I: Life and Energy

- Lecture 1: What is life? An attempt at definition.
- Energy, heat, and work: Temperature and thermal equilibrium. The First Law. Thermodynamic states and state functions. Reversible and real processes. The Second Law and free energy. Why do living systems need energy? (B Lentz)

- Lecture 2: Solutions and chemical potential; Osmotic pressure (B Lentz).

- Lecture 3: Mother Nature plays dice: the Boltzmann distribution, partition functions and en
tropy. (B Lentz)

Chemical Thermodynamics

While Thermodynamics is familiar to engineers and physicists, the thermodynamics most useful in Biophysics is that familiar to chemists: solution, reaction, and phase equilibria.

We have already defined the thermodynamic quantity essential to describing these phenomena, the chemical potential or molar Gibbs free energy:

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{T,P,n_{j\neq i}} = \mu_i^0 + \text{concentration dependent term}$$

We will use this quantity to describe:

1] solutions

2] chemical equilibria

3] phase equilibria

4] binding equilibria

5] osmotic effects

Solutions

We will review four types of solutions:

Ideal Gas: precursor to the ideal solution

Ideal Solutions

Dilute Solutions that behave according to Raoult's and Henry's Laws.

Non-Ideal or Real Solutions.

Ideal Gas

An Ideal Gas is a hypothetical state in which the particles in the gas have a mass but do not interact, and occupy no significant volume.

Boyle observed experimentally that a very dilute gas behaved according to the following equation of state:

$PV=Nk_BT$*

*Note that k_B (Boltzmann constant) has units of energy/temperature/molecule or per mol, depending on the context in which it is used:

1.99 cal/K/mol=8.33J/K/mol or 1.38×10^{-23} J/K in molecular units

From this, you can show that:

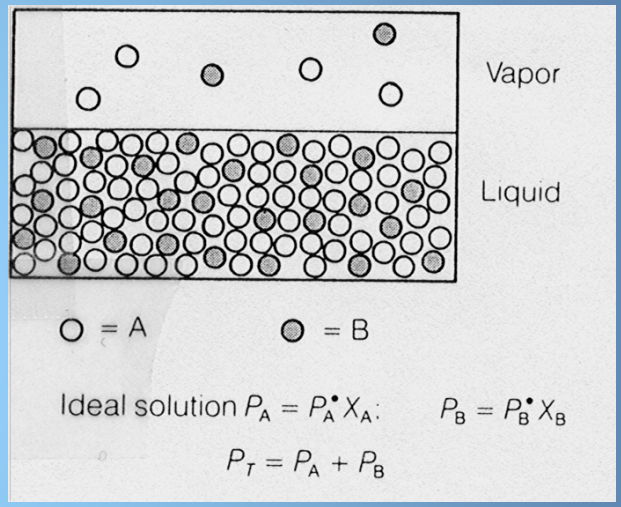
$$\mu = \mu_v^0(T, P=1) + k_B T \ln P = \mu_v^\dagger(T, \frac{N}{V}=1) + k_B T \ln \frac{N}{V}$$

We shall see that this is easily derived from the canonical partition function for a non-interacting particle mixture, but you can derive it from Boyle's Law using the total differential of G.

Ideal Solution

An Ideal Solution might better be called an Ideal Mixture, since, as in an Ideal Gas, no distinction is made between solute and solvent.

In an Ideal Mixture, all components have the same size and they interact with each other uniformly.



All components of an ideal solution have chemical potentials of the form:

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{T,P,n_{j\neq i}} = \mu_i^\bullet + k_B T \ell n X_i$$

$\mu_i^\bullet$ = μ of pure component *i* at T,P.

We can prove this to ourselves using the statistical approaches in Lecture 3.

Real Dilute Solutions

Very low solute concentration:

Henry's Law applies to chemical potentials of solutes.

Raoult's Law applies to chemical potential of low vapor pressure solvent (*e.g.*, water).

Henry's Law

Solutes: $$\mu_i = \mu_{i,x}^{\circ}(T,P) + k_B T \ln X_i = \mu_{i,c}^{\circ} + k_B T \ln c_i$$

Not identical!

