

SEMINAR: RELATING LANGMUIR ADSORPTION TO BIOLOGICAL ION CHANNELS

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Today everything is based upon the following

Papers:

- Roux, “Statistical mechanical equilibrium theory of selective ion channels”, *Biophys J*, 1999.
- Im, Wonpil, Stefan Seefeld, and Benoit Roux. "A grand canonical Monte Carlo–Brownian dynamics algorithm for simulating ion channels." *Biophysical Journal* 79.2 (2000): 788-801.
- Swedson, “Statistical Mechanics of Classical Systems with Distinguishable Particles”, *Journal of Statistical Physics*, Vol. 107, Nos. 5/6, June 2002.
- Cheng, “Thermodynamics of the System of Distinguishable Particles”, *Entropy* 2009, 11, 326-333;
- Our arxiv paper.

Books:

- Reif:” *Fundamentals of Statistical and Thermal Physics*”.
- Landau: “*statistical physics*”.
- Newman: “*Monte Carlo methods in statistical physics*”.
- McQuarie: “*Statistical mechanics*”.
- Adamson: “*Physical Chemistry of surfaces*”.

And many more!

Today we will discuss

- ⦿ Background concepts in: statistical theory
- ⦿ Adsorption of gases with a focus on:
Langmuir adsorption
- ⦿ Adsorption of liquids with a non-zero potential equivalent to a simplified version of our model of Coulomb blockade in a channel.

Introduction: Background concepts

- **Microstates**:- represents a microscopic configuration of the system, i.e. the number of states are described by microscopic variables: velocity and position of particles. It is related to entropy (for a closed system) by the 2nd law or Boltzmann's law,

$$S = k \ln \Omega$$

- **Macrostate**:- represents a macroscopic configuration of the system, describable by thermodynamic variables such as: number of particles, internal energy, pressure etc.

Introduction: Background concepts

Typically we describe physical situation with ensembles:

- Ensembles:

- **Microcanonical** (ME)-Isolated system and closed system, thus its energy is fixed. Transitions are only possible between degenerate states, although in a system with a continuum of energy states there may be a continuous set of degenerate levels from which statistical properties can be calculated.

In general however we allow the energy of the system to vary with the introduction of reservoirs [Newman]:

1. **Canonical** (CE)-System coupled to an energy reservoir (open w.r.t energy).
2. **Grand canonical** (GCE)-System coupled to a particle and energy reservoir (open w.r.t energy and number of particles).

- Note that **all ensembles are equivalent** when the system is large [Reif].

Introduction: Background concepts

- Free energy represents the amount of work that can be achieved or the energy that can be converted to work.

Helmholtz free energy: $F = U - TS$

Gibbs free energy: $G = U - TS + PV$

Landau free energy (Grand potential): $\Omega = F - \mu N$

- Chemical potential** is defined to be: the potential energy released or absorbed during a phase transition or the energy change when adding a particle,

$$\mu = \frac{\partial F}{\partial N}, \quad \text{or,} \quad F(N+1) - F(N)$$

Continuous and discrete

- Note we can replace the Helmholtz free energy with the Gibbs or even the internal energy.

Ensemble average

- ⦿ This represents the mean of an observable quantity as a function of the microstates, i.e.

