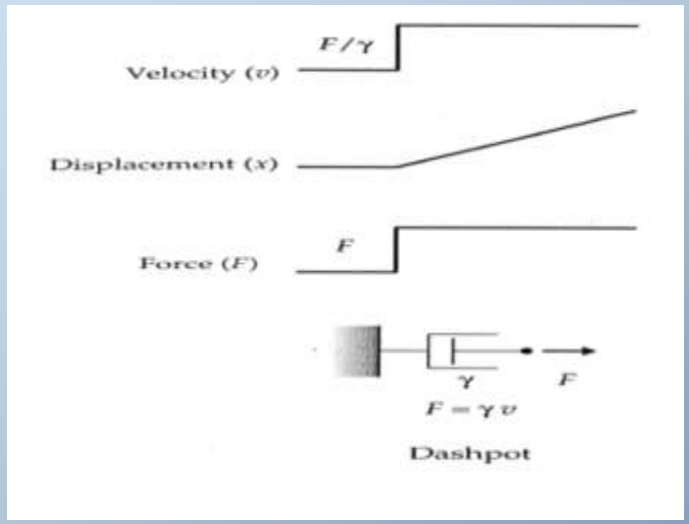


- Dashpot

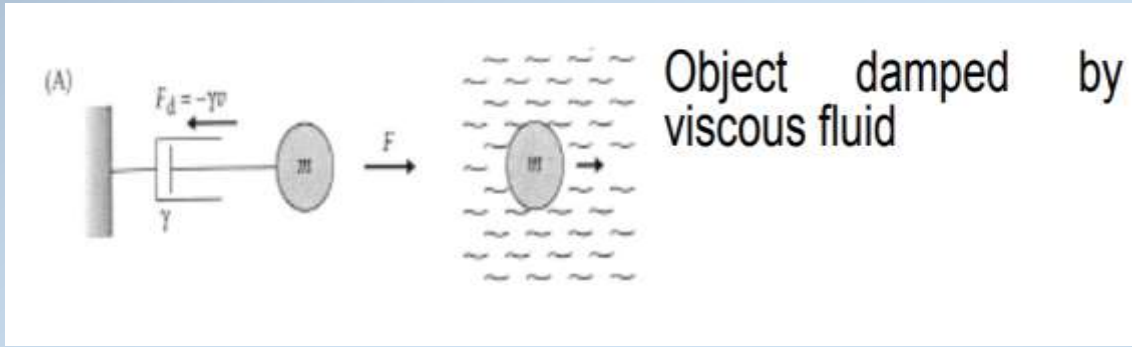
i)No net force

ii) Used to describe

how an object move in fluid



MODEL 1 COMBINATION: DASHSPOT AND MASS IN SERIES

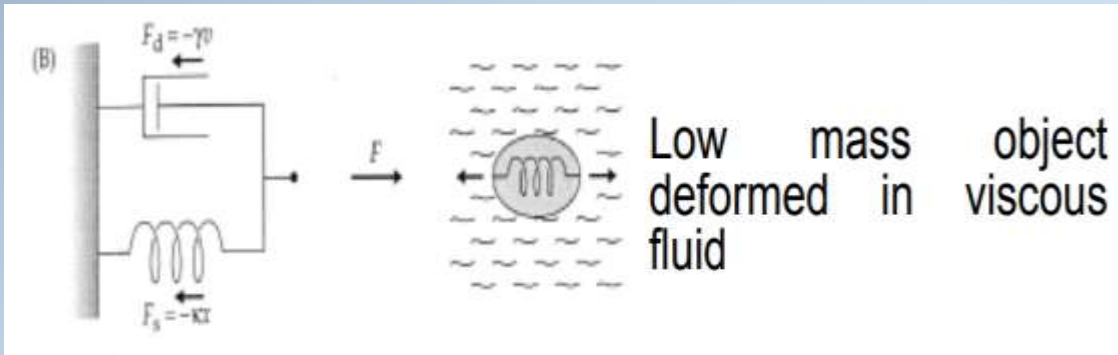


(A) Mass & Dashpot

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

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

MODEL 2 COMBINATION: DASHSPOT AND SPRING IN PARALLEL

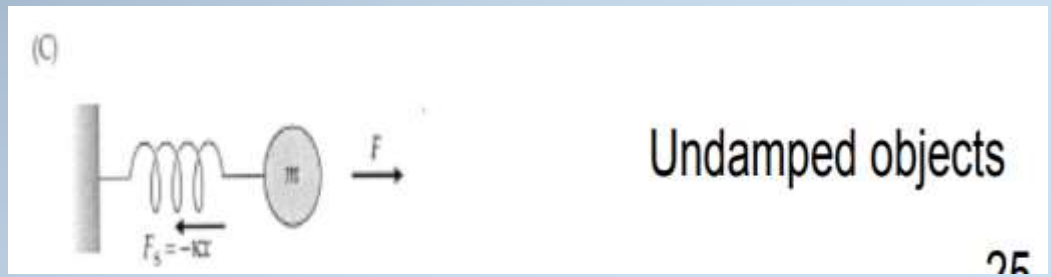


(B) Spring & Dashpot

$$\gamma \frac{dx}{dt} + \kappa x = F$$

$$x(t) = \frac{F}{\kappa}[1 - exp(-\frac{t}{\tau})]$$

MODEL 3 COMBINATION: MASS AND SPRING IN SERIES

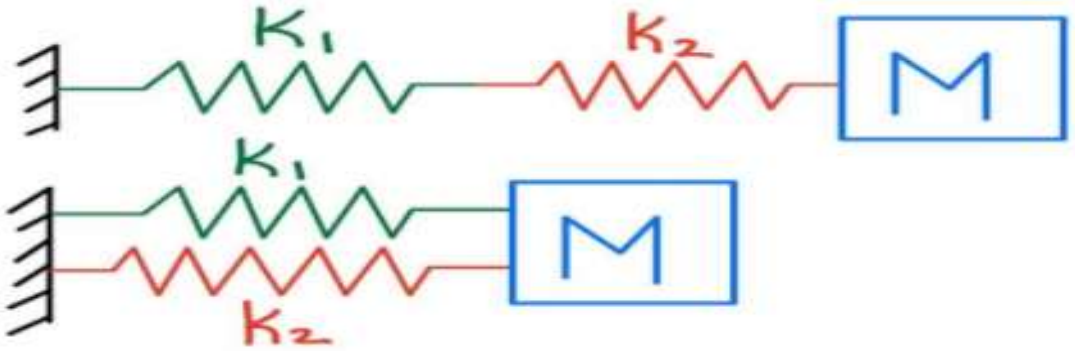


(c) Mass & Spring

$$m\frac{d^2x}{dt^2} + \kappa x = F$$

$$x(t) = \frac{F}{\kappa}[1 - cos(\omega t)]$$

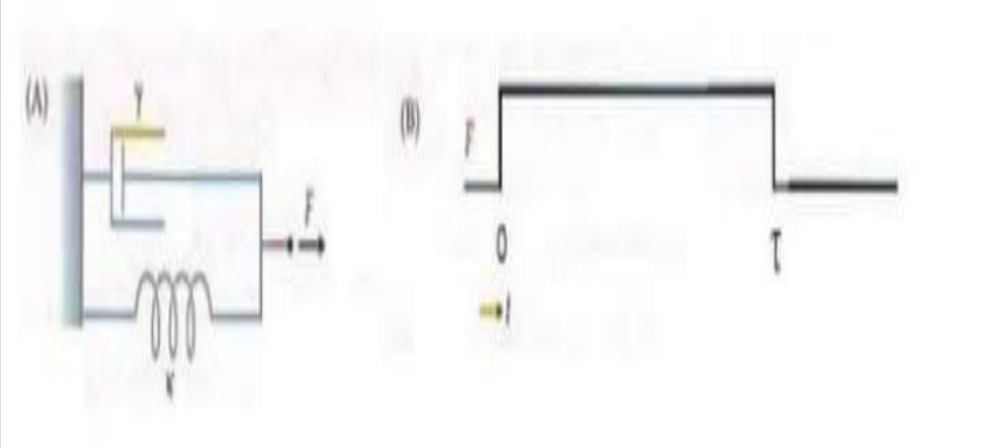
KEY TAKEAWAYS



Quantity	In Parallel	In Series
Equivalent spring constant	$k_{eq} = k_1 + k_2$	$\frac{1}{k_{eq}} = \frac{1}{k_1} + \frac{1}{k_2}$
Equivalent compliance	$\frac{1}{c_{eq}} = \frac{1}{c_1} + \frac{1}{c_2}$	$c_{eq} = c_1 + c_2$
Strain (elongation)	$x_{eq} = x_1 = x_2$	$x_{eq} = x_1 + x_2$
Stress (applied force)	$F_{eq} = F_1 + F_2$	$F_{eq} = F_1 = F_2$
Stored energy	$E_{eq} = E_1 + E_2$	$E_{eq} = E_1 + E_2$

PS :For Dashpot replace x with v!!!!

Question 2:
Consider a system consisting of a spring and dashpot in parallel as shown in figure (A). The stiffness or spring constant of the spring is k and drag coefficient of dashpot is γ. Initially both spring and dashpot are at rest. Suppose a constant force F is abruptly applied to this system as at t=0 and is maintained till time $t = \tau$ as shown in figure (B), and force is abruptly removed thereafter (i.e. F=0 for $t > \tau$). Find out the expression for displacement x(t) of the system for $t \leq \tau$ and for $t > \tau$



STEP 1: WRITE THE EQUATION OF MOTION AND INITIAL CONDITIONS

The equation of motion for $t \leq \tau$ is given by

$$kx + rv = F \quad \text{or} \quad kx + r\frac{dx}{dt} = F$$

$$\Rightarrow r\frac{dx}{dt} = F - kx$$

STEP 2: INTEGRATE FOR DISPLACEMENT

$$\Rightarrow r\frac{dx}{dt} = F - kx$$

$$\Rightarrow \int_0^x \frac{dx}{F-kx} = \int_0^t \frac{dt}{r}$$

$$\Rightarrow -\frac{1}{k}\left[\ln(F-kx)\right]_0^x = \frac{1}{r}\left[t\right]_0^t$$

$$\Rightarrow \ln\frac{F-kx}{F} = -\frac{k}{r}t$$

$$\Rightarrow \frac{F-kx}{F} = e^{-\frac{k}{r}t}$$

$$\Rightarrow F-kx = Fe^{-\frac{k}{r}t}$$

$$\Rightarrow kx = F - Fe^{-\frac{k}{r}t}$$

$$\Rightarrow x(t) \text{ or } x = \frac{F}{k}\left[1-e^{-\frac{k}{r}t}\right]$$

$\therefore$ Displacement at $t=\tau$ is given by

$$x(\tau) = \frac{F}{k}\left[1-e^{-\frac{k}{r}\tau}\right]$$

STEP 3: ONCE THE FORCE IS REMOVED AGAIN WRITE THE EQUATION OF MOTION

For $t > \tau$, equation of motion is given by

$$kx + r\frac{dx}{dt} = 0 \Rightarrow \frac{dx}{x} = -\frac{k}{r}dt$$

$$\int_{\tau}^{t} \frac{dx}{x} = -\frac{k}{r}\int_{\tau}^{t} dt$$

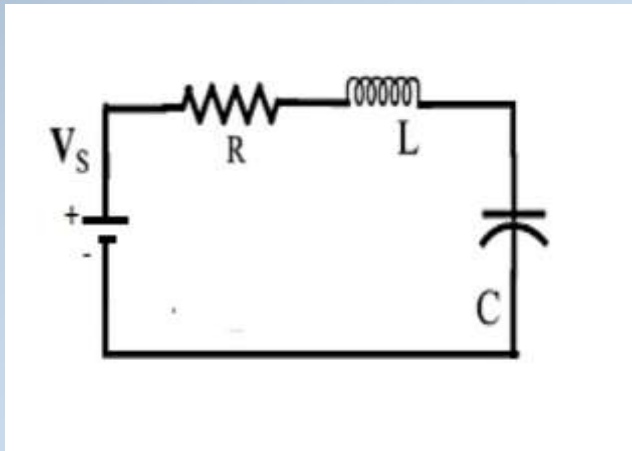
$$\ln [x]_{x_\tau}^{x} = -\frac{k}{r}[t]_{\tau}^{t} \Rightarrow$$

$$\ln \frac{x(t)}{x(\tau)} = -\frac{k}{r}[t-\tau]$$

or $$x(t) = x(\tau)\, e^{-\frac{k}{r}(t-\tau)}$$

or $$\boxed{x(t) = \frac{F}{k}\left[1 - e^{-\frac{k}{r}\tau}\right] e^{-\frac{k}{r}(t-\tau)}}$$