NOTE: X_i = mole fraction is the "natural" unit of concentration!

μ_i° is the "unitary" chemical potential

$k_B \ln X_i$ is the "cratic" chemical potential

$$X_i = n_i \Big/ \sum_j n_j$$

μ_i^0 = μ of solute in an imaginary state at unit concentration but surrounded by solvent.

Raoult's Law

Low vapor Pressure Solvent:

$$\mu_0 \approx \mu_{0,L}^{\circ}(T,P) - k_B T \sum_{i>0} X_i$$

μ_0° = μ of pure solvent (component 0) at T,P; standard state for solvent.

∴ dilute solutions often called ideal, but are not!

Real Solutions

$$\mu_i = \mu_{i,x}^{\circ} + k_B T \ln a_i$$

a_i is the activity of component i

$a_i = \gamma_i (X_i) \times X_i$

γ_i = *"activity coefficient"* is a function of X_i!

$\gamma_i (0) = 1$; $\gamma_i \setminus 0$ as X_i increases.

In itself, this expresses nothing and is not very useful! Only if we know γ is it useful. *Useful* when $\gamma = 1 - \varepsilon$, with $\varepsilon << 1$

Conditions of Equilibria

Recall that the basic condition of equilibrium in a system is that the entropy be maximized or, equivalently, that the free energy be minimized.

There are many types of equilibria, but often we are interested in determining the number of molecules present in an open system.

- molecules distributing between two phases
- molecules A & B reacting to form molecule C
- a ligand molecule moving from solution to a binding site on a protein

These are all examples of MASS EQUILIBRIUM in an OPEN SYSTEM.

Equilibrium: Gibbs-Duhem Equation

For Open Systems, the condition that dG = 0 leads to a well known expression for mass equilibrium at fixed T and P.

Recall that Integrating the work function differential dG at fixed T and P ⇨

$$G = \sum n_i \mu_i$$

Write the total differential of G for both n_i and μ_i as variables:

$$dG_{tot} = \sum n_i d\mu_i + \sum \mu_i dn_i$$

Work Function for the Combined 1st and 2nd Law:

$$dG_{WF} = -SdT + Vdp - dw - \sum n_i d\mu_i$$

At Equilibrium, $dG_{tot} = dG_{WF} = 0$

At fixed T, P, and no work done:

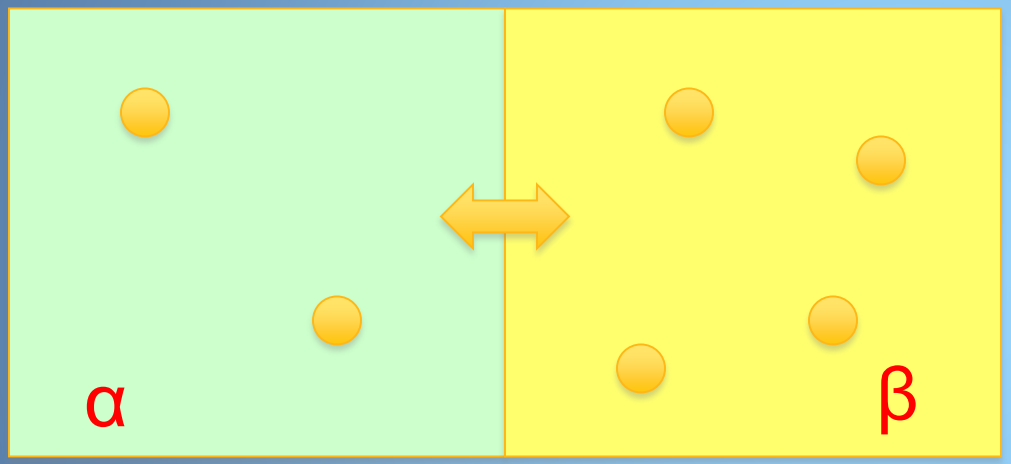
$$\sum n_i d\mu_i = 0$$

This is the famous Gibbs-Duhem Equation.