$$\langle A \rangle = \sum_i A(u_i)P(u_i)$$

- ⦿ or for solutions

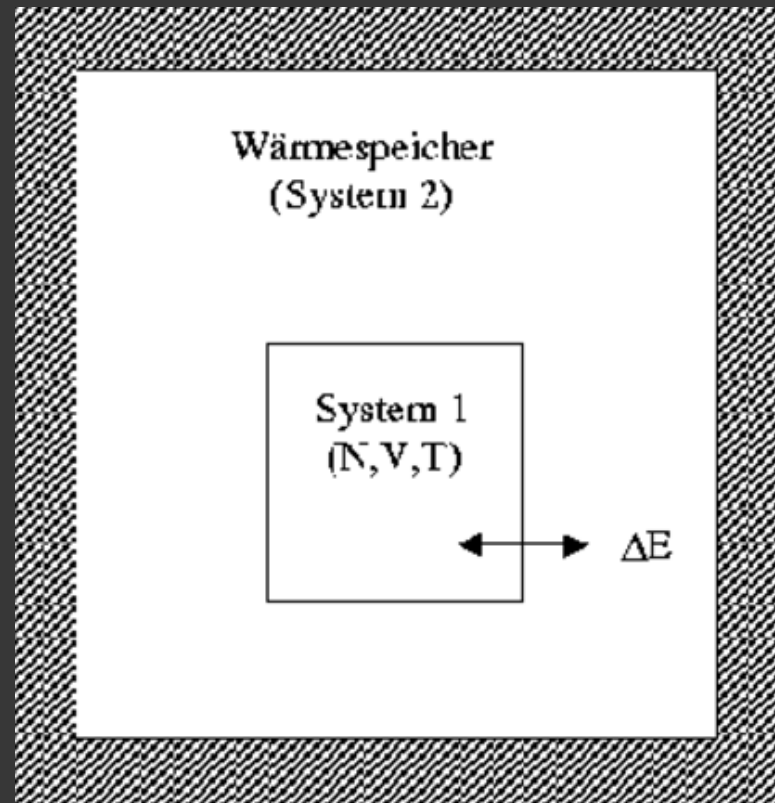
$$\langle A \rangle = \int A(u)P(u) du$$

Example: Consider the average number of particles between states $n=0$ and $n=1$ if there is an equal 50% probability for the particle to be in either state,

$$\langle n \rangle = 0 \times \frac{1}{2} + 1 \times \frac{1}{2} = \frac{1}{2}$$

Introduction: focus on CE

- A system is coupled to an energy reservoir at equilibrium and therefore it is **closed**.
- Energy of the system can vary but total energy is fixed.
- Movement of particles can occur within the system but not between systems and hence the number in the system is fixed.
- The **constant variables** here are: N, V, T , and so we have a constant number of particles.



Introduction: focus on CE

Key points:

- ⦿ A system is coupled to an energy reservoir at equilibrium and therefore it is **closed**.
- ⦿ The **constant variables** here are: N, V, T , and so we have a constant number of particles.
- ⦿ The CE **partition function** has the following form,

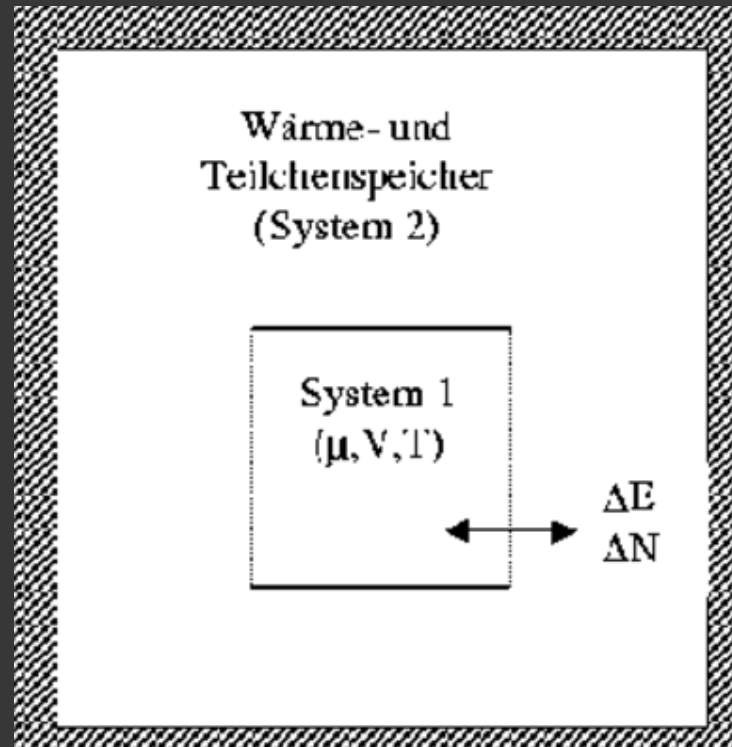
$$N = N_s \text{ and } E_s + E_b = E.$$

$$Z_{ce} = \sum_{\text{micro-states}} \exp \left[\frac{-E(N_s, V_s)}{kT} \right]$$

E represents total energy of the system in the given microstate.

Introduction: focus on GCE

- A system is coupled to a particle and energy reservoir at equilibrium hence it is **open**.
- Energy and number of particles can vary in the system.
- It applies to systems of any size; it is only necessary to **assume that the reservoir with which it is in contact is much larger**.



