# Lattice Simulations of Biological Membranes

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# The Dynamics of Biological Membranes: The Phospholipid Bilayer

- Biological Membranes consist of two layers of phospholipid molecules stacked on top of each other, with extra molecules embedded in the bilayer.

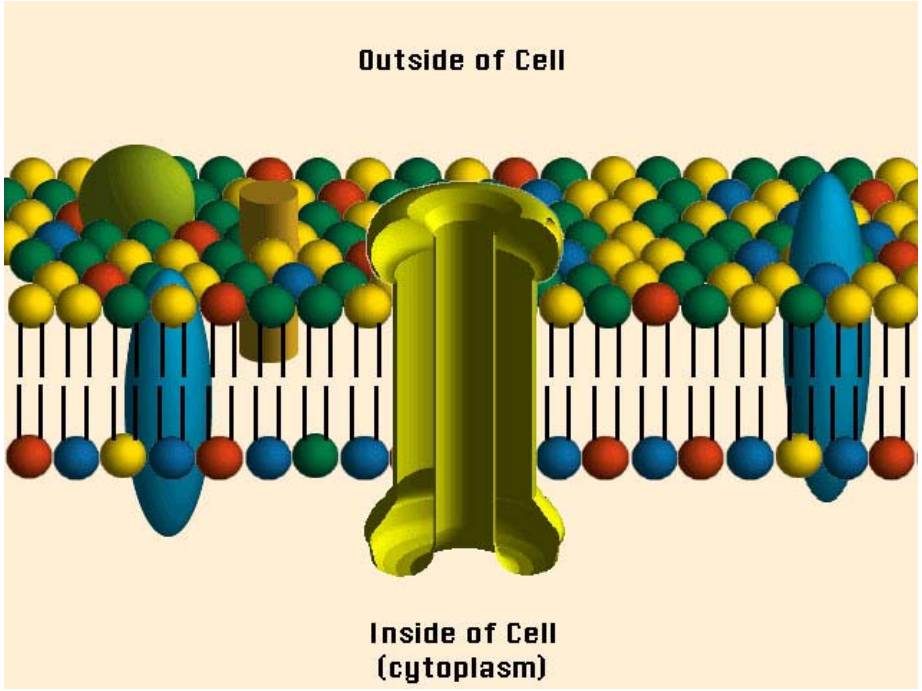
- The membranes main purpose is to encapsulate the biological molecules of a cell and regulate movement of water, ions, and molecules.

- We want to consider the cooperative effects of a collection of phospholipid molecules, the principle component of cell membranes.

# A Close-Up of the Phospholipid Bilayer

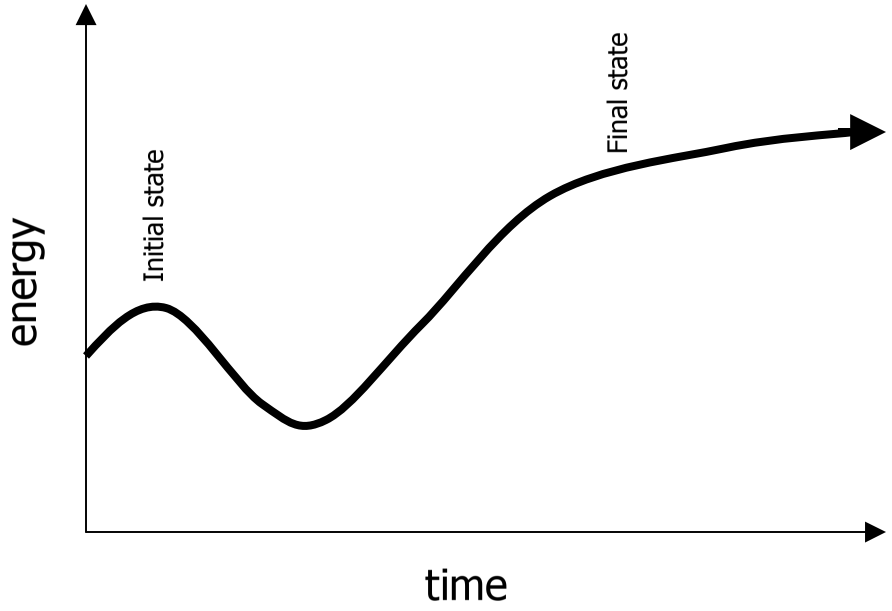
Phospholipids are comprised of two parts:

- A polar head that is hydrophilic or attracted to water.
- Two hydrocarbon chains that are hydrophobic or repel water.