It established the condition of mass equilibrium in an open system

Gibbs-Duhem 2: Phase Equilibrium

The Gibbs-Duhem Equation establishes the principle that the chemical potentials of the components of a mixture cannot change independently. This provides us with the conditions of phase and chemical equilibrium.



$$\ell n\left(\frac{a_\alpha}{a_\beta}\right) = \frac{\mu_\beta^0}{\mu_\alpha^0} = \ell n K_p$$

Partition coefficient

Balance between unitary and cratic terms

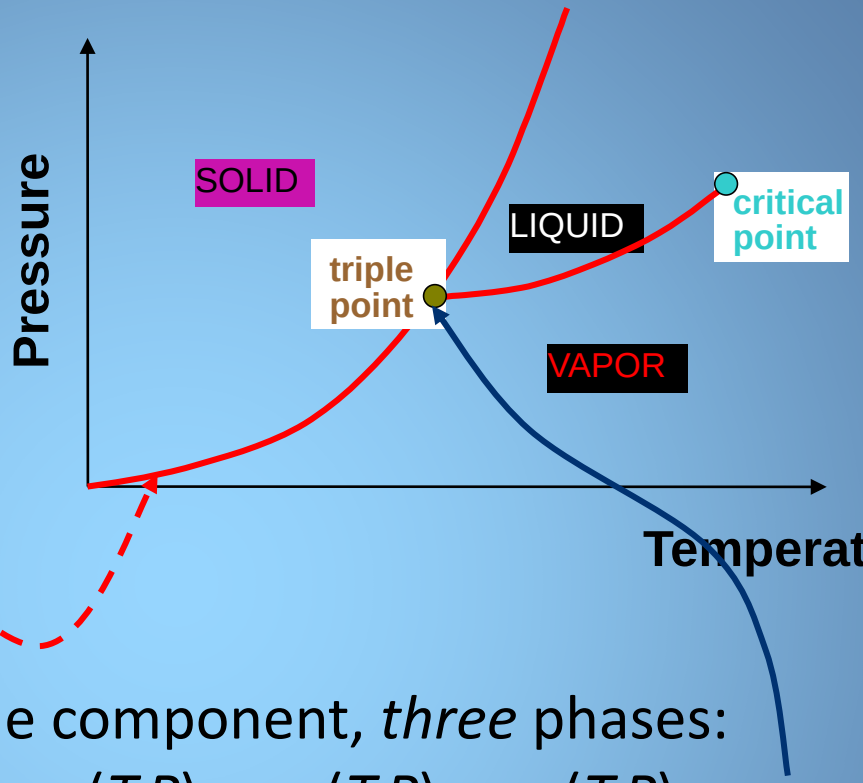
For Phase Equilibrium, the Gibbs-Duhem Equation implies the condition of equilibrium:

$$\mu_i^\alpha = \mu_i^\beta = \mu_i^\gamma = \cdots; \text{ for each } i$$

Single Component Phase Diagram: *T* and *P*

One component, *two* phases:

$$\mu_A(T,P) = \mu_B(T,P)$$



Pick any *T*, then the requirement of phase equilibrium => *P* is defined => a "phase line"