Introduction: focus on GCE

Key points:

- ⊙ A system is coupled to a particle and energy reservoir at equilibrium hence it is **open**.
- ⊙ It applies to systems of any size; it is only necessary to **assume that the reservoir with which it is in contact is much larger**.
- ⊙ The **constant variables** here are: μ, V, T , meanwhile **number of particles** are given by,

$$N_s + N_b = N, \text{ with } N_s \ll N_b, E_s + E_b = E, \text{ with } E_s \ll E_b$$

$$Z_{gce} = \sum_{\text{micro-states}} \exp \left[\frac{N_s \mu - E(N_s, V_s)}{kT} \right]$$

Note this is for distinguishable particles.

Introduction: derive partition function for GCE

- **Goal:** derive partition function.
- **Approach:** expand entropy and relate to no. of microstates.

Define our system (s) to be in contact with our reservoir (b), hence we have

$$N_s + N_b = N, \text{ with } N_s \ll N_b.$$

$$V_s + V_b = V, \text{ with } V_s \ll V_b.$$

$$E_s + E_b = E, \text{ with } E_s \ll E_b.$$

$$S = S_b(N_b, V_b, E_b) + S_s(N_s, V_s, E_s) + S_0(N_b, N_s)$$

S_0 additive components from bulk, system and “configurational degeneracy” i.e. effect of interaction. For **indistinguishable** particles: $S_0 = k \ln \frac{(N_s + N_b)!}{N_s! N_b!}$
and note that if we have **distinguishable** particles then: $S_0 = k \ln(N_s + N_b)!$

- Expand entropy of the reservoir

$$\begin{aligned}
 S_b(N_b, V_b, E_b) &= S_b(N, V, E) + \frac{\partial S}{\partial N} (N_b - N) + \frac{\partial S}{\partial V} (V_b - V) + \frac{\partial S}{\partial E} (E_b - E) \\
 &= S_b(N, V, E) - \frac{\mu}{T} (N_b - N) + \frac{P}{T} (V_b - V) + \frac{1}{T} (E_b - E)
 \end{aligned}$$

Now because $S_b \gg S_s$ we neglect it and find the total entropy as,

$$S = S_b(N, V, E) - \frac{\mu}{T} (N_b - N) + \frac{P}{T} (V_b - V) + \frac{1}{T} (E_b - E) + k \ln \frac{(N_s + N_b)!}{N_s! N_b!}$$

- Now we know that probability is directly proportional to the number of microstates in the system+reservoir and hence

$$P = C\Omega \text{ therefore } C = 1/\sum \Omega$$

- and **No. of micro-states** is related to entropy by,

$$\Omega = \exp[S/k]$$

Note to use the 2nd law we must have a finite or total number of particles i.e. reservoir+system is closed (i.e. it is equivalent to the CE).

- Thus we can find the number of microstates as,

$$\Omega = \exp \left[\frac{S_b(N, V, E) - \frac{\mu}{T}(N_b - N) + \frac{P}{T}(V_b - V) + \frac{1}{T}(E_b - E) + k \ln \frac{(N_s + N_b)!}{N_s! N_b!}}{k} \right]$$

A constant that factors out.

- And because it is proportional to P and $\sum P = 1$, the **partition function** is given by the sum over all microstates of Ω ,

$$Z = \sum_{\text{micro-states}} \frac{1}{N_s!} \frac{N!}{N_b!} \exp \left[\frac{N_s \mu - P V_s - E_s}{kT} \right] \approx \sum_{\text{micro-states}} \frac{1}{N_s!} \exp \left[\frac{N_s \mu - E(N_s, V_s)}{kT} \right]$$

Energy of each microstate includes pressure contribution

Introduction: Adsorption

- **Adsorption** represents the process by which particles (an adsorbate) attach to a surface (adsorbent) and it can occur in two forms;

1) **Physical**-lower strength adsorption associated with van-der-Waals forces and hence reversible.