Comparison with LCR circuit



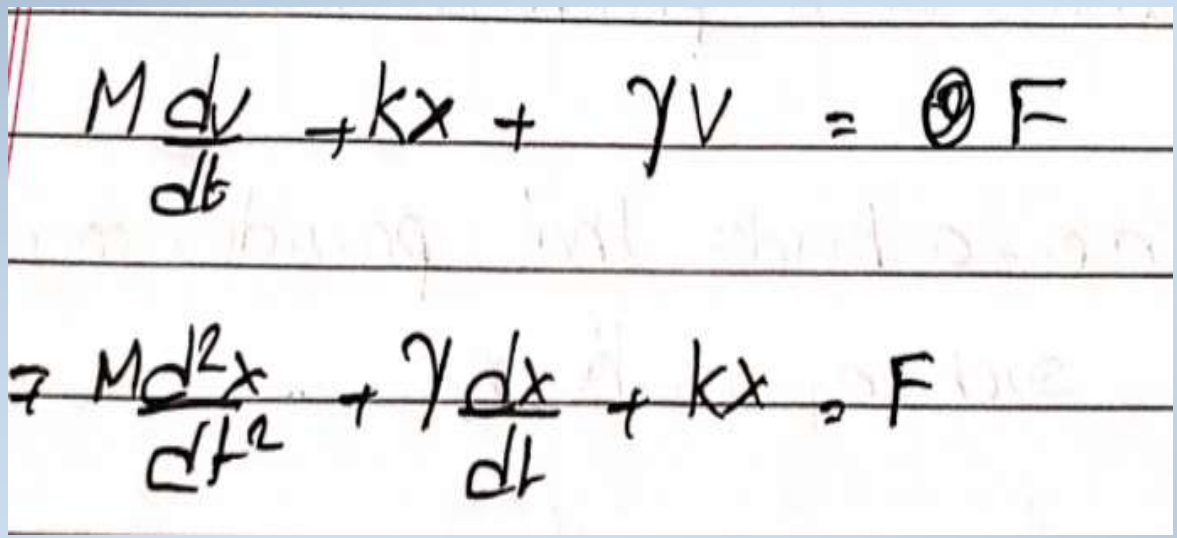
Translational Mechanical System	Electrical System
Force(F)	Voltage(V)
Mass(M)	Inductance(L)
Frictional Coefficient(B)	Resistance(R)
Spring Constant(K)	Reciprocal of Capacitance $\left(\frac{1}{c}\right)$
Displacement(x)	Charge(q)
Velocity(v)	Current(i)

Question 3:
The equation relating current i and charge q for a circuit consisting of an inductance L, capacitance C and a resistance R connected to a constant source of emf ξ is given by

$$L\frac{di}{dt}+\frac{q}{C}+Ri=\xi$$

Write down the corresponding equation for a mechanical system, driven by constant force F, consisting of a mass m, spring with spring constant k and dashpot with drag coefficient γ in terms of only displacement x. Either full marks or zero marks in this question.

MODEL ASNWER



CRTICAL FORCE AND ITS APPLICATION

$$f_{critical} = \frac{\eta^2}{\rho}$$

If applied force f is less than $f_{critical}$ then fluid can be called “thick” and flow will be laminar. Friction will quickly damp out inertial effects. Flow is dominated by friction.

REYNOLD'S NUMBER

- It is the ratio of viscous forces to inertial forces

$$\mathrm{Re} = \frac{Inertial\ force}{Viscous\ force} = \frac{\rho R v}{\eta}$$

Question 4:
Calculate Reynolds number for a spherical organism of radius 100 micro-m swimming at speed 10 micro-m/s in a medium whose viscosity is hundred times that of water and density is ten times that of water.The density of the organism is thousand times that of water

MODEL ANSWER

$$Re = \frac{\rho R v}{\eta} = \frac{10 \times 10^{+3} \times 100 \times 10^{-6} \times 10 \times 10^{-6}}{100 \times 10^{-3}}$$

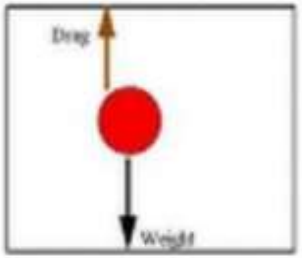
$$= \frac{10^{7-12}}{10^{-1}} = 10^{7-12+1} = 10^{8-12} = 10^{-4}$$

$$\therefore Re = 10^{-4}$$

Stokes Law

Stokes' Law

- Calculates the drag force on a sphere as it travels through a fluid.
- F = viscous drag force acting on the sphere
- r = radius of the sphere
- n = viscosity of the fluid
- v = velocity of sphere



$$F = 6\pi r \eta v$$

Question 5:

Consider the sedimentation of a spherical bio-molecule of radius 1 nm, initially right below the surface, in an Eppendorf tube of length 1 centimeters filled with water. Suppose that density of this biomolecule is 7.5 times that of water and this bio-molecule sediments under the effect of gravity. Further assume that this bio-molecule attains a constant velocity as soon as it starts to
descend in the Eppendorf tube. How much time (in seconds) this bio-molecule would take to descend 1mm in Eppendorf tube (Density water=1000 Kg m-3 and g=10m/s2)?

Step 1 : Write Equation of Motion

The equation of motion is given by

$$rv = mg - \rho Vg$$

$$= 7.5\rho Vg - \rho Vg$$

$$= 6.5\rho Vg$$

$$= (6.5)\rho \cdot \frac{4}{3}\pi r^3 g$$

Step 2 : Find Velocity

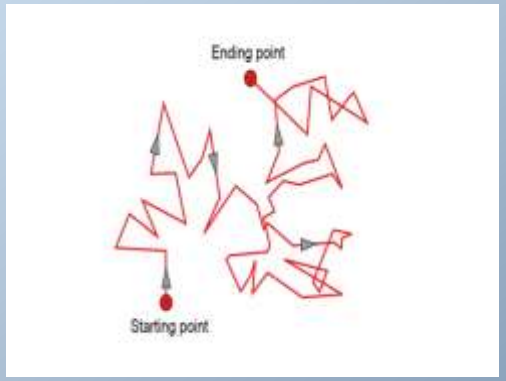
$$\Rightarrow v = \frac{6.5 \times \rho \times 4\pi r^3 g}{3 \times 6 \times \pi \times \eta \times r}$$

$$= \frac{26 \rho r^2 g}{18 \eta} = \frac{26 \times 10^3 \times 10^{-9} \times 10^{-9} \times 10}{18 \times 10^{-3}}$$

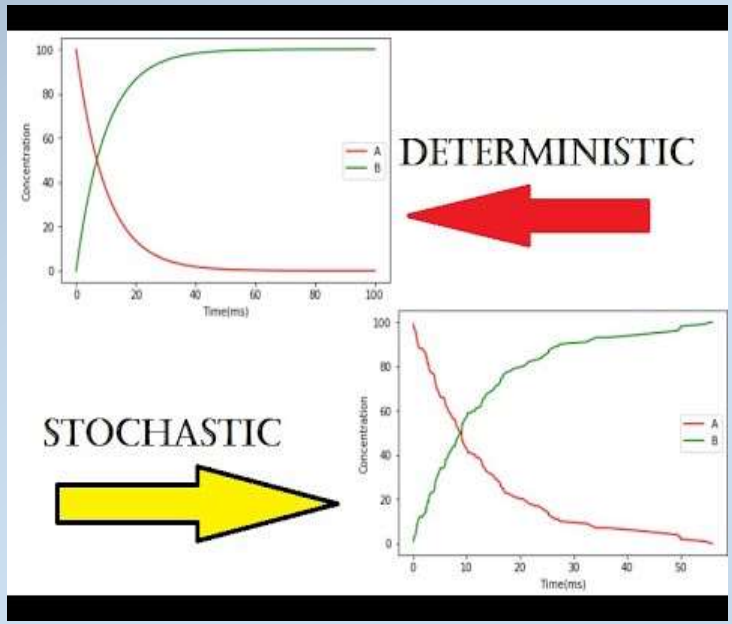
$$= \frac{26}{18} \times 10^{-11} \text{ m/s}$$

THERMAL ENERGY

- Proportional to the temperature of the molecule/body
- Since thermal forces are **randomly directed**, the resulting thermal motion is characterized by **frequent changes in direction** and is called diffusion
- Diffusion of a free particle or object is called Brownian motion



Importance of Thermal Energy



STOCHASTIC VS DETERMINISTIC FORCES

i) Stochastic :Having a random probability distribution or pattern that may be analysed statistically but may not be predicted precisely.

ii) Deterministic : Can be easily determined by specific mathematical relations

Importance of Thermal Energy

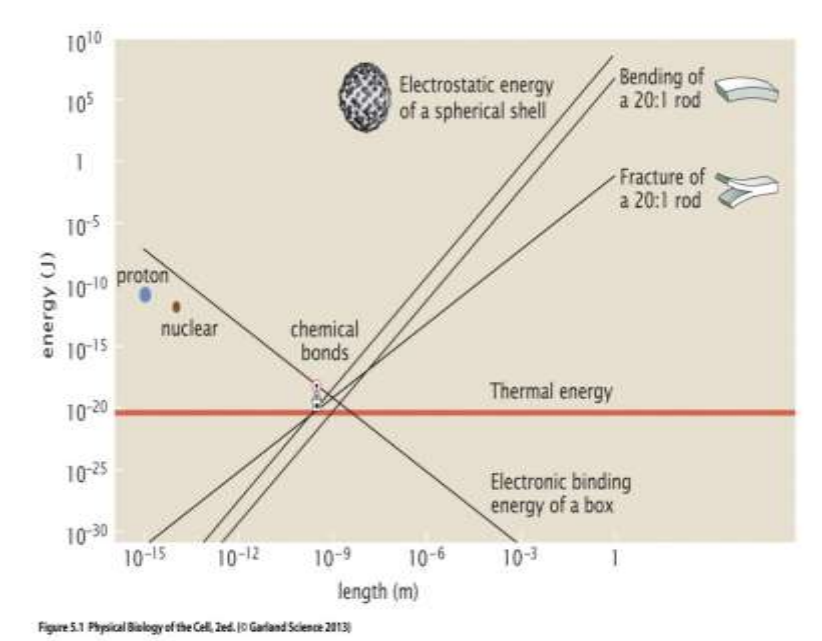


Figure 5.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Thermal Energy is **independent of the size/scale** of the object
- In **macroscopic scale** , the deterministic forces heavily dominate
- In **microscopic scale** (scale of molecule and chemical bonds), the thermal and deterministic energy are comparable and both play a significant role in determining the state of biomolecule