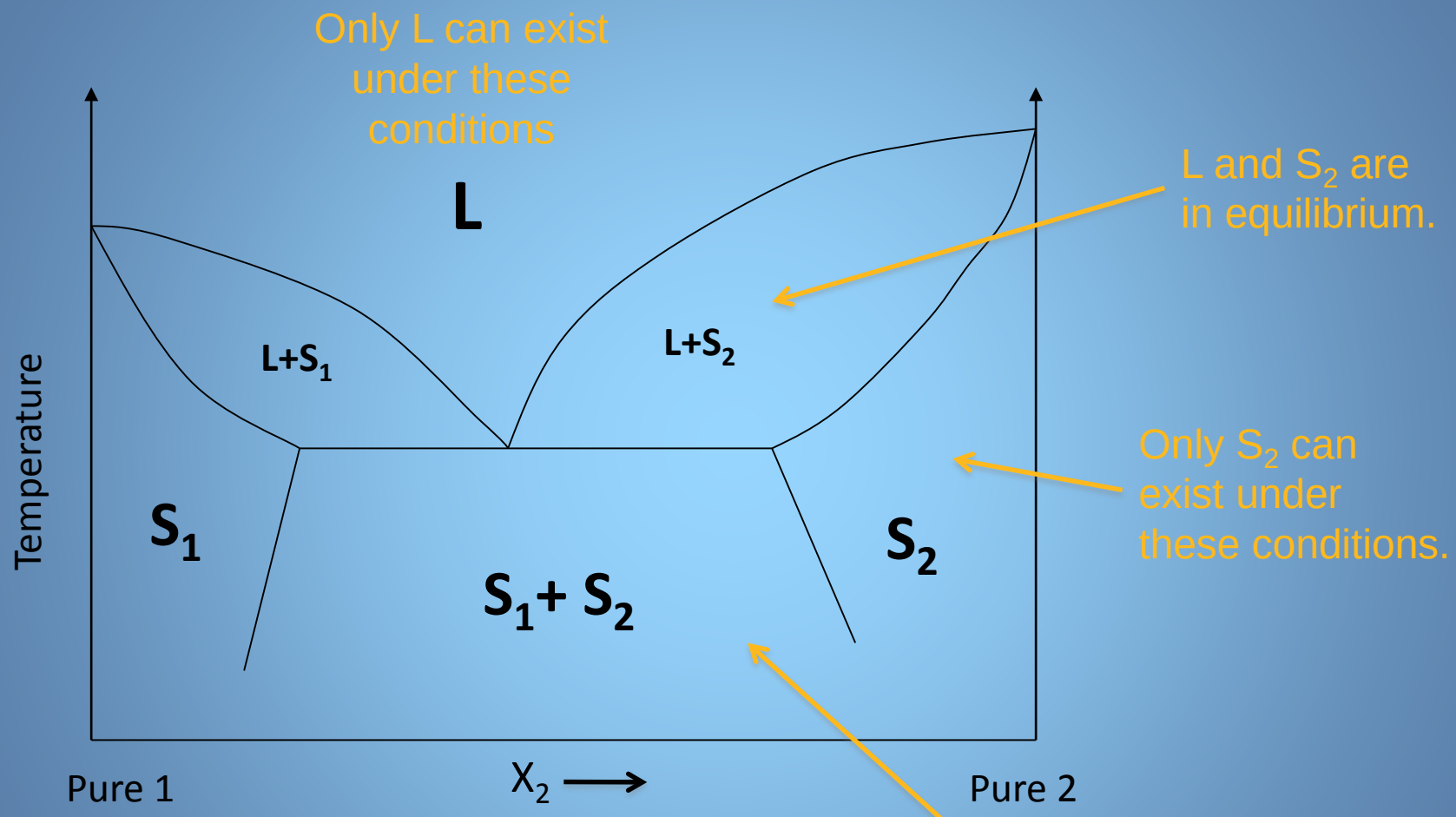
One component, *three* phases:

$$\mu_A(T,P) = \mu_B(T,P) = \mu_C(T,P)$$

Only one pair of values of *T* and *P* can satisfy these two equalities

Gibbs Phase Rule: Deg Freedom = 2 – Phases + Components

Phase Diagrams for Two-Component Systems: T & X_i



Often describes equilibrium between lipids in different "domains" in a biomembrane.

Gibbs-Duhem 3: Chemical Equilibrium

In a chemical reaction, several types of molecules are converted to other types by a rearrangement of electronic motions. Equilibrium is also achieved when there is a balance between the unitary and cratic contributions to the chemical potential of each species.