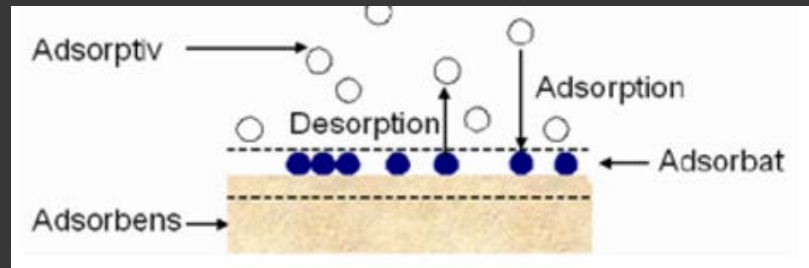
2) **Chemical**-higher strength adsorption with any chemical forces as such irreversible.

Adsorption can have a single (mono-layer) occupation of binding sites or multiple occupation. We focus on the single occupancy type which is known as **Langmuir adsorption**.

Introduction: Langmuir adsorption

Based upon the following assumptions

- All binding sites are equivalent, hence we can divide into two groups vacant and occupied.
- Each site can hold at most one molecule.
- Zero interactions between molecules at each site and their adjacent occupied sites. i.e. completely random surface process.
- The system is at equilibrium.



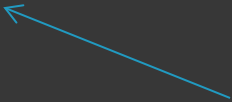
Introduction: Statistical description of Langmuir adsorption

Checklist:

- **Equilibrium** in the system but varying number of particles in the system.
- A well defined system and a particle and energy reservoir.
- Indistinguishable particles and indistinguishable sites.

Describable by the **GCE**.

All sites are equally probable to be occupied



Introduction: How does it relate to ion channels

- ⦿ In our ion channel model we consider indistinguishable sites and typically reduce to the transition between: N to $N+1$ ions which is equivalent to the 0 to 1 transition (with some energy cost).
- ⦿ There are no other channels to interact with but also all sites are assumed to be indistinguishable and hence there is no interaction between sites.
- ⦿ The 1D motion and geometry constraints ensure only 1 ion occupies each site.
- ⦿ Experimentally single channels are known to display MM saturation of current a closely related phenomena.

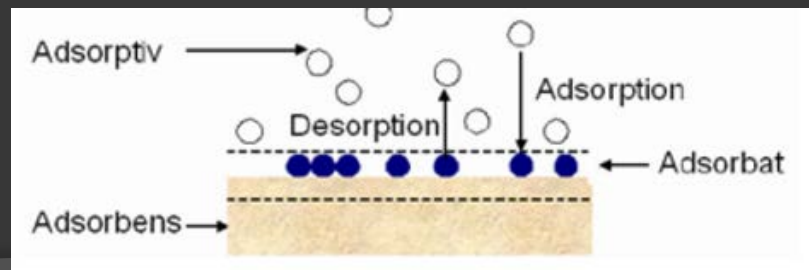
How does it differ from our channel theory

- ⦿ There are some subtle differences.
- ⦿ In our channel theory we consider a liquid solution rather than a gas (although liquid adsorption is discussed).
- ⦿ As such water molecules and ions fill the channel so that although our occupancy (of ions) fluctuates each site is filled by some particle. This has a slight effect on the chemical potentials which I will discuss later.

Derivation of the Langmuir adsorption: ideal gas

- First of all we will consider a classical ideal gas interacting with a surface.
- The goal is to write the occupancy of the surface in terms of macroscopic variables such as pressure.
- Occupancy is related to the mean number of particles (ensemble average).

Example 1: consider adsorption and desorption between an indistinguishable ideal gas cloud and a surface. We introduce the notation that s implies surface and b the bulk, K means total number of sites.



Derivation of the Langmuir adsorption: ideal gas

- First of all we will consider a classical ideal gas interacting with a surface.
- The **goal is to write the occupancy of the surface in terms of macroscopic variables such as pressure.**
- As shown the partition function can take the following form,

$$Z_{gce}(\mu, V, T) = \sum_{N=0}^K \exp\left[\frac{N\mu}{kT}\right] \frac{\zeta^N}{N!} \frac{K!}{(K-N)!} = (1+x)^K$$

$$x = \zeta \exp[\mu/kT]$$

And the **Grand potential** is given by,

Binomial expansion

$$\Omega = \langle E \rangle - TS - \mu \langle N \rangle, = -kT \ln (Z_{gce})$$

Can define **occupancy** of the surface

Can be written as Helmholtz free energy $\langle F \rangle$

$$\frac{\partial \Omega}{\partial \mu} = -\langle N \rangle \Rightarrow \theta = \frac{\langle N \rangle}{K} = \frac{\zeta \exp[\mu/kT]}{1 + \zeta \exp[\mu/kT]}$$