# Phase Transitions:
# How the Affect Phospholipid Molecules

- A number of different phase transitions can occur in the bilayer. These include the *main* or *chain-melting transition* which we will consider, *tilted* phase, and *ripple* phase.
- We want to consider the cooperative effects of a collection of phospholipid molecules.



# Chain-Melting Transition: What is There to Simulate?

- The Chain-Melting Transition is the transition from a gel or solid-like state to a fluid-like state.
- What does this mean to us?
  - ⇨ Gel state – hydrocarbon chains are in their lowest energy state
  - ⇨ Fluid state – hydrocarbon chains are in their highest energy state
- During this transition, hydrocarbon molecules in the hydrocarbon chain are going to change energy states, altering the cooperative effects of the phospholipid molecules.
- Let's Simulate…

# What kind of Simulation?
# What to Simulate?

- What do we want?

  An approximate for the forces between every atom of any two lipid molecules.
- Problem:

  In a Monte Carlo or molecular-dynamics simulation, there are 100 atoms in each molecule. No good…
- Solution:

  Simplify the model by considering the essential features of the molecular interactions.
- Pink, Green, and Chapman did just that.

  The result: The PGC model.

# The PGC Model: How Does it Work?

- Based on a triangular lattice
- Each point of the lattice corresponds to one chain of a lipid
- Each site of the lattice is in one of ten chain sites:

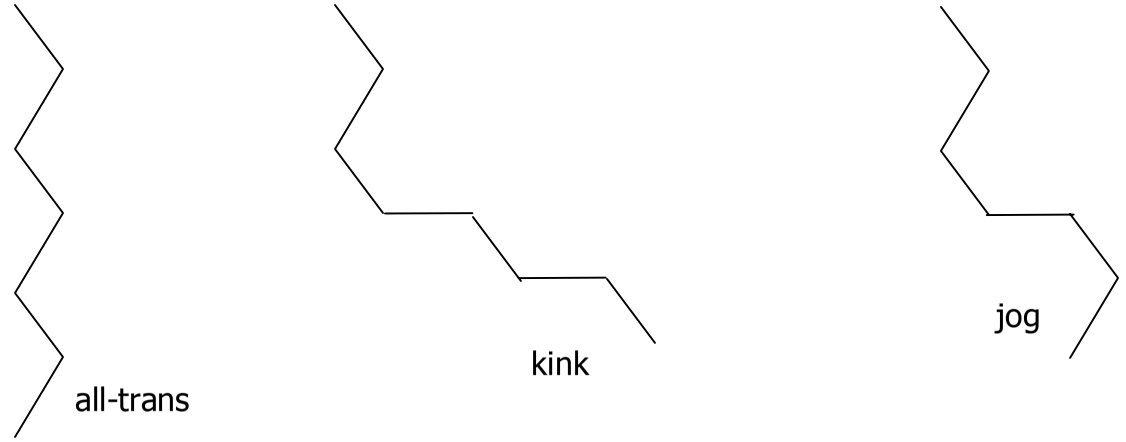
  1) a ground state (all-*trans*)

  2 – 9 ) the first eight excited states

  10) a disordered state characteristic of the fluid phase
- Two nearest neighbor lattice sites correspond to a single lipid molecule
- The bilayer is simulated as if it were a monolayer – the chain conformations of one layer have little effect on the chain conformations of another layer

# The PGC Model: What Does it Look Like?

- Each hydrocarbon chain consists of $CH_2$ groups linked like beads on a necklace
- In the lowest energy state, the groups are at 120°
- The excited states add kinks and jogs to the all-*trans* state



# Variables in the Equation: What is Considered in Energy?

- We will need the following definitions in order to run our simulation:
  1. $\alpha$ – state – 1 ⇨low energy & 10 ⇨high energy
  2. For each site i, in state $\alpha$, define:
     - -- $\varepsilon_{\iota,\alpha}$ – energy relative to the all-*trans state*
     - -- $A_{\iota,\alpha}$ – cross sectional area
     - -- $l_{\iota,\alpha}$ – length
     - -- $D_{\iota,\alpha}$ – degeneracy
     - -- $A_{\iota,\alpha}l_{\iota,\alpha}$ – volume, a constant
- We will define each of these variables according to $\alpha$ and in terms of M (monomers in hydrocarbon chain) based on experiments, constant-volume criterion, and knowledge of geometry.