Boltzmann Law

- Probability of finding a molecule in a certain state depends on the energy of that state and surrounding temperature

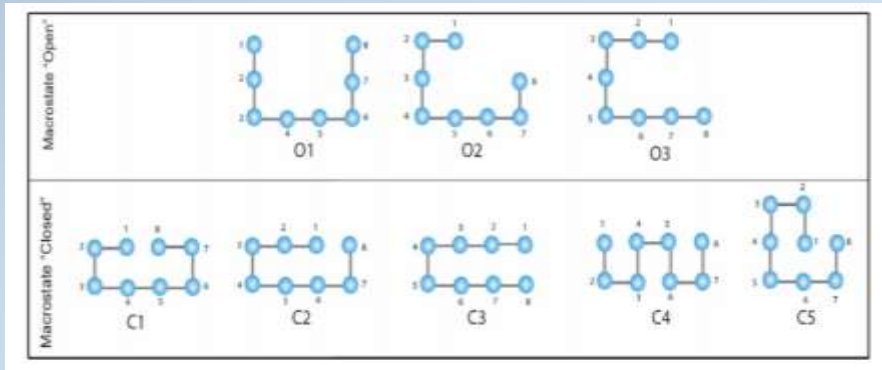
$$p_i = \frac{1}{Z} e^{-\frac{E_i}{k_B T}}$$

Where $z = \sum_i e^{-\frac{E_i}{k_B T}}$ is called partition function

The exponential term is called Boltzmann factor

Question 6

Consider a protein consisting of eight amino acids at temperature T. The sequence of the amino acids is PPHHHPPP. H and P denote the Hydrophobic and Polar amino acids respectively. Bond length between two amino acids is b. Suppose that this protein can be found in two different macrostates- "Open" or "Closed". The microstates corresponding to these macrostates are shown in the figure below.



Suppose that this protein is kept in a solvent (water) such that energy increases by ε for every contact of H with either a solvent molecule or a P molecule within distance b (consider the initial energy of the protein to be zero when it is not in solvent)

(i) What are the energies of the protein in different microstates i.e. O1, O2, O3, C1, C2, C3, C4 and C5?

(ii) What are the free energies of "Open" and "Closed" macrostates?

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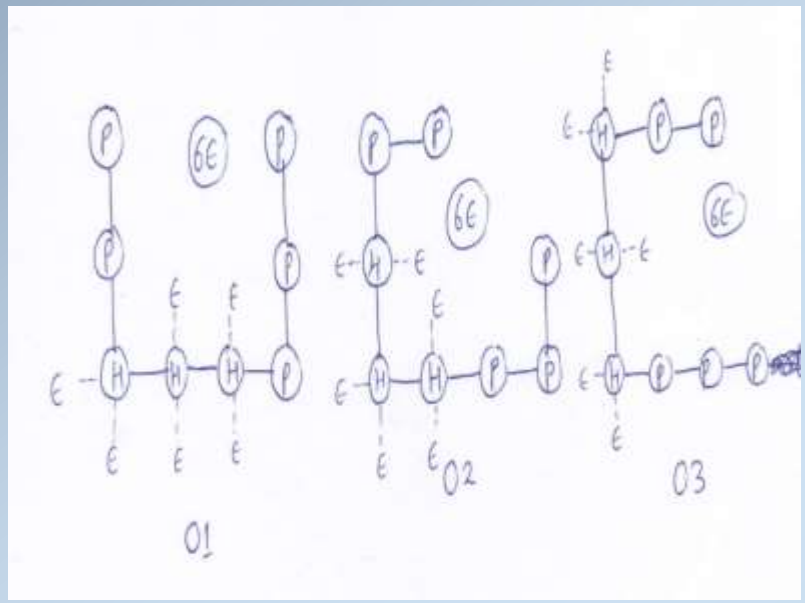
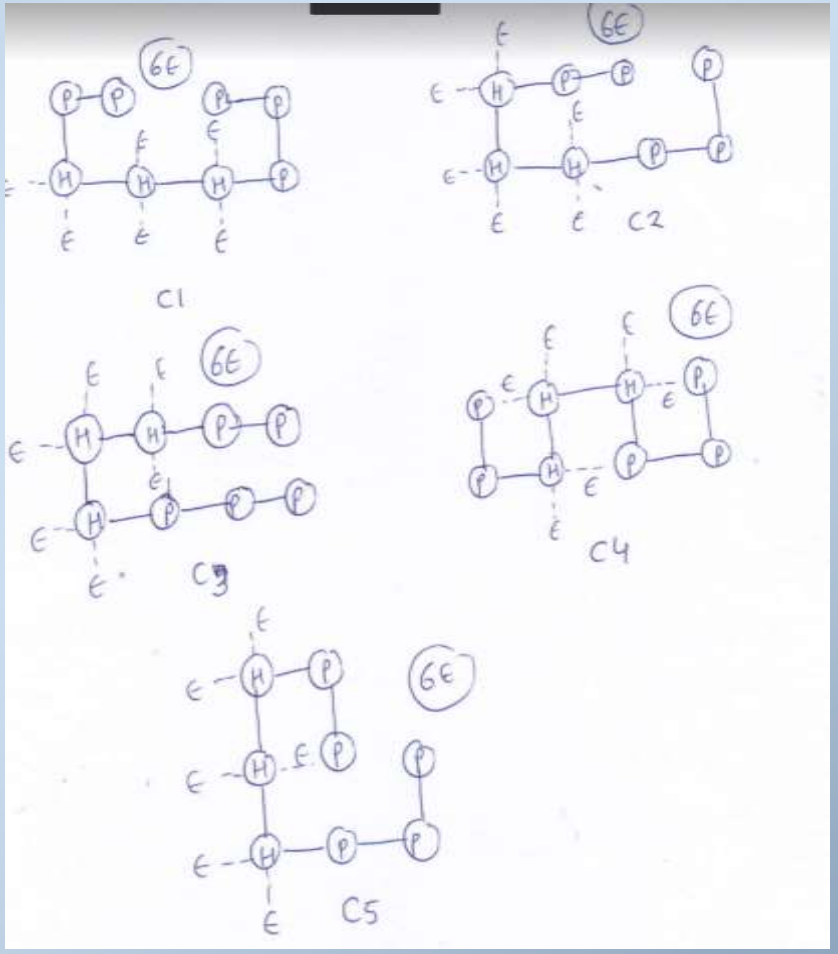
1)Energies of the states



Opened States



Closed States

ii) Free Energy

Gibbs free energy $G = H - TS$

$$S = k_B \ln W$$

(iii) Free energies of "Open" macrostate

$G_{open} = U_{open} - T S_{open}$

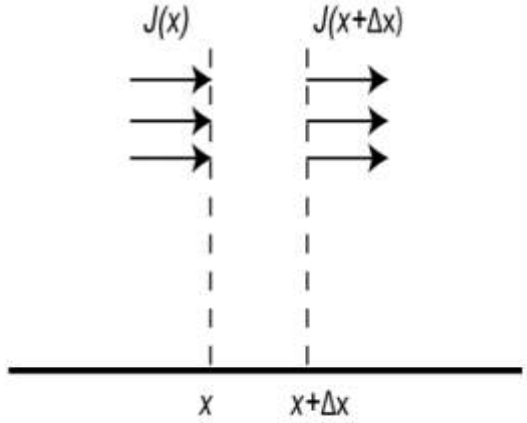
$= 6\epsilon - T k_B \ln 3$

Free energy of "closed" macrostate

$G_{closed} = U_{closed} - T S_{closed}$

$= 6\epsilon - T k_B \ln 5$

CONTINUITY EQUATION



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

Comparison of two States

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

If there are just two states with energies E_1 and E_2 (and energy difference $\Delta E = E_2 - E_1$) then

$$\frac{p_2}{p_1} = e^{-\frac{\Delta E}{k_B T}}$$

QUESTION 7

Consider a two-state model of proteins: the folded macro-state has two micro-states, each with energy −ε0(where ε0 > 0) and the unfolded macro-state has four microstates, each with energy +ε0 (where ε0 > 0).

(i) Find out the partition function of the system?

(ii) Find out the ratio $P_{unfolded}$ / P_{folded} in terms of ε0 and temperature T,

where $P_{unfolded}$ and P_{folded} denote probability of finding the protein in unfolded and folded macro-state respectively?

ANSWER:

(2) (i) The partition function z is given by

$$z = 2e^{+G_0/k_BT} + 4e^{-G_0/k_BT}$$

(ii) $$\frac{P_{unfolded}}{P_{folded}} = \frac{4e^{-G_0/k_BT}}{2e^{+G_0/k_BT}} = 2e^{-2G_0/k_BT}$$

QUESTION 8:

Consider a hypothetical polymer chain consisting of four monomers which can exist in five conformations. The distance between chain ends is 1 nm in compact conformation, 3 nm in extended conformation, and $\sqrt{5}$ nm each of the three intermediate conformations.

I) Calculate end-to-end distance of the polymer at temperature T if the energy of the polymer chain in all possible conformations is ε ($\varepsilon > 0$)?

II)Which conformation will be preferred for any finite value of temperature T?