Derivation of the Langmuir adsorption: ideal gas part 2

- Goal: write the occupancy in terms of macroscopic variables.
- Approach: calculate the chemical potential.
- Target the chemical potential of the bulk particles knowing it is equivalent to the chemical potential on the surface.

h because we cannot specify position and momentum together.

$$F = kT \ln Z_{ce} \text{ and } Z_{ce} = \frac{1}{N_b! h^{dN_b}} \int \int \exp[-H(p, q)/kT] \prod dpdq$$

- The Hamiltonian represents the total energy and is given by,

Potential not volume!

$$H = T(p) + V(q)$$

- Assuming ideal gas and zero potential the Hamiltonian becomes,

$$H = \frac{1}{2m} p^2 + 0$$

- And hence chemical potential (remember derivative of free energy),

$$\mu = -kT \ln \left(V \left(\frac{2\pi m kT}{h^2} \right)^{\frac{3}{2}} \right)$$

Ideal gas Hamiltonian consists of: translational, electronic and rotational components. The latter two are small and the translational component gives the kinetic energy terms. [McQuarrie]

We lose the N! in the derivation process

V is volume of the "system" in this case the gas cloud

Discuss pressure here

- ⦿ Although chemical potential is dependent on V we often want this in terms of pressure.
- ⦿ In mixed species (i) the pressure often used is the partial pressure ,

$$p_i = p \times x_i \text{ where } p = \sum_i p_i$$

- ⦿ Although of course with a single species $x_i = 1$.
- ⦿ We can derive our ideal gas law from

$$p = -\frac{\partial F}{\partial V} \text{ therefore } pV = kTN \text{ [Landau]}$$

- ⦿ Hence we can relate volume to pressure.

Pressure in a liquid

- One of the conditions of equilibrium is that the pressure of the channel and bulk are equivalent to each other. Hence calculable from,

$$P = - \frac{\partial \Omega}{\partial V}$$

- However **if** we considered a semi-permeable membrane such that water particles cannot enter the channel then a pressure difference “**Osmotic pressure**” exists.
- This controls the flow of ions (solvent) until the water chemical potential equilibrates.

Osmotic pressure

- ◉ In which case the osmotic pressure equals,

$$P_{OS} = P_b - P_s$$

- ◉ And it can easily be shown [Landau], by expanding the chemical potential around P_{OS} (because it is small), and if the number of ions in the bulk is \gg than the channel we can recover an equation similar to the ideal gas equation,

$$P_{OS}V = nkT$$

- ◉ Another assumption in this model is of dilute solutions such that the ion-ion interaction is neglect-able (although the ion-water interaction isn't).

Derivation of the Langmuir adsorption: ideal gas part 3

- Thus upon substitution we arrive at our final result that occupancy can be written in terms of pressure as,

$$\theta = \frac{p}{p_0 + p} \text{ where } p_0 = \frac{kT}{\zeta} \left(\frac{2\pi m kT}{h^2} \right)^{3/2}$$

- Applying a stress i.e. pressure to a system at equilibrium causes the nature of the equilibrium to shift Le Chatelier's principle.

Some comments

- ⦿ **Saturation of occupancy** similar to MM.
- ⦿ If we **reduce to our system of a single channel** $K=1$, with the following changes;
 - The GCE partition function resembles the FD version because we only have two states 0 and 1. Although it actually represents a classical exclusion principle partition function because we have a classical gas [Landau].
 - Occupancy is solely given by the mean number of particles $\langle N \rangle$ and is of course therefore the same. Thus our final result is the same.

