Lipid and DNA Modeling

General Lipid Structure

Lipid Aggregates (Phases)

- Bilayer – gel phase
- Micelle
- Hexagonal tube
- Bilayer – liquid crystalline phase
Greatest Challenge

- Setting up an appropriate starting system
  - Conformation of lipid chains
  - Surface area/lipid head group
  - Solvation

Acyl Chain Disorder

- Liquid crystalline phase lipids (most relevant for studying biological membranes) have increased mobility relative to gel phase lipids
- Increased mobility gives rise to ‘gauche defects’ which are found in increasing concentration toward the center of the bilayer
- The acyl chain disorder can be represented by statistically averaged molecular order parameters

Molecular Order Parameters

\[ S_j^{mol} = 0.5 \langle 3 \cos^2 \phi_j - 1 \rangle \]
Experimental Order Parameters

- $^2$H NMR with deuterium labeled lipids
  - Series of measurements made on lipids with deuterium at different positions down the chain
  - Angle measured is between magnetic field and carbon-deuterium bond
  - NMR order parameter profile must be multiplied by $-0.5$ for comparison to previously defined profile

Example Experimental Order Profile

Lipid Surface Areas

- Examples
  - Dilauroylphosphatidylethanolamine (DLPE)
    - Ammonium head group
    - 39-51 Å$^2$
  - Dimyristoylphosphatidylcholine (DMPC)
    - Tetraalkylammonium head group
    - 60-70 Å$^2$
**Hydration**

- Most lipid headgroups are hydrated with water and may require counterions.
- Bilayer surfaces are subject to hydration pressure when they are brought into close proximity.
- These repulsive forces may require substantial layers of water if periodic boundary conditions are used.

**DNA Structure – Class Exercise**

- Download a segment of double-stranded DNA from the protein databank.
- Examine the structure for the following features:
  - Charged groups
  - Hydrogen bonding interactions
  - Overall morphology (shape)

**Greatest Challenge**

- Electrostatic Treatment and Counterions
  - Polyanionic DNA chain is surrounded by a cloud of ions that compensate for the concentration of anionic groups.
  - This ion cloud is referred to as the ion atmosphere.
  - The ions are mobile as they are not covalently attached to any particular phosphate group.
Manning Theory

- \( \xi = \frac{q^2}{\varepsilon kTb} \)
  - \( q \): charge on the counterion
  - \( \varepsilon \): solvent dielectric
  - \( k \): Boltzmann constant
  - \( T \): temperature
  - \( b \): distance between backbone phosphates along axis

- Net charge on phosphate = \( 1/(N \xi) \) where \( N \) is the valency of the counterion
  - -0.24 with Na\(^+\) counterions
  - -0.12 with Mg\(^{2+}\) counterions

Applying Manning Theory

- DNA simulations lacking explicit counterions utilize Manning Theory to assign charges
  - Usually to phosphorous and attached oxygens
    - Either scaled by a factor of 0.24-0.34
    - Or assigned to sum to \(-0.34\)
  - Sometimes all charges in DNA scaled by 0.25

Explicit Counterions

- Placement – First method
  - Solvate DNA
  - Compute electrostatic potential (EP) on each water
  - Replace those with highest negative EP with counterions

- Placement – Second method
  - Calculate electrostatic potential around DNA
  - Place counterion at grid point with highest negative EP
  - Repeat

- Placement – Third method
  - Place ions 4.5-6.0 Å from P bisecting the O-P-O angle
Counterion Equilibration

- Regardless of placement method, counterion positions need sufficient equilibration to find optimal positions
- Often such equilibration is performed while holding the DNA fixed and just allowing the water and counterions to relax
Subsequent Modeling (DNA and Lipid)

- Once the initial challenges are met, subsequent modeling of these systems can be done with methods we've already discussed

Further (optional) Reading

- Reviews in Computational Chemistry, volume 11, chapter 6 (DNA counterion treatment)
- Reviews in Computational Chemistry, volume 5, chapter 5 (Lipid simulations)