ANSWERS:

(3) The partition function can be written as following if we assume that energy is ϵ in each configuration

$$Z = e^{-\epsilon/k_BT} + 3e^{-\epsilon/k_BT} + e^{-\epsilon/k_BT} = 5e^{-\epsilon/k_BT}$$

$$P_{extended} = \frac{e^{-\epsilon/k_BT}}{5e^{-\epsilon/k_BT}} = \frac{1}{5}, \quad P_{compact} = \frac{e^{-\epsilon/k_BT}}{5e^{-\epsilon/k_BT}} = \frac{1}{5}$$

$$P_{Intermediate} = \frac{3e^{-\epsilon/k_BT}}{5e^{-\epsilon/k_BT}} = \frac{3}{5}$$

ANSWER:

$$\therefore \langle R \rangle = R_{open} P_{open} + R_{intermediate} P_{intermediate} + R_{extended} P_{extended}$$

$$= \frac{1}{5} \cdot 3 + \frac{3}{5} \cdot \sqrt{5} + \frac{1}{5} \cdot 1$$

$$= \frac{1}{5}\left(3 + 3\sqrt{5} + 1\right)$$

$$= 2.142 \text{ nm}$$

NERST EQUATION

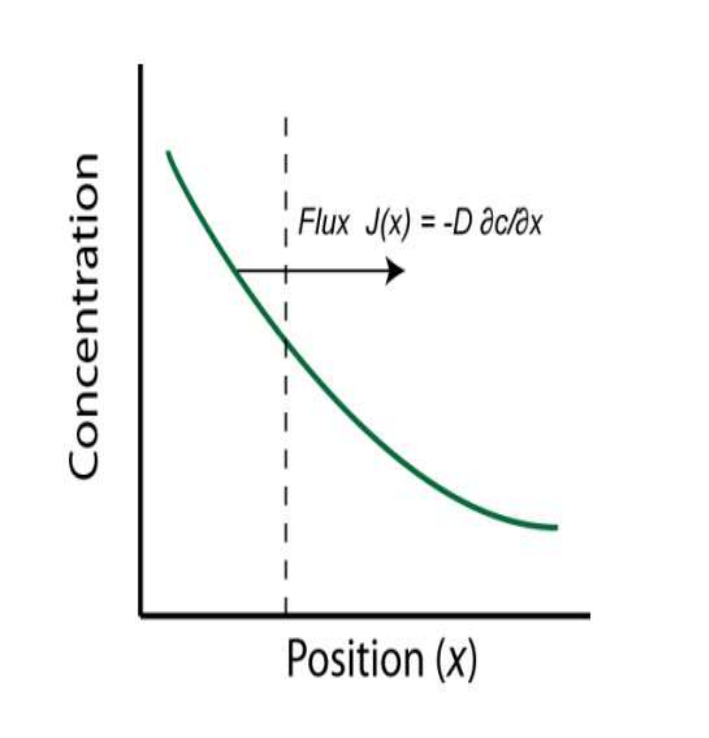
$$\frac{p_1}{p_2} = \frac{C_1}{C_2} = \frac{e^{-\frac{zeV_1}{k_B T}}}{e^{-\frac{zeV_2}{k_B T}}}$$

$$V_2 - V_1 = \frac{k_B T}{ze} ln \frac{C_1}{C_2}$$

z is valancy of ion and $e = 1.6 \times 10^{-19} C$

$z = +1$ for Na^+ and $z = -1$ for Cl^-

FICK'S LAW



DIFFUSION AND CONTINUITY EQUATION

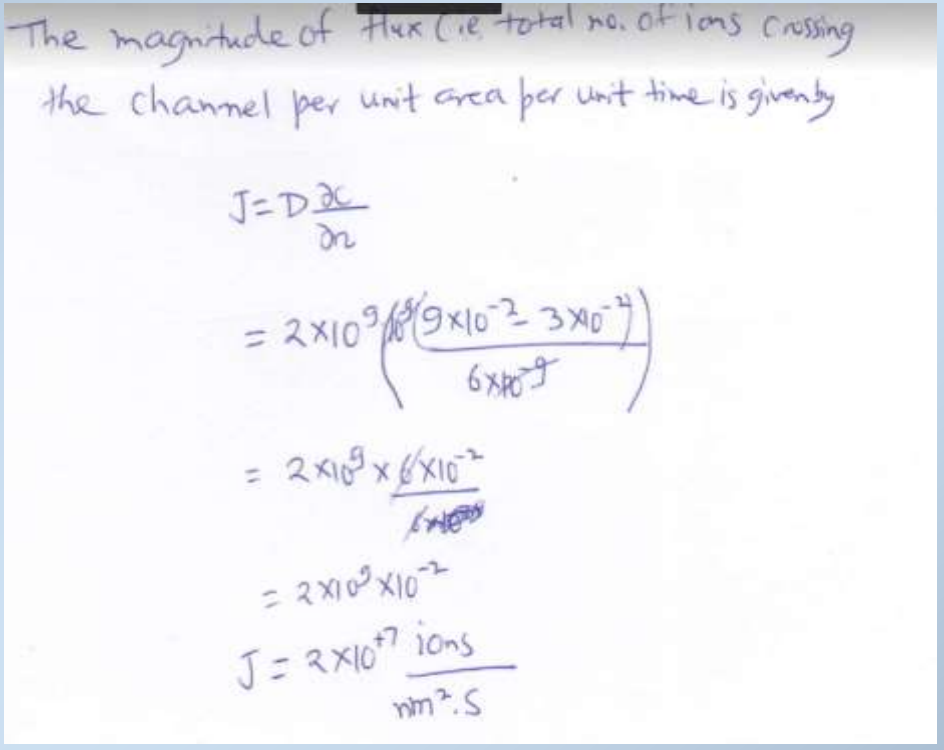
Combine Fick's Law and Continuity Equation

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

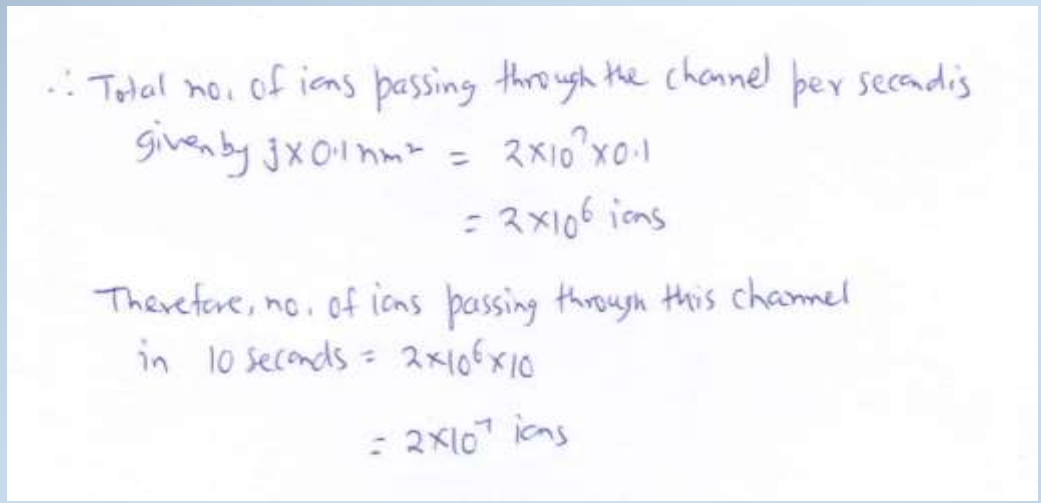
QUESTION 9:

- Suppose that intra-cellular and extra-cellular concentrations of an ion Y across a cell membrane are 9×10^{-2} molecules/ nm^3 and 3×10^{-2} molecules/ nm^3 respectively. The diffusion constant for ion Y is 2×10^9 nm^2 /s. Suppose that cell membrane has an ion channel of length 6 nm and area 0.1 nm2.Calculate the number of Y ions passing through this ion channel in 10 seconds?

ANSWER:
STEP1: FIND THE FLUX(J)



ANSWER:
STEP 2: MULTIPLY THE FLUX WITH AREA AND THE WITH TIME



REMEMBER: FLUX = NO OF MOLECULES PASSING PER UNIT AREA PER UNIT TIME

FICK'S LAW AND DIFFUSION

Which one(s) of the following functions is/are solutions of diffusion equation in one dimension

(i) $C(x,t) = \exp(-\alpha t^2)\sin(-\sqrt{\frac{\alpha}{D}}x)$ (ii) $C(x,t) = \exp(-\alpha t)\sin(\sqrt{\frac{\alpha}{D}}x^2)$

(iii) $C(x,t) = \exp(-\alpha t)\cos(\sqrt{\frac{\alpha}{D}}x^2)$ (iv) $C(x,t) = \exp(-\alpha t)\sin(\sqrt{\frac{\alpha}{D}}x)$ **[2 Marks]**

(i) $\frac{\partial c}{\partial t} = -\alpha t e^{-\alpha t^2} \sin\left(\sqrt{\frac{\alpha}{D}} x\right)$, $\frac{\partial c}{\partial x} = \sqrt{\frac{\alpha}{D}} e^{-\alpha t^2} \cos\left(\sqrt{\frac{\alpha}{D}} x\right)$

$\frac{\partial^2 c}{\partial x^2} = \frac{\alpha}{D} e^{-\alpha t^2} \sin\left(\sqrt{\frac{\alpha}{D}} x\right)$

$\because \frac{\partial c}{\partial t} \neq D \frac{\partial^2 c}{\partial x^2} \Rightarrow$ It is not a solution

(ii) $\frac{\partial c}{\partial t} = -\alpha e^{-\alpha t} \sin\left(\sqrt{\frac{\alpha}{D}} x^2\right)$, $\frac{\partial c}{\partial x} = 2x\sqrt{\frac{\alpha}{D}} e^{-\alpha t} \cos\left(\sqrt{\frac{\alpha}{D}} x^2\right)$

$\frac{\partial^2 c}{\partial x^2} = \frac{1}{D}\left[2e^{-\alpha t}\left\{D\sqrt{\frac{\alpha}{D}} \cos\left(x^2\sqrt{\frac{\alpha}{D}}\right) - 2\alpha x^2 \sin^2\left(\sqrt{\frac{\alpha}{D}} x^2\right)\right\}\right]$

$\because \frac{\partial c}{\partial t} \neq D\frac{\partial^2 c}{\partial x^2} \Rightarrow$ It is not a solution

(iii) $\frac{\partial c}{\partial t} = -\alpha e^{-\alpha t} \cos\left(x^2\sqrt{\frac{\alpha}{D}}\right)$, $\frac{\partial c}{\partial x} = -2x\sqrt{\frac{\alpha}{D}} e^{-\alpha t} \sin\left(\sqrt{\frac{\alpha}{D}} x^2\right)$

$\frac{\partial^2 c}{\partial x^2} = -\frac{1}{D}\left(2e^{-\alpha t}\left\{D\sqrt{\frac{\alpha}{D}} \sin\left(x^2\sqrt{\frac{\alpha}{D}}\right) + 2\alpha x^2 \cos\left(\sqrt{\frac{\alpha}{D}} x^2\right)\right\}\right)$

$\because \frac{\partial c}{\partial t} \neq D\frac{\partial^2 c}{\partial x^2} \Rightarrow$ It is not a solution

(iv) $\frac{\partial c}{\partial t} = -\alpha e^{-\alpha t} \sin\left(\sqrt{\frac{\alpha}{D}} x\right)$, $\frac{\partial c}{\partial x} = \sqrt{\frac{\alpha}{D}} e^{-\alpha t} \cos\left(\sqrt{\frac{\alpha}{D}} x\right)$

$\frac{\partial^2 c}{\partial x^2} = -\frac{\alpha}{D} e^{-\alpha t} \sin\left(\sqrt{\frac{\alpha}{D}} x\right)$

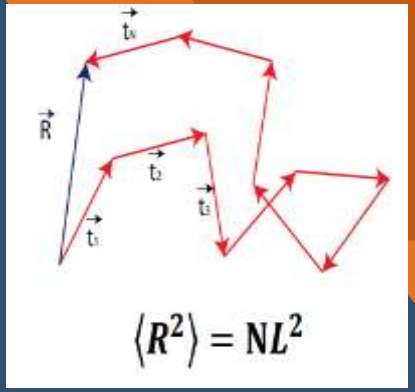
$\Rightarrow \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$ $\therefore$ This is a solution.