Discussion: What changes when we add a non-zero potential to the gas

- If we add a non-zero potential then the Hamiltonian is more complicated and an immediate analytic solution is rarely possible.
- This additional integral is known as a **configurational integral**.

$$H = T + V$$

- This potential term V must be integrated over the d -dimensional position coordinates.

$$\int \exp\left[\frac{-V}{kT}\right] dx_1 dy_1 dz_1 \dots dz_N \approx \exp\left[-\frac{N\bar{\mu} + N\bar{\phi}}{kT}\right]$$

- To analytically solve it we will assume a mean field and so each ion is influenced by a mean voltage and hydration effect and hence,

What changes when we move to a liquid

- ⦿ A solution must be electrically neutral and so immediately we have a minimum of three species (water, cation and anion).
- ⦿ Although because the anion cannot enter the channel I will ignore it because it represents a constant energy term.
- ⦿ This mixture means that we have an additional entropy factor from mixing and this leads to the notion of mole fraction or concentration.
- ⦿ Note in what lies ahead I neglect the presence of a) anions and b) water although I include the mole fraction.
- ⦿ This is because the mole fraction is very close to 1, it is electrically neutral and so doesn't undergo influence from voltage potential, it doesn't dehydrate so I assume the difference in excess chemical potentials as small, and most importantly we are talking about adsorption or single molecule occupancy of a site. (although if we consider knock-on of ions then the water molecules would represent a constant energy term to be added.)

Derivation of the Langmuir adsorption for liquids and ICB effects

- ◉ **What changes:** we have to account for **mixing** of the solutions, we can't make use of our **ideal gas law** because of the hydration interaction (hence $\bar{\mu}$ is a function of volume), we have to introduce a potential.
- ◉ Introduce little n and script c to mean in the channel, meanwhile b implies bulk..
- ◉ Total number of particles: $N = N^b + n$ and b imply channel.
- ◉ We will account for all ICB effects here as seen in our channel, so we introduce the **simplified Gibbs free energy**,

$$G = \epsilon(n) + nq\phi^c + n\bar{\mu}^c + N^b q\phi^b + N^b \bar{\mu}^b + kTN^b \ln(x) + kT \ln n! + E_0$$

Interaction with channel charge, channel voltage and hydration.

Mean field voltage, hydration and mole fraction from mixing in the bulk.

- ◉ Also we are neglecting effect of water (although including mole fraction) for this simplified example!

Derivation of the Langmuir adsorption for liquids and ICB effects

$$G = \epsilon(n) + nq\phi^c + n\overline{\mu^c} + N^b q\phi^b + N^b \overline{\mu^b} + kTN \ln(x_i) + kT \ln n! + E_0$$

- Hence our Gibbs free energy represents energy levels of the system plus a chemical potential i.e. it is written in the form

$$G = P_e + \sum n_i \mu_i$$

- First derive chemical potential for the bulk solution, so proceed as before.

There should be a similar permutations factor for number of sites K and water molecules, and it slightly varies if we enforce the rule of at least one water molecule between sites. (for more details see the arxiv paper).

Derivation of the Langmuir adsorption for liquids and ICB effects

$$Z_{ce} = \frac{1}{N^b! h^{dN^b}} \int \int \exp[-H(p, q)/kT] \prod dpdq$$

$$\approx \left(\frac{2\pi mkT}{h^2}\right)^{\frac{3}{2}N^b} \times (-x^{N^b}) \times \exp\left[-\frac{N^b q \bar{\phi}^b + N^b \bar{\mu}^b}{kT}\right]$$

Obviously would have water terms here

- Where we have defined all ion energy terms with a mean field $\bar{\phi}$ or $\bar{\mu}$ i.e. using the configurational integral defined earlier and we have included the water molecules via mixing and the kinetic energy.
- Hence our chemical potential takes the form (3D),

$$\mu = -kT \left(\ln \left(\frac{2\pi mkT}{h^2} \right)^{\frac{3}{2}} - \ln(x) + \left(-\frac{q \bar{\phi}^b + \bar{\mu}}{kT} \right) \right)$$

Discussion about deriving chemical potential from the channel

- Discrete energy levels in the channel ensure that the channel is either fixed (blockade) in one configuration or can fluctuate between two (resonant).
- Hence the channel chemical potential is calculated by time averaging the energy (equivalent to averaging over all microstates which occur with the same frequency Ergodic hypothesis). Hence chemical potential is,

$$\Delta\epsilon(n) + q\phi^c + \overline{\mu^c} + kT \ln n!$$

- And hence at resonant transition between channel and bulk we recover the barrier-less knock-on conditions of CB,

$$\mu^c = \mu^b \text{ therefore}$$

$$\Delta\epsilon(n) + q\phi^c + \overline{\mu^c} = -kT \left(\frac{3}{2} \ln \left(\frac{2\pi mkT}{h^2} \right) - \ln(x) - \frac{q\overline{\phi^b} + \overline{\mu^b}}{kT} \right)$$