Any Chemical Reaction can be written as:

$$\sum_j \nu_j M_j$$

where ν_i is the stoichiometry of reactant M_i.

e.g.: 3A+B $\longleftrightarrow$ 2C; ν = -3,-1,2; reactants, products

The change in Gibbs Free Energy (dG) for a small change in extent of reaction (dε) is

$$dG = \sum_j \nu_j \mu_j d\varepsilon$$

This leads to the condition of Chemical Equilibrium:

$$\sum_j \nu_j \mu_j = 0$$

Eq Constant.

$$K_{AB \leftrightarrow C} = \frac{a_C^2}{a_A^3 a_B}$$

$$\sum_j \nu_j \mu_j^0 = -k_B T \sum_j \nu_j \ell n\{a_j\}$$

$$K_{eq} = \prod_j a_j^{\nu_j} = e^{-\sum_j \nu_j \mu_j^0 / k_B T}$$

Cratic Unitary

Chemical Equilibria -2-

Reactants (A) $\longleftrightarrow$ Products (B)

$$-k_B T \ln K_{eq} = -\sum_{i \in \mathbf{A}} \nu_i \mu_i^{\circ} + \sum_{i \in \mathbf{B}} \nu_i \mu_i^{\circ} = \Delta G^{\circ}$$

ΔG^0 = *Standard* Free Energy Change for the reaction = free energy difference between the products and reactants in their standard chemical potential states.

This is a measure of how much the reactants *intrinsically* want to convert to product.

ΔG^0 = negative $\Rightarrow$ product wants to form.

Why not go completely to product???

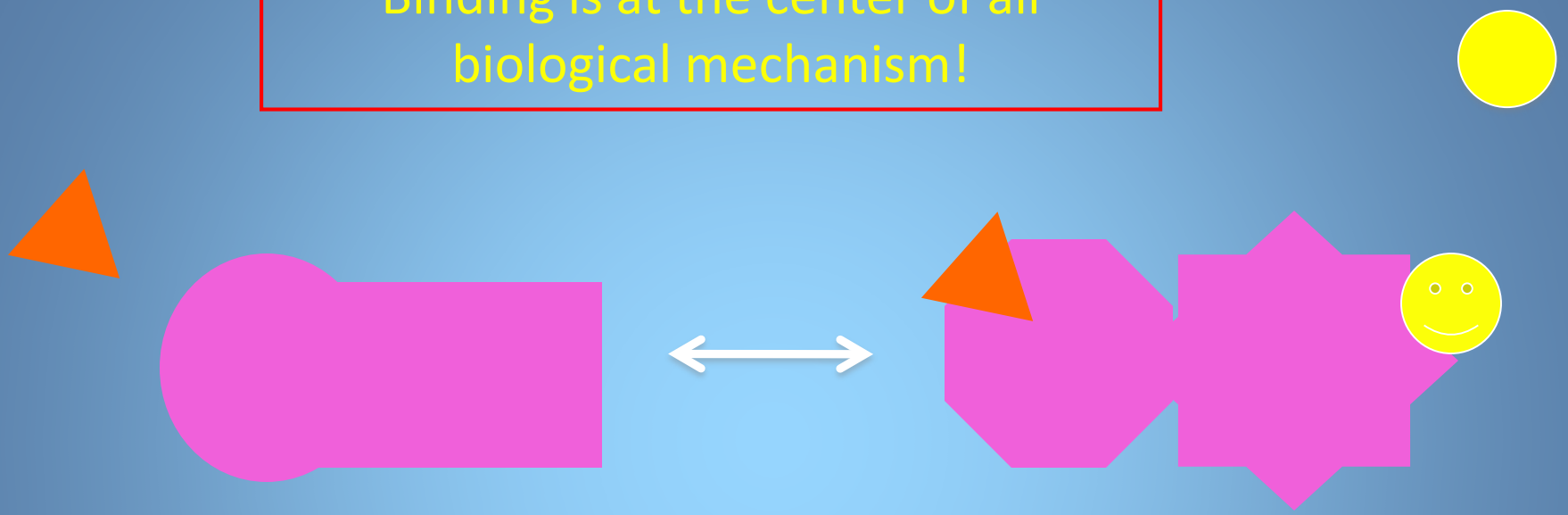
ENTROPY is max when we have a mix of products and reactants. Equilibrium is again the balance between these unitary and cratic effects.