Random Walk as a Model for conformation of polymer

Conformation of Polymer as Random Walk

- Regard polymer as a string of N units, where each unit is joint to the next by a perfectly flexible joint. In the thermal equilibrium, joints will be at [illegible] angles. Freely Jointed Chain (FJ

$$\langle R^2 \rangle = NL^2$$



- A polymers can be treated as consisting of a number of linear segments
- Persistence length is what determines the whether the polymer is bent or straight

LENGTH OF POLYMER

Calculate root-mean-square (RMS) end-to-end distance of a hypothetical freely jointed chain of 100 segments, where length of each segment is 3Å. **[1 Mark]**

$$\sqrt{\langle R^2 \rangle} = \sqrt{NL^2} = \sqrt{N}\,L$$

$$= \sqrt{100} \times 3$$

$$= 30\ \text{Å}$$

Persistence Length

$$g(s) = e^{-\frac{s}{\xi_p}}$$

- If g(s)=1: Straight , else if g(s)=0: Bent

$$\xi_p = \frac{k_b}{k_B T}$$

Note: k_b is the binding stiffness, k_B is the Boltzmann constant

CLICKER QUESTION 1

- Suppose the persistence length of actin filaments at T=300K is 3micrometer. Will the appearance of action film of length 1500nanometer kept in water at 300K be bent or straight?
- A)Bent
- B)Straight
- C)Cant comment

Protein Structures are free energy minimizers

- In presence of thermal fluctuations, a protein folds into the structure which minimizes free energy, out of all the possible ways that a particular chain of amino acids can fold up

- What is free energy?

- Helmholtz free energy $$A = U - TS$$

- Gibbs free energy $$G = H - TS$$

$$H = U + pV$$

Entropy

- Entropy is a measure of the microscopic degeneracy of a macroscopic state ("macro-state"

- In other words, entropy can be computed by counting the number of possible microscopic arrangements/states ("micro-states") for a given macroscopic state ("macro-state")

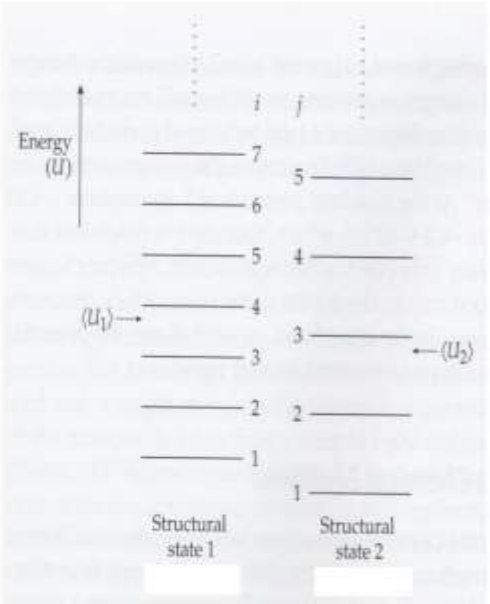
$$S = k_B \ln W$$

W is the number of possible microscopic arrangements (or "micro-states")

Micro-state and Macro-state

- We know that probability of finding protein any microstate i or j is given by Boltzmann law

$$p_i = \frac{1}{Z} e^{-\frac{U_i}{k_B T}} \qquad p_j = \frac{1}{Z} e^{-\frac{U_j}{k_B T}}$$

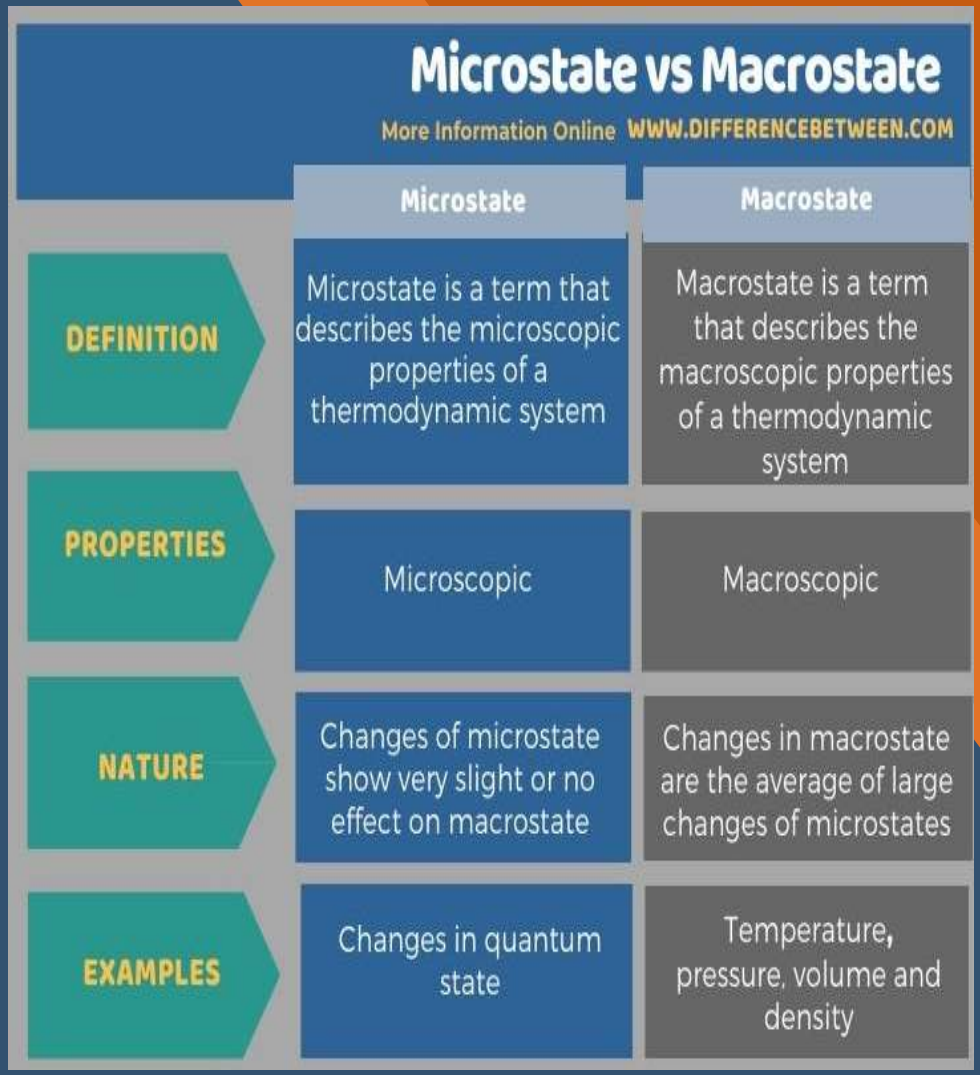


- What is the probability of finding protein in a given macrostate?

- The probability of finding protein in a given macrostate is given sum of all p_i or p_j

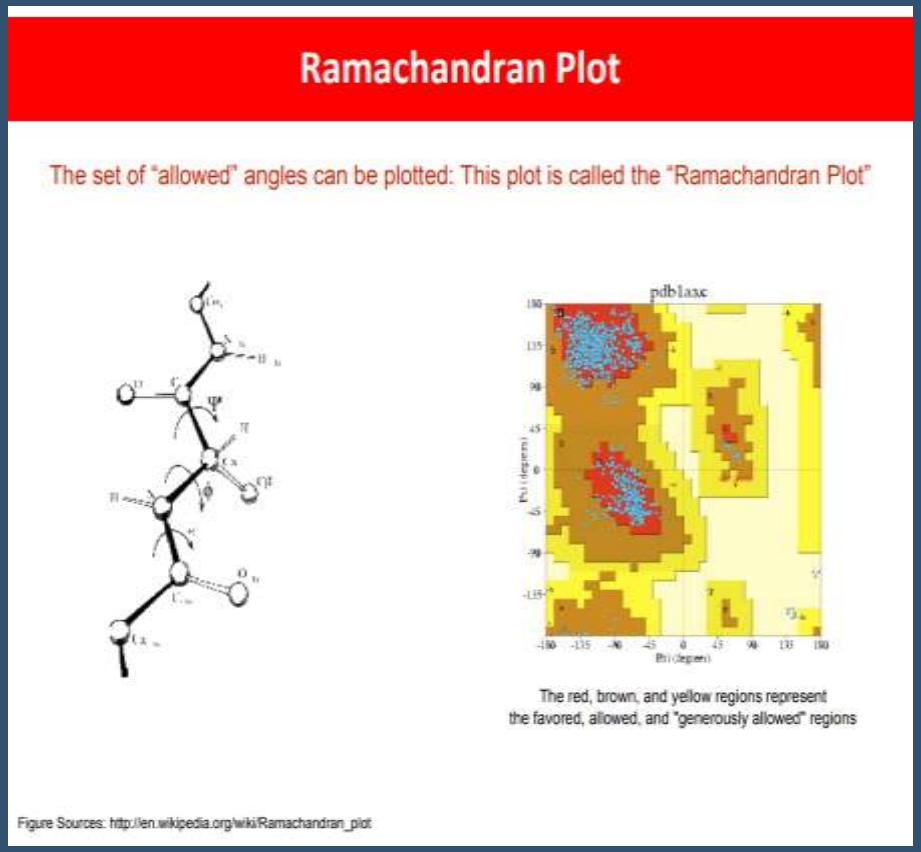
Final Relation for a Macrostate

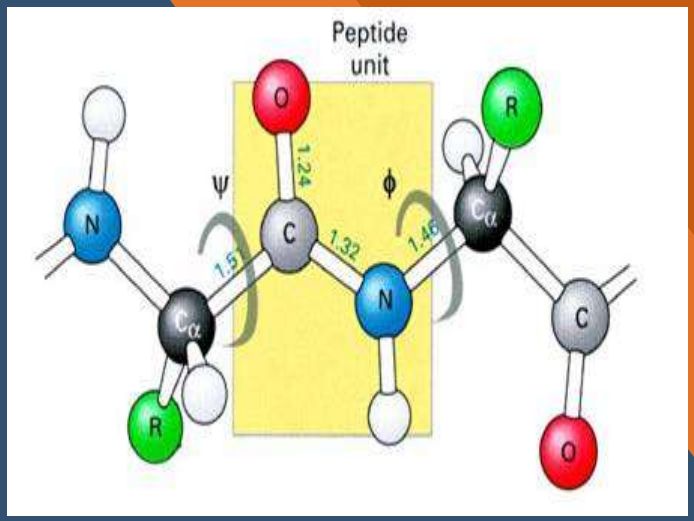
$$p(X) = \frac{1}{Z} e^{-\frac{G(X)}{k_B T}}$$



Source:https://www.differencebetween.com/difference-between-microstate-and-macrostate/

