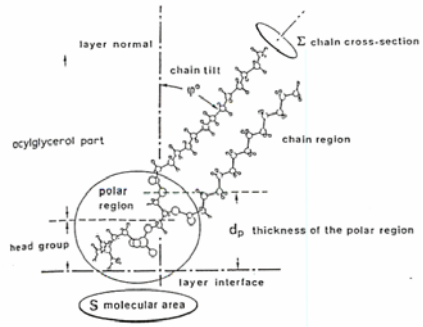
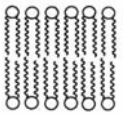
# Lipid and DNA Modeling

## General Lipid Structure

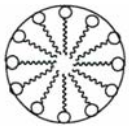





## Lipid Aggregates (Phases)

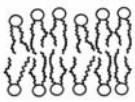


Bilayer – gel phase



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



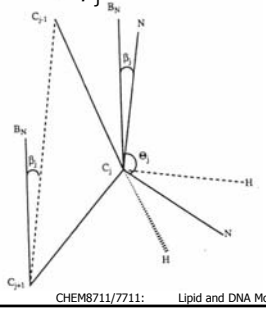
## Acyl Chain Disorder

- 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

- $S_j^{mol} = 0.5 \langle 3 \cos^2\beta_j - 1 \rangle$

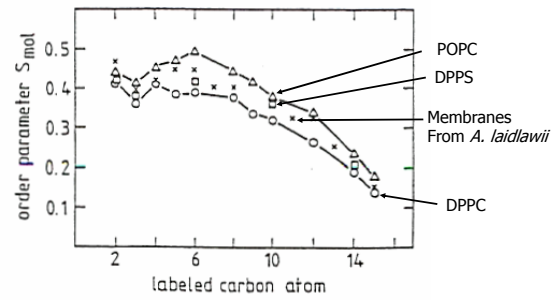


## Experimental Order Parameters

- $^2H$ 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

- $\xi = q^2/(\varepsilon kTb)$
  - 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

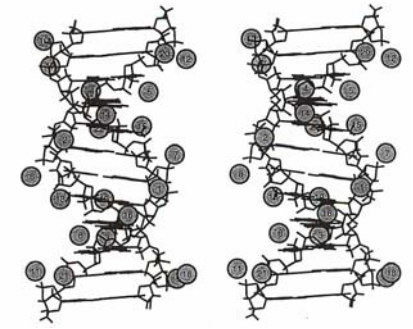
- DNA simulations lacking explicit counterions utilize Manning Theory to assign charges
  - Usually to phosphorous and attached oxygens
    - Either scaled by a factor of 0.24-0.34
    - Or assigned to sum to –0.34
  - Sometimes all charges in DNA scaled by 0.25



## Explicit Counterions

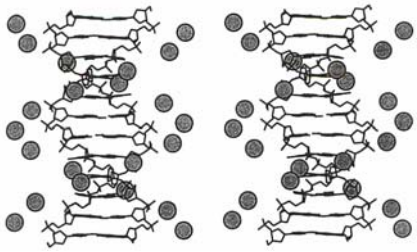
- Placement – First method
  - Solvate DNA
  - Compute electrostatic potential (EP) on each water
  - Replace those with highest negative EP with counterions
- Placement – Second method
  - Calculate electrostatic potential around DNA
  - Place counterion at grid point with highest negative EP
  - Repeat
- Placement – Third method
  - Place ions 4.5-6.0 Å from P bisecting the O-P-O angle

## Placement Example (Method 2)





## Placement Example (Method 3)





## 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)