The van 't Hoff equation gives the reaction's standard enthalpy change:

$$\Delta H^{\circ} = \frac{\partial [\Delta G^{\circ} / T]}{\partial [1/T]} = -k_B \frac{\partial \ln K_P}{\partial [1/T]} = k_B T^2 \frac{\partial \ln K_P}{\partial T}$$

Binding Equilibria

Binding is at the center of all biological mechanism!



Binding always reflects a playoff between the favorable free energy (mainly due to a reduction in internal energy) of occupying a binding site (unitary effect) and the unfavorable entropy change (cratic effect) associated with bringing ligands out of solution to binding sites.

The balance between these two effects determines the fraction of sites occupied at any free ligand concentration.

Binding 2

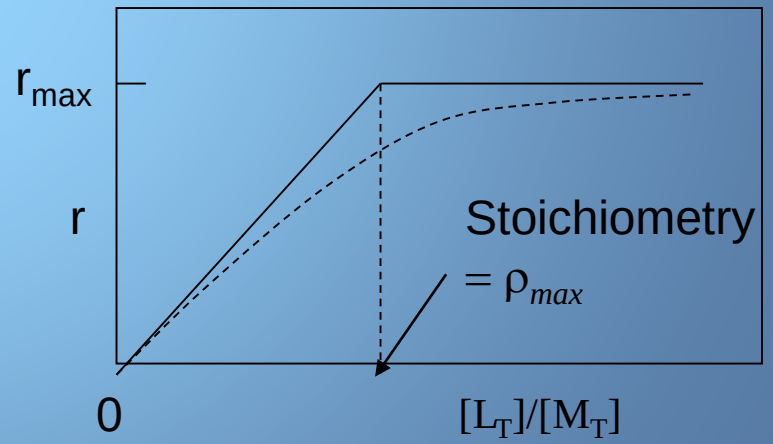
Simplest Case: single ligand to a single site on a "macromolecule" (M)

$$M + L \leftrightarrow ML$$

The "site association constant" (K_a) is simply the equilibrium constant for this reaction, where [L] is free ligand concentration. From this, one easily obtains the fraction of sites occupied, *v*.

$$K_a = \exp\left\{\frac{\mu^0_{ML} - \mu^0_L - \mu^0_M}{k_B T}\right\} = \frac{a_{ML}}{a_L a_M}; \quad \nu = \frac{K_a a_L}{1 + K_a a_L}$$

$$\Delta G^0 = \mu^0_{ML} - \mu^0_L - \mu^0_M = \text{unitary site binding free energy}$$



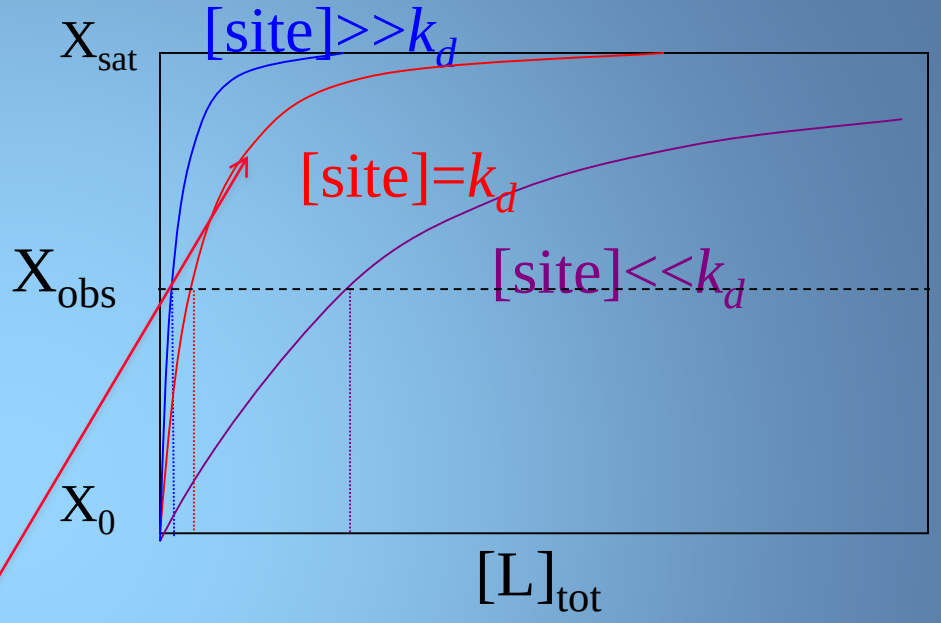
If M contains *n* equivalent sites, the number of ligands bound, *r*, is easily obtained. Here the equilibrium constant, κ, is a "stoichiometric" binding constant for the association of *n* ligands with M.