Ramachandran Plot



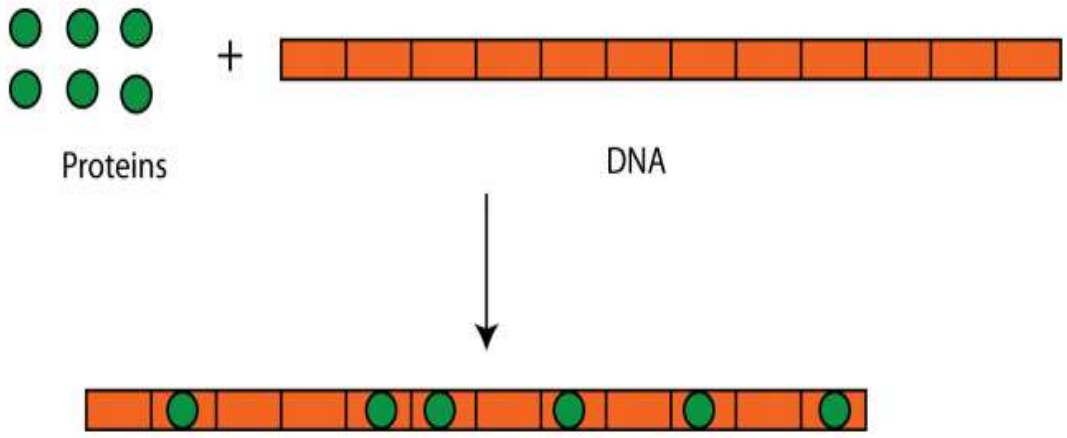


Dihedral Angle Source:https://www3.cmbi.umcn.nl/wiki/index.php/Phi-psi_angle

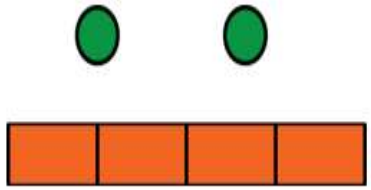
- Used to predict the stable structure of proteins

Protein-DNA Binding

- Typically, proteins and DNA are oppositely charged
- Interaction energy favors binding; just like positive and negative charges to come together



Protein-DNA Binding



Imagine a “state” with m proteins bound. (m<N)

In this picture m=2, N=4

Protein-DNA Binding

- Assume each protein binding gives a constant energy change $-\varepsilon k_B T$
- If m proteins are bound then What is the total energy change?

Protein-DNA Binding

$$U = -m\varepsilon k_B T = -N\rho\varepsilon k_B T$$

In other words, ε is the binding energy of a protein

Densityof proteins $\rho = \frac{m}{N}$

Protein-DNA Binding

"m" proteins, "N" binding locations

Number of arrangements (number of "micro-states")

$$W = \frac{N!}{m!\,(N-m)!}$$

$$S = k_B \, lnW = k_B \, ln\left(\frac{N!}{m!\,(N-m)!}\right)$$

Use Sterling's Approximation

$$\ln p! \approx plnp \; - p$$

Protein-DNA Binding

With Stirling's approximation, one can rewrite entropy as

$$S = -k_B N[\rho ln\rho + (1-\rho)\ln(1-\rho)]$$

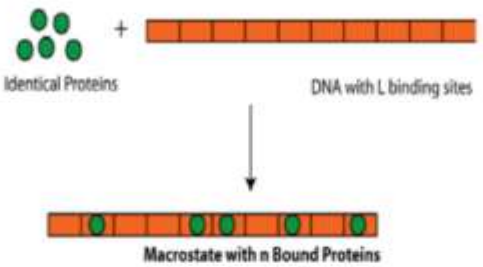
$$G = U - TS$$

$$G = -N\rho\varepsilon k_B T - k_B TN[\rho ln\rho + (1-\rho)\ln(1-\rho)]$$

$$\boxed{\frac{G}{Nk_B T} = -\rho\varepsilon - \rho ln\rho + (1-\rho)\ln(1-\rho)}$$

CLICKER QUESTION 4

10. Consider the Protein-DNA system discussed in lecture where identical protein molecules can bind to a DNA with total L binding sites as shown in figure below.



Suppose different possible macrostates of this protein-DNA system are characterized by the parameter ρ which measures the density of protein molecules bound to DNA. ρ=n/L where n is the number of protein molecules bound to DNA and L=10. Consider the three macrostates A, B and C of this protein-DNA system with densities ρ=0.2, ρ=0.5 and 0.8 respectively.

(i) Calculate the number of microstates corresponding to macrostates A, B and C **[1.5 Marks]**

(ii) Calculate the free energies of the macrostates A, B and C if energy (internal energy) of this system is zero and binding of protein does not increase/decrease energy. **[1.5 Marks]**

(iii) Which macrostate has lowest free energy at temperature T= 300 K? **[1 Marks]**

PART 1

No. of proteins in macrostate A = $0.2 \times 10 = 2$

" " " " macrostate B = $0.5 \times 10 = 5$

" " " " macrostate C = $0.8 \times 10 = 8$

(i) No. of microstates in macrostate A = $\frac{10!}{2!(10-2)!}$

$= \frac{10!}{2!8!} = \frac{\overset{5}{\cancel{10}} \times 9 \times \cancel{8!}}{\cancel{2} \times \cancel{8!}}$

$= 45$

No. of microstates in macrostate B = $\frac{10!}{5! \times (10-5)!} = \frac{10!}{5! \times 5!}$

$= \frac{2 \overset{3}{\cancel{10}} \times \cancel{9} \times \cancel{8} \times 7 \times 6 \times \cancel{5!}}{\cancel{5!} \times \cancel{5} \times \cancel{4} \times \cancel{3} \times \cancel{2} \times 1}$

$= 2 \times 3 \times 7 \times 6$

$= 252$

No. of microstates in macrostate C = $\frac{10!}{8!(10-2)!} = \frac{10!}{8! \times 2!}$

$= \frac{\overset{5}{\cancel{10}} \times 9 \times \cancel{8!}}{\cancel{8!} \times \cancel{2!}}$

$= 45$

PART 2 AND 3

= 45

(ii) Free energy of macrostate A = $0 - Tk_B \ln 45 = -k_B T \ln 45$

" " " B = $0 - Tk_B \ln 252 = -k_B T \ln 252$

" " " C = $0 - Tk_B \ln 45 = -k_B T \ln 45$

(iii) Macrostate B will have lowest free energy at T = 300K

QUESTION 1: DIFFUSION EQUATION

It observed that hemoglobin was undergoing diffusive motion in water with diffusion constant $D = 6.90 \times 10^{-7}$ $cm^2 s^{-1}$ at T=300 K such that its motion was confined in one-dimension. Compute the surface area of the hemoglobin. Assume that hemoglobin spherical in shape. **[1.0 Mark]**

STEP 1:USE EINSTEIN EQUATION

Given $D = 6.90 \times 10^{-7} \frac{cm^2}{s} = 6.90 \times 10^{-7} \times 10^{-4} \frac{m^2}{s} = 6.9 \times 10^{-11} \frac{m^2}{s}$

we know that

$$\gamma D = K_B T$$

or

$$6\pi\eta r D = K_B T$$

STEP 2: FIND RADIUS AND THEN THE SURFACE AREA

$$\Rightarrow \quad \pi r = \frac{K_B T}{6 \eta D}$$

$$= \frac{1.38 \times 10^{-23} \times 300}{6 \times 10^{-3} \times 6.9 \times 10^{-11}}$$

$$= 10 \times 10^{-23} \times 10^{3} \times 10^{11}$$

$$= 10 \times 10^{-23+14} = 10^{-23+15} = 10^{-8}\ m$$

Surface area $= 4\pi r^2$

$$= 4(\pi r) r$$

$$= 4 \times 10^{-8} \times \left(\frac{10^{-8}}{\pi}\right) m^2$$

$$= \frac{4}{\pi} \times 10^{-16}\ m^2$$

$$\approx 1.274 \times 10^{-16}\ m^2$$

QUESTION 2:PROTEIN DNA BINDING

Consider a lattice with N sites and n green particles. Consider another lattice, adjacent to the first, with M sites and m red particles. Given $M > m$ and $N > n$.

(a) Assume that the green and red particles cannot switch lattices. This is state A. What is the total number of configurations W_A of the system in state A?

(b) Now assume that all $N+M$ sites are available to all the green and red particles. The particles remain distinguishable by their color. This is state B. what is the total number of configurations W_B of the system in state B?

Now take $N = M$ and $n = m$ for part (c) and part (d) of this question

(c) Using Stirling's approximation, what is the ratio W_A/W_B?

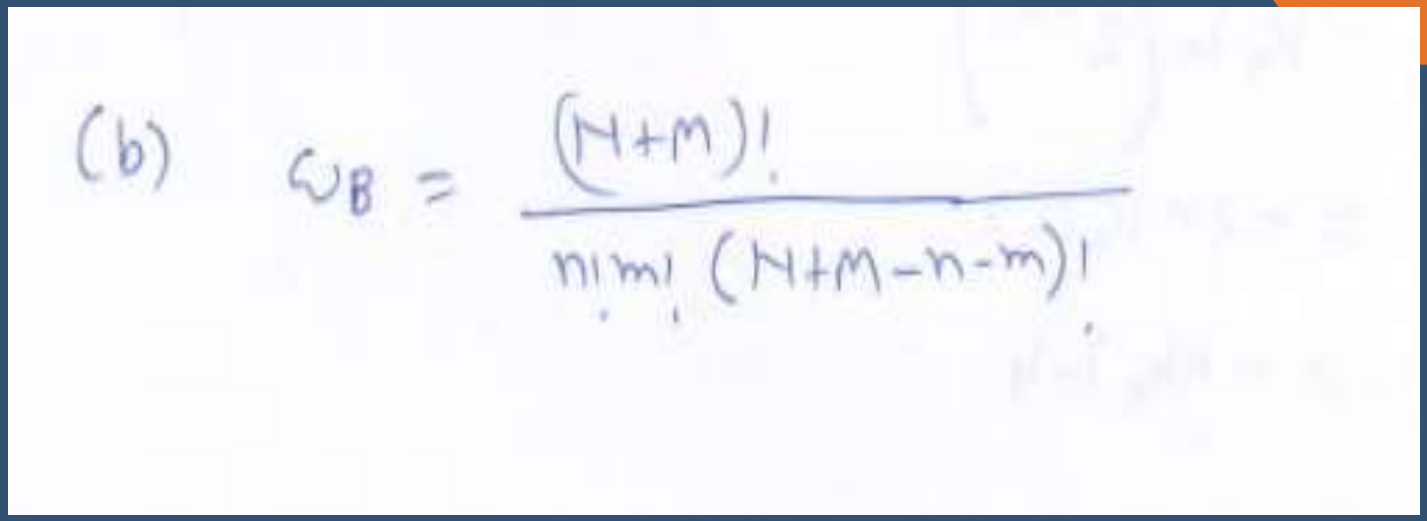
(d) Which state, A or B, has the greatest entropy? Calculate the entropy difference given by $\Delta S = S_A - S_B$, where S_A and S_B are entropies in state A and state B respectively. **[1+1+1+1 Mark]**

PART 1: KEEPING IN MIND THE INDEPEDENCE , USE COMBINATION FORMULA

(a) $\Omega_A = \Omega_N \Omega_m$ since two lattices are independent in state A

$$= \frac{N!}{n!(N-n)!} \times \frac{M!}{m!(M-m)!}$$

PART 2: COMBINE THE SYSTEM(N+M) AND USE COMBINATION FORMULA.SELECT n from N+M. Then select m from rest N+M-n. The vice versa case also gives same result