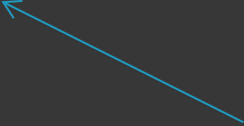
- ◉ We factorise our free energy to find:

$$G = \epsilon(n) + nq\phi^c + n\bar{\mu}^c + (N - n)q\phi^b + (N - n)\bar{\mu}^b + kT(N - n)\ln(x_i) + kT\ln n! + E_0$$

- ◉ Thus our partition function takes the form,

$$Z_{gce} = \sum \frac{1}{n!} \exp[(-\epsilon(n) - nq\phi^c - n\bar{\mu}^c + n\mu)/kT]$$

Can factor out the constant terms



- ◉ Which we can immediately see from our derivation earlier,

$$Z = \sum_{micro-states} \frac{1}{N_s!} \frac{N!}{N_b!} \exp \left[\frac{N_s\mu - PV_s - E_s}{kT} \right] \approx \sum_{micro-states} \frac{1}{N_s!} \exp \left[\frac{N_s\mu - E(N_s, V_s)}{kT} \right]$$

- Thus our partition function takes the form,

$$Z_{gce} = \sum \frac{1}{n!} \exp[(-\epsilon(n) - nq\phi^c - n\bar{\mu}^c + n\mu)]/kT]$$

- Where again,

$$\mu = -kT \left(\ln \left(\frac{2\pi mkT}{h^2} \right)^{\frac{3}{2}} - \ln(x) + \left(-\frac{\overline{q\phi^b} + \bar{\mu}}{kT} \right) \right)$$

- Note that because of the polynomial dependence on n in the electrostatic energy we can't binomially expand!
- We will derive in general with the sum over microstates before reducing to a Langmuir adsorption i.e. by considering two levels 0 and 1.

- The occupancy is thus given by,

$$\langle n \rangle = \frac{\sum n \frac{1}{n!} \exp[(-\epsilon(n) - nq\phi^c - n\bar{\mu}^c + n\mu)/kT]}{Z_{gce}}$$

Sum over
micro-states i.e.
states of the
channel

$$\langle n \rangle = \frac{\sum n \times x \times \left(\frac{2\pi mkT}{h^2}\right)^{-\frac{3}{2}} \frac{1}{n!} \exp[(-\epsilon(n) - nq\phi^c - n\bar{\mu}^c + n(q\phi^b + \bar{\mu}^b))/kT]}{Z_{gce}}$$

- We can't simplify further because of the electrostatic term, and the fact that we are dealing with a liquid.
- So we shall consider a the two state example similar to adsorption.

Example: reducing to a two state system

- Why is this system relevant in a multi-occupied channel?- Even though KcsA is known to be a multi-ion channel the optimal transport regime is the transitions between 2 and 3 occupying ions via knock-on.
- What does it mean?-We only consider the states 2 and 3 which is equivalent to 0 and 1 states of occupancy with some constant energy difference.
- What should we expect?-A sigmoid function dependent on the energy levels i.e. Langmuir adsorption.

Example: reducing to a two state system (0 and 1)

- Occupancy reduces to,

- $\langle n \rangle =$

$$\frac{x \times \left(\frac{2\pi m k T}{h^2}\right)^{-\frac{3}{2}} \exp[(-\epsilon(1) - q\phi^c - \bar{\mu}^c + (q\phi^b + \bar{\mu}^b))/kT]}{\exp[-\epsilon(0)/kT] + x \times \left(\frac{2\pi m k T}{h^2}\right)^{-\frac{3}{2}} \exp[(-\epsilon(1) - q\phi^c - \bar{\mu}^c + (q\phi^b + \bar{\mu}^b))/kT]}$$

$$= \frac{x}{\left(\frac{2\pi m k T}{h^2}\right)^{\frac{3}{2}} \exp[(\Delta\epsilon + q\phi^c + \bar{\mu}^c - (q\phi^b + \bar{\mu}^b))/kT] + x}$$

- Saturation of occupancy with concentration.

Summary

- Introduced key statistical theory concepts.
- Derived the Langmuir adsorption occupancy relation between a gas and a surface.
- Derived occupancy for a liquid with CB potential energy interactions.