$$\kappa = \frac{[ML_n]}{[M][L]^n}; \qquad r = \frac{n k_a [L]}{1 + k_a [L]}$$

Detecting Binding

Direct Measurement: measure "ligand" [L] and "protein-ligand complex" [PL] by equilibrium dialysis or by potentiometric measurement of free ligand activity (a_L) *versus* total protein concentration ([P]).

Most often, measure a quantity X that is proportional to [PL] and use this quantity at increasing ligand concentration ($[L]_{tot}$) to determine the fraction of sites occupied.



$$\nu = \frac{X - X_0}{X_{sat} - X_0} = \frac{\Delta X}{\Delta X_T} = \frac{K[\mathrm{L}]}{1 + K[\mathrm{L}]}$$

$$X = \Delta X_T \frac{K[\mathrm{L}]}{1 + K[\mathrm{L}]} + X_0$$

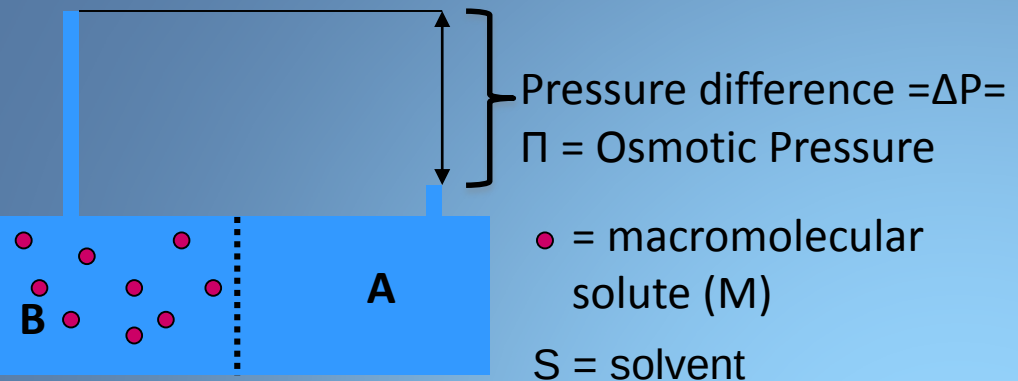
$$\frac{X - X_0}{X_{sat} - X_0} = \frac{1}{2[\mathrm{P}]_{tot}} \left\{ a \pm \sqrt{a^2 - 4[\mathrm{P}]_{tot} \frac{[\mathrm{L}]_{tot}}{n}} \right\}$$

$$a = \frac{1}{nK} + \frac{[\mathrm{L}]_{tot}}{n} + [\mathrm{P}]_{tot}$$

The binding isotherm is approximately hyperbolic, and it takes a minimum of three parameters to define an hyperbola. A carefully planned experiment will define both K and X_{sat}. Get X_0 by inspection.

When multiple ligands bind, we must also estimate *n*, the stoichiometry. In general, the information in a single binding isotherm is insufficient to obtain n, and another experiment may be needed.