PART 3: Use Stirling approx

$$\ln n! = n \ln n - n$$

(c) Now $N=n$ and $m=n$

$$\Rightarrow \frac{\omega_A}{\omega_B} = \frac{(N!)^2 (2N-2n)!}{(2N)!\,[(N-n)!]^2}$$

$$\ln \frac{\omega_A}{\omega_B} = 2\ln(N!) + \ln(2N-2n)! - \ln(2N)! - 2\ln(N-n)!$$

$$= 2\left[N\ln N - N + (2N-2n)\ln(2N-2n) - (2N-2n) - 2N\ln 2N + 2N - 2(N-n)\ln(N-n) + 2(N-n)\right]$$

$$= 2N\ln N - 2N - 2N + 2n + 2N + 2N - 2n + (2N-2n)\ln(2N-2n) - 2N\ln 2N - 2(N-n)\ln(N-n)$$

$$= -2N\left[\ln 2N - \ln N\right] + 2(N-n)\left[\ln(2N-2n) - \ln(N-n)\right]$$

$$= -2N\ln[2] + 2(N-n)\left[\ln 2\right]$$

$$= \ln 2\left[-2N + 2N - 2n\right] = \ln 2\,(-2n)$$

$$\Rightarrow \frac{\omega_A}{\omega_B} = 2^{-2n}$$

PART 4 : Use entropy formula involving microstates

(d) $\Delta S = S_A - S_B$

$= k_B \ln \Omega_A - k_B \ln \Omega_B$

$= k_B \ln \left(\frac{\Omega_A}{\Omega_B} \right)$

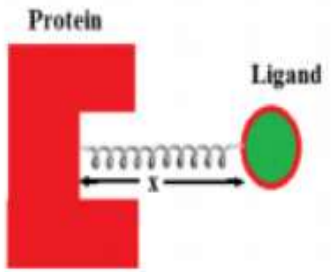
$= k_B \ln \left(2^{-2n} \right)$

$= -2n k_B \ln 2$

$= -n k_B \ln 4$

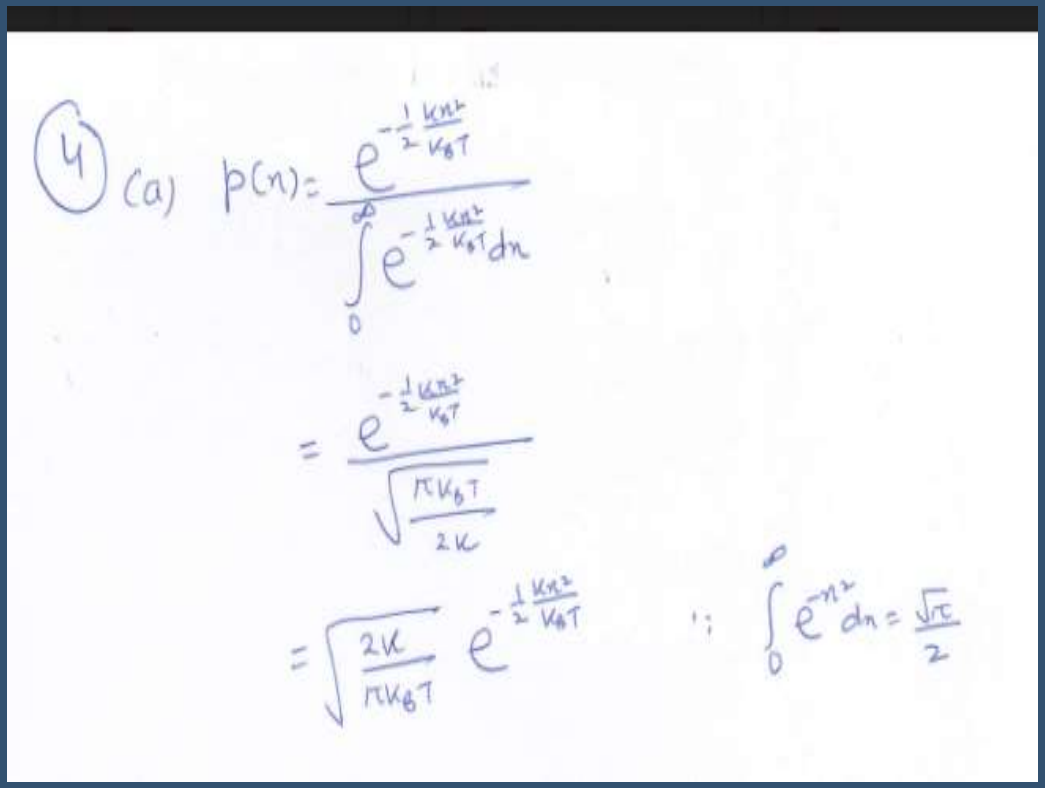
QUESTION 3: WEIGHTED AVERAGES

Consider a ligand bound to a protein with a spring-like square-law energy $\varepsilon(x) = (1/2)kx^2$, where x is the distance between the ligand and protein as shown in figure below and k is a constant

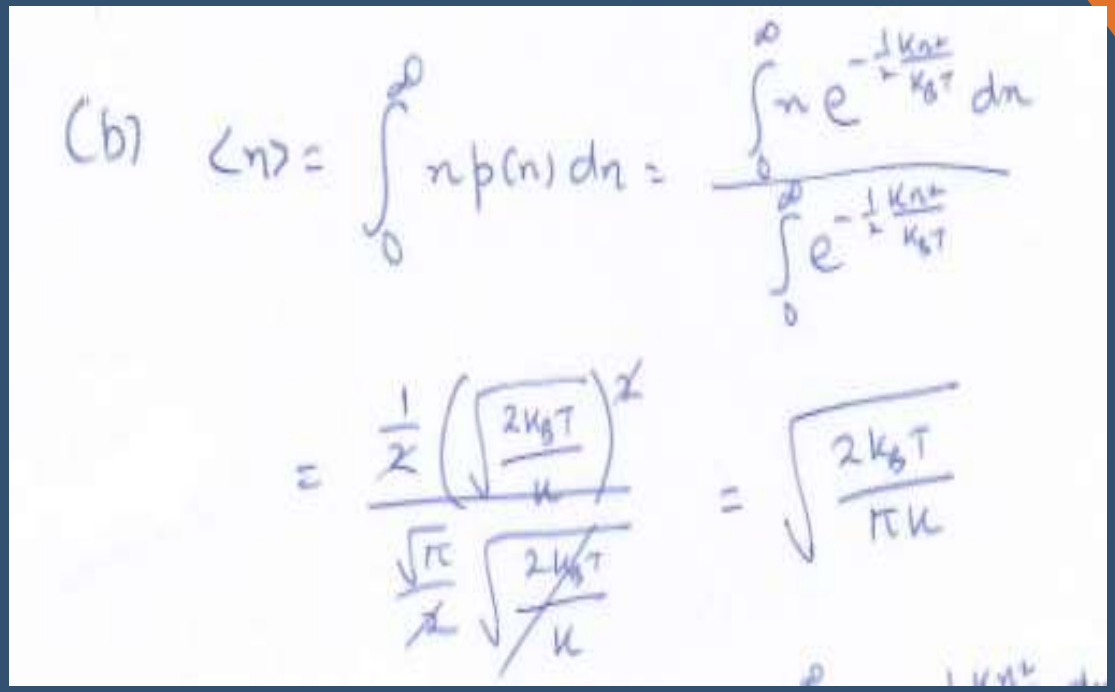


(a) Derive expression for the probability distribution $p(x)$ of the ligand separation from the protein.
(b) Find out the average location of the ligand, $\langle x \rangle$.
(c) Find out the second moment of the location of the ligand i.e. $\langle x^2 \rangle$.
(d) Calculate the average energy of the system, $\langle \varepsilon \rangle$

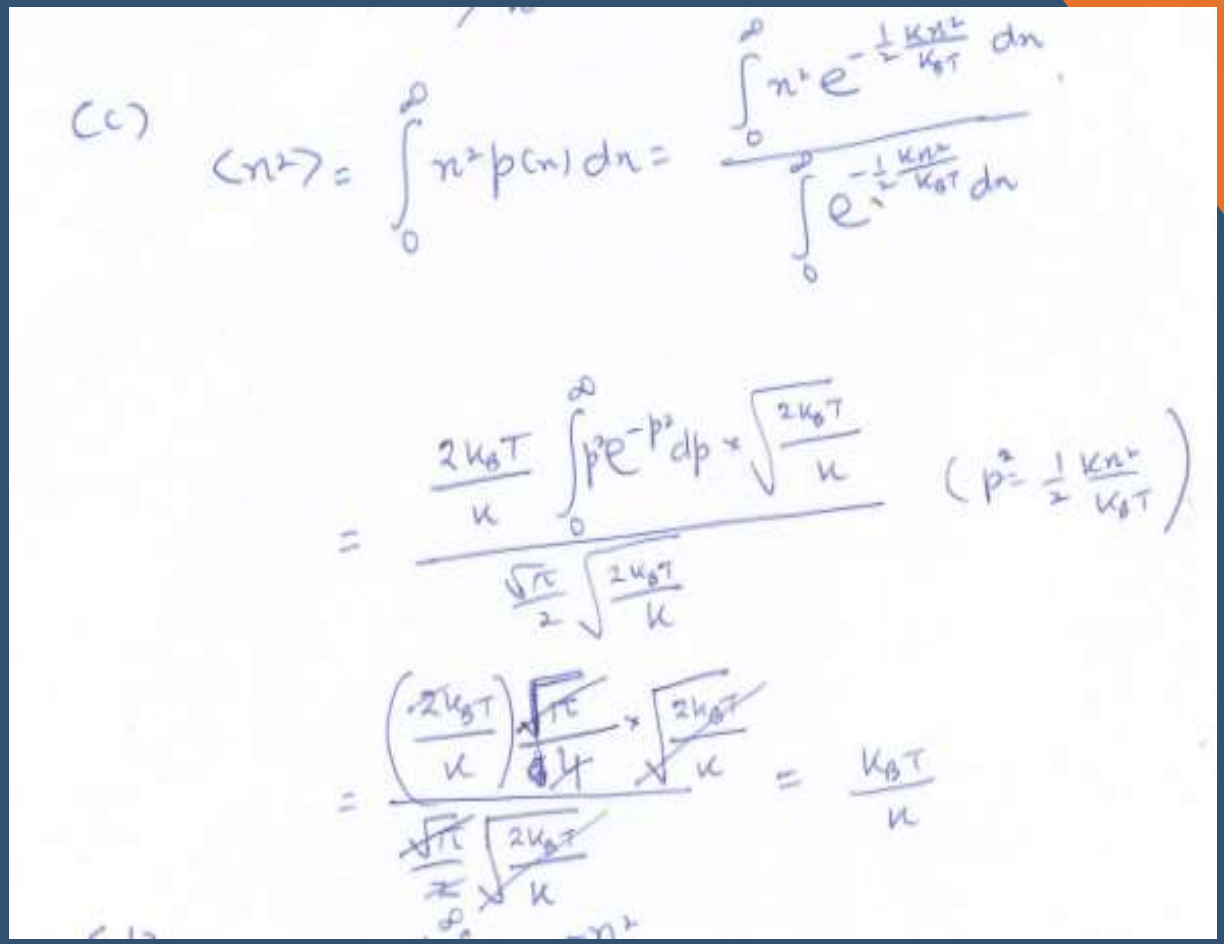
PART 1: Use Boltzmann formulas . Remember here the partition function is continuous