# A Hamiltonian: a mathematical function used to generate equations of motion of a dynamic system

- $H = H_{\varepsilon} + H_{head} + H_{vdW} + H_{mis}$

- $H_{\varepsilon}$ = the sum of all energy stored in chains
  $= \mathbf{E}_{\iota=1\ldots N}\ \varepsilon_{\iota,\alpha}$
- $H_{head}$ = osmotic pressure
  $= \Pi\ \mathbf{E}_{\iota=1\ldots N}\ A_{\iota,\alpha}$
- $H_{vdW}$ = van der Waals interactions
  $= -\ J\ \mathbf{E}_{<\iota j>} S_{\iota,\alpha} S_{\iota,\beta}$
- $H_{mis}$ = accounts for chains of differing lengths
  $= \gamma_{mis} \mathbf{E}_{<\iota j>} |l_{\iota} - l_{j}|$

# PGC Model:
# Computer Pseudocode

- pick an initial state
- for(i<numberSteps)

    for(j<N)

        choose a random chain x

        change chain x

        calculate new energy level

        if($E_{new} < E_{old}$) keep change

          else r = Uniform(0, 1)

        if(r<$e^{[-(\Delta E)/(kT)]}$) then keep change

          else do not accept change

        calculate statistics

# The PGC Model: What Are We Missing?

- This code must be modified to account for the degeneracy of the chain states.
- How?

  We could modify our site choice by choosing trial states with a higher degeneracy more often than those with a lower degeneracy.

  But, then the fluid like state (higher degeneracy) would be chosen more, and other states would not be well sampled.
- So?

  Incorporate degeneracy into $\Delta E$

# The PGC Model: Incorporating Degeneracy

- Replace $\Delta E$ with $\Delta F$
- Instead of :

  $$\Delta E = E_{new} - E_{old}$$

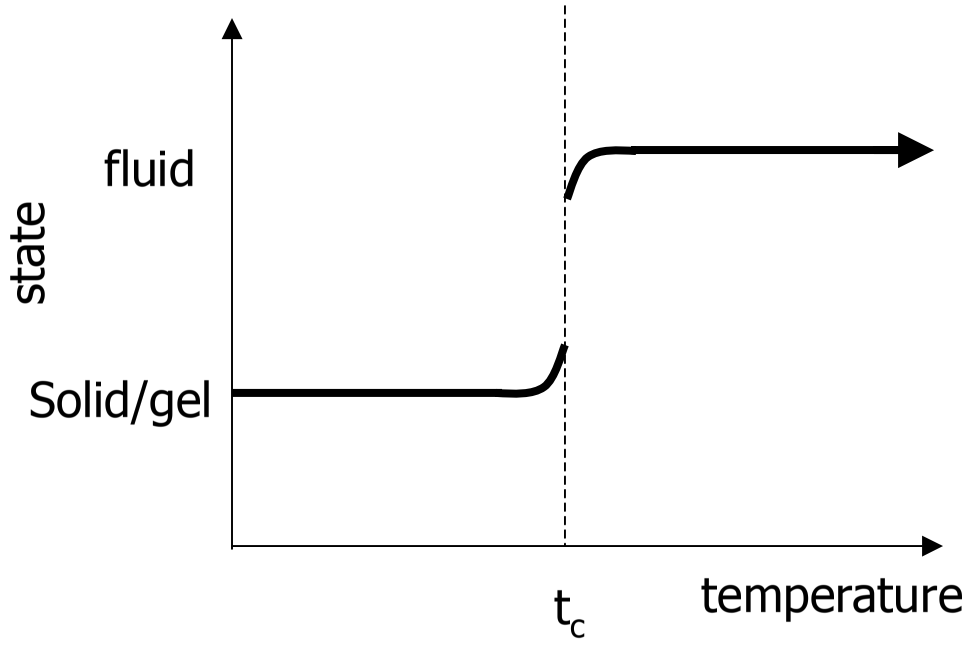
  Use:

  $$\Delta F = \Delta E - kT \ln D_{\beta} / D_{\alpha}$$

  where the chain state is a change from $\alpha$ to $\beta$.

# The PGC Model:
# The Results Analyzed

- One of the most important results: the main phase transition is only weakly first order with strong fluctuations near the transition. ie, a smeared first order transition.



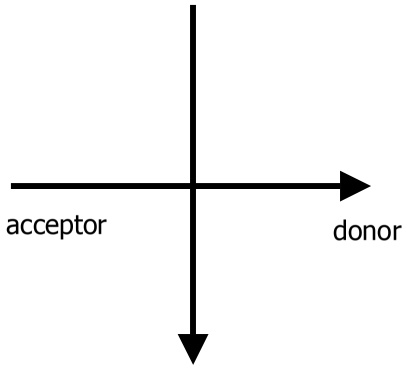
# The PGC Simulation: How Good Are Our Results?