Osmotic Pressure



Pressure difference =ΔP=
Π = Osmotic Pressure

● = macromolecular solute (M)

S = solvent

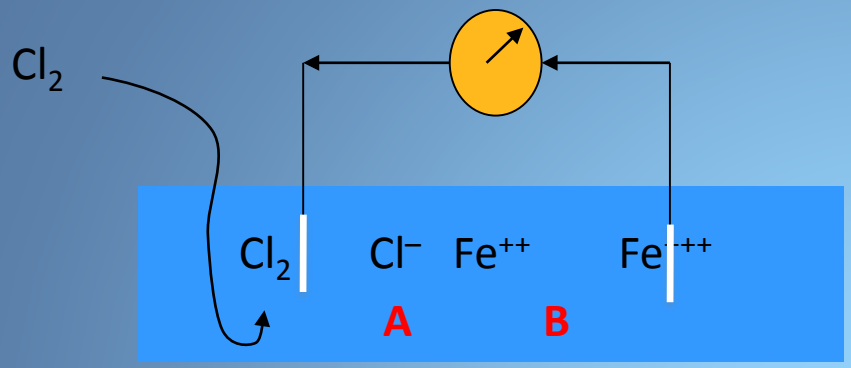
Semipermeable membrane: water pass between A and B but not M. At constant volume, the system will maximize S (minimize X_S in B) to achieve equilibrium. ⇒ move water from A to B, ⇒ increased pressure in B.

$$\mu_S^B = \mu_S^*(T, P+\delta P) + k_B T \cdot \ell n X_S^B \approx \mu_S^*(T, P+\delta P) - k_B T \cdot X_M^B = \mu_S^A = \mu_S^*(T, P)$$

from definition of G: $\left(\frac{\partial \mu_S^*}{\partial P}\right)_{T,N_S} = v_S = \left(\frac{\partial V}{\partial N_S}\right)_{T,P}$

$$\mu_S^*(T, P+\Delta P) = \mu_S^*(T, P) + \int_P^{P+\Delta P} v_S dP = \mu_S^*(T, P) + v_S \Delta P; \quad \rightarrow \quad v_S \Pi = k_B T \cdot X_M^B$$

Ionic Equilibria: Electromotive Force



$Cl_2 + 2\ e^- \square 2\ Cl^-$

$2\ Fe^{++} \square 2\ Fe^{+++} + 2\ e^-$

$Cl_2 + 2\ Fe^{++} \square 2\ Cl^- + 2\ Fe^{+++}$

The Rxn is favorable but can occur only if electron can get from B to A.

Chemical Rxns that produce an electrical potential (V^{EMF}) have the ability to do work.

Gibbs-Duhem when $dw \neq 0$: $-dw - \sum n_i d\mu_i = 0$

$$\sum_i \mu_i \nu_i - w = 0 \Rightarrow -\mu_{Fe2+} + \mu_{Fe3+} - \tfrac{1}{2}\mu_{Cl_2} + \mu_{Cl-} - eV_{EMF} = 0$$

The work performed by an ionic gradient:

$$-eV_{EMF} = \mu^{o}_{Fe3+} - \mu^{o}_{Fe2+} - (\tfrac{1}{2}\mu^{o}_{Cl_2} - \mu^{o}_{Cl^-}) + k_B T \ln \frac{a_{Fe^{3+}} a_{Cl^-}}{a_{Fe^{2+}} \sqrt{a_{Cl_2}}}$$

The ability of an electrode couple to do work: Standard EMF

$$V^0_{EMF} = -\frac{\mu^{o}_{Fe3+} - \mu^{o}_{Fe2+} - (\tfrac{1}{2}\mu^{o}_{Cl_2} - \mu^{o}_{Cl^-})}{e} = E^0_{Fe^{3+}/Fe^{2+}} - E^0_{Cl_2/Cl^-}$$

Electromotive force can report activities using Ion-Specific Electrodes.

Electromotive force can do work: Electric Cars

Study Questions

1] What is an Ideal Solution? How does the chemical potential of a solute in an ideal solution differ from that in a dilute solution?

2] Derive the chemical potential of a component of an ideal from Boyle's Law.

3] Can you suggest two physical reasons for the activity coefficient being less than one? That is, for the effective concentration to be less than the real concentration.

4] In all types of equilibria, we see that there is a unifying principle: the unitary free energy is balanced by the cratic free energy at equilibrium. What does this mean in simple terms?

5] We saw that binding of one ligand to a site on a macromolecule can affect the way another ligand binds to a different site. What is this called? If a ligand were to bind to the second site, would this alter binding to the first site?