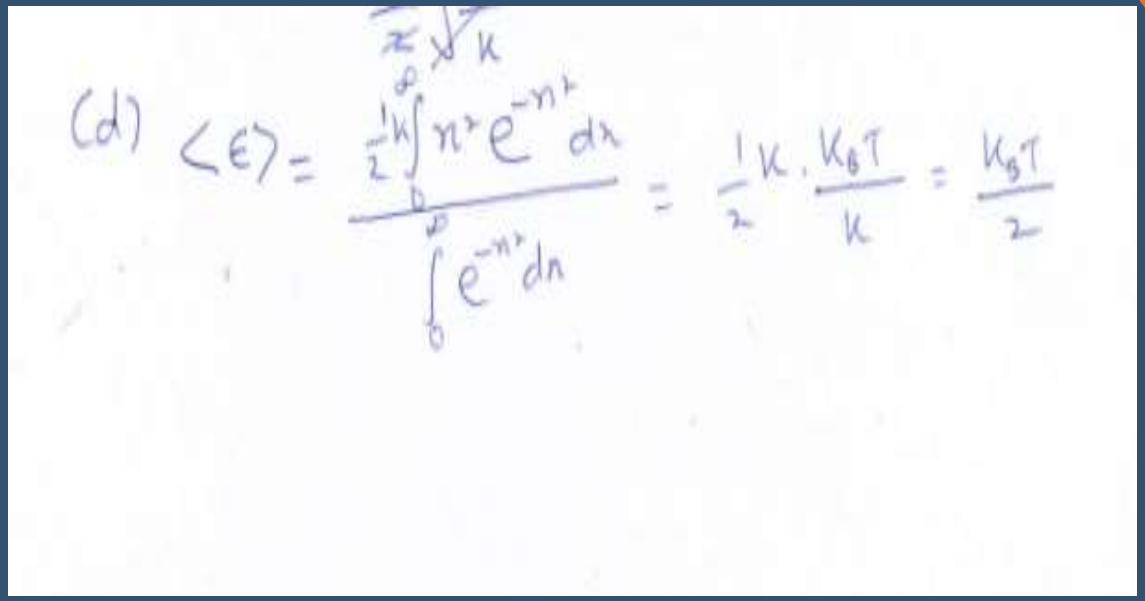
PART 2 : USE WEIGHTED AVERAGE



PART 3:SAME AS PREVIOUS

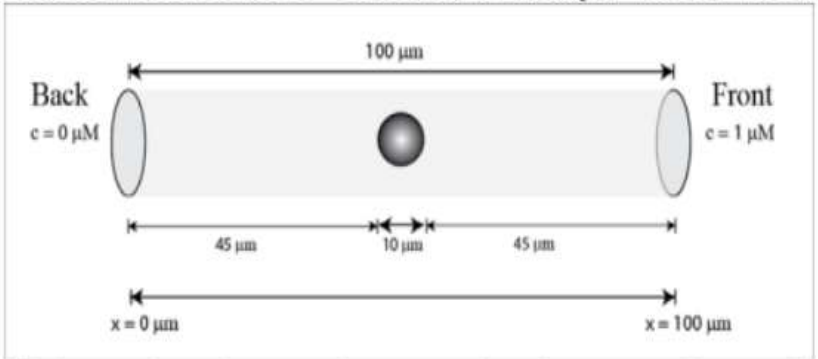


PART 4:WEIGHTED AVERAGE OF ENERGY TERMS



QUESTION 4:DIFFUSION EQUATION

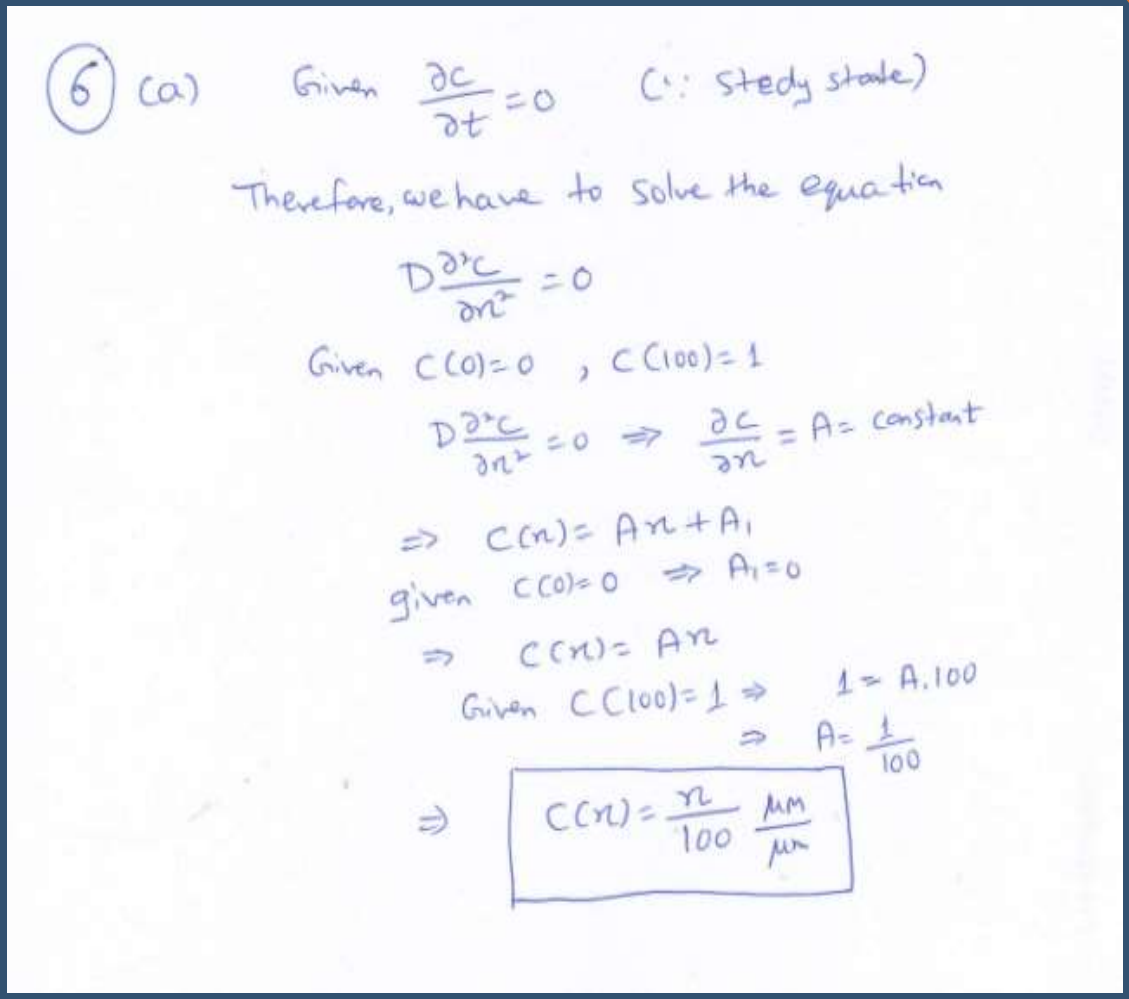
Some cells have the ability to undergo chemotaxis i.e. the cell can sense a gradient of a chemical attractant from its front to its back, and move in the up-gradient direction. Figure below shows a cell that is initially stationary in the middle of a tube. The tube is 100μm long and the cell can be approximated as sphere 10μm in diameter. Independent flows can be used to control the concentration c of an attractant molecule A at each end of the tube. The concentration at the front end of the tube is maintained at 1μM, and the concentration at the back end is maintained at 0 μM. Assume that a steady-state concentration profile has been reached inside the tube at T = 300 K and the viscosity of water is 1 m Pa s.



(a) Solve the diffusion equation and compute the concentration of attractant, c(x), across the tube.
(b) What is the difference in concentration felt by the front of the cell versus the back of the cell?
(c) Upon binding to a receptor on the cell surface, attractant A triggers phosphorylation of another intra-cellular protein, B, at the front-end of the cell. Assume that B can diffuse in the cytoplasm only along the diameter of cell, and does so with a diffusion constant $D = 10^{-10}\ m^2\ s^{-1}$. How long does it take for the phosphorylated protein B to diffuse to the back-end of the cell? Assume cell membrane has zero thickness for this part of question.
(d) Now, instead assume that B is a protein that can only diffuse on outer cell membrane, and it does so with a diffusion constant $D = 10^{-11}\ m^2\ s^{-1}$. How long does it take now for B to diffuse from front-end to the back-end of the cell?

[1.5+0.5+1+1 Mark]

PART 1: USE CONTINUITY EUATION AND FICK'S LAWS ALONG WITH B.C



(6) (a) Given $\frac{\partial c}{\partial t} = 0$ (∵ steady state)

Therefore, we have to solve the equation

$$D\frac{\partial^2 c}{\partial x^2} = 0$$

Given $C(0) = 0$, $C(100) = 1$

$$D\frac{\partial^2 c}{\partial x^2} = 0 \Rightarrow \frac{\partial c}{\partial x} = A = \text{constant}$$

$$\Rightarrow C(x) = Ax + A_1$$

given $C(0) = 0 \Rightarrow A_1 = 0$

$$\Rightarrow C(x) = Ax$$

Given $C(100) = 1 \Rightarrow 1 = A.100$

$$\Rightarrow A = \frac{1}{100}$$

$$\Rightarrow \boxed{C(x) = \frac{x}{100}\ \frac{\mu m}{\mu m}}$$

PART 2: SUBSITUTE THE VALUES IN EXPRESSION OF C AND FIND THE DIFFERENCE

(b) front of cell is located at $x = 55\mu m$

$\therefore C(55) = \frac{55}{100}\ \mu m = 0.55\mu m$

Back of the cell is located at $x = 45\mu m$

$\therefore C(45) = \frac{45}{100}\ \mu m = 0.45\mu m$

$\therefore$ Difference in concentration $= (0.55 - 0.45)\ \mu m$

$= 0.1\ \mu m$

PART 3: Use relation for One Dimensional Equation for x

(c) Time taken can be calculated by using relation $x^2 = 2Dt$

$$\Rightarrow t = \frac{x^2}{2D} = \frac{(10\mu m)^2}{2\times10^{-10} m^2 s^{-1}}$$

$$= \frac{10\times10^{-6}\times10\times10^{-6}\ m^2}{2\times10^{-10}\ m^2 s^{-1}}$$

$$= \frac{10^{-10}\ m^2}{2\times10^{-10}\ m^2 s^{-1}}$$

$$= \frac{1}{2} s = 0.5 \text{ second}$$

PART 3: Use relation for two Dimensional Equation for x

(d) Time taken can be calculated using relation

$x^2 = 4Dt$

$\Rightarrow \quad t = \frac{x^2}{4D}$

$= \frac{x^2}{4D} = \frac{(\pi R)^2}{4D}$

$= \frac{\pi^2 R^2}{4D} = \frac{(3.14)^2 (5\times10^{-6})^2 m^2}{4\times10^{-10} m^2 s^{-1}}$

$= \frac{246.5\times10^{-12}}{4\times10^{-10}} = \frac{2.465\times10^{-10} s}{4\times10^{-10}}$

$= 0.616$ second

$\simeq 0.62$ second

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