- The following compare well with experimental results
  - Cross-sectional area
  - Compressibility
  - Heat capacity
- These comparisons suggest that the PGC model captures the essence of molecular interactions responsible for main transition.
- The simulations also provide knowledge on:
  - Spatial correlation of the chain sites
  - Geometry of domains of chains in the all-*trans* state

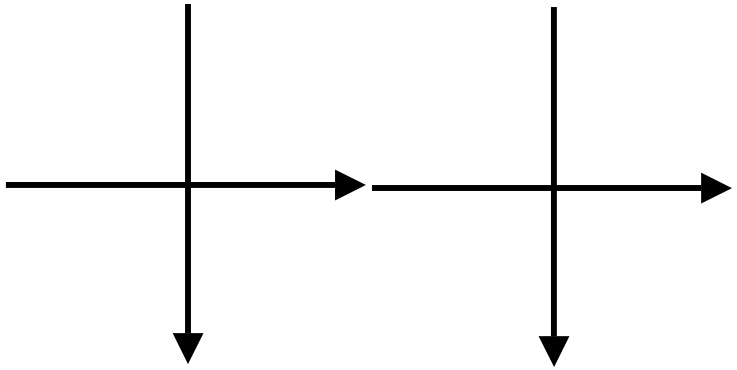
# The Anhydrous Model: Polar Head Group phosphatidylethanolamine

- All we have looked at so far is the system that is fully hydrated.
- What about anhydrous systems where water has been expelled?
  - This creates a new interaction: the hydrogen bond
  - The hydrogen bond is an electrostatic interaction
  - This bond is weaker than chemical bonds, but stronger than our previous van der Waals force
- Other than value, how is it different?
  - Hydrogen bonds are directional
  - Therefore, only in certain instances do they create bonds, or force
- Once we add this in, we'll have a relatively complete model of PE lipid bilayers.

# Hydrogen Bonds Between Polar Heads: Diagram

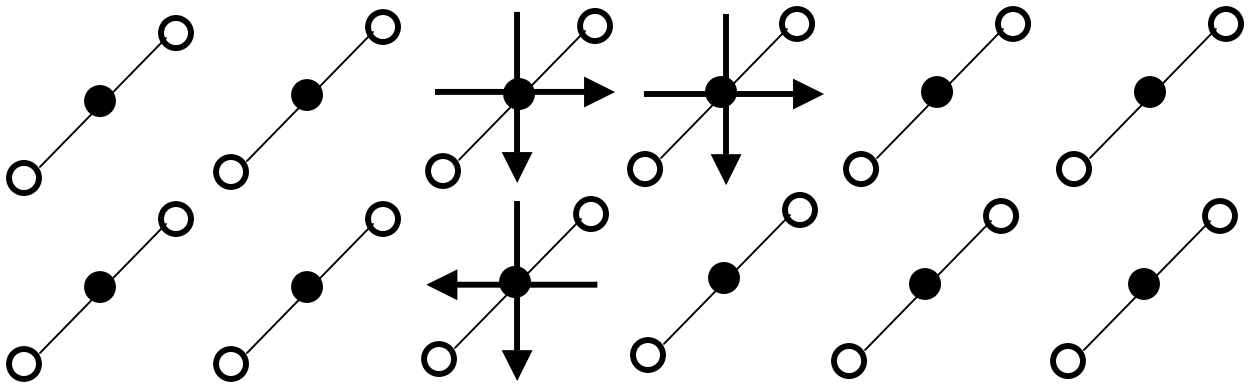



Hydrogen Bond



# Putting It All Together: A Relatively Complete Model Diagram

- Combining our triangular lattice of hydrocarbon chains and our model of the polar heads with hydrogen bonds, we arrive at this model:



# How Do We Account for Polar Heads: The Values of Hydrogen Bonds

- Zhang and others developed a model that assigns a value to each polar head.
- The value is one of five polar head states.
- The first four states consist of two donors at right angles to each other and two acceptors opposite to the donors.
- The fifth state is one that cannot bond to any other state, and has a large degeneracy $D_u$. This state represents orientations that cannot bond, as well as the polar head in the presence of water, which does not produce bonds.
- A bond depends on the state of two sites, as well as their direction (as depicted.)

# Evaluation of Our Model: What Does it Leave Uncovered?

- Models and simulations of bilayers with embedded protiens and cholesterols.
- Mixing different types of phospholipids.
- Dynamical properties of lipid membranes.