Phase transitions in lipid membranes

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Abstract: Lipids are biological polymers with both a hydrophilic and a hydrophobic part. When in solution, lipids can regroup to form vesicles. These vesicles have membranes which undergo phase transitions. Here we explore the properties emerging from the lipid stacking and particularly underline their usage in recent literature.

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Introduction

Lipids are integral parts of the cell membrane. The understanding of their behavior is therefore essential for the study of cell functions. Because lipids exhibit both a water-soluble and a water-insoluble domain, many properties emerge from their interactions. Here we look at experiments which uniquely describe or exploit these evolving properties of lipid interactions.

Lipid self-assembly

Lipids are amphiphilic molecules with typically a non-polar tail (hydrophobic) and a polar head (hydrophilic) group ***Scheme 1***. In water, these molecules reorganize to conceal their hydrophobic tails. Two structures are known to arise from this reorganization: micelles and vesicles. These structures are self assembling and have a wide range of applications in biological sciences.

In micelles the lipids regroup through tail associations creating a three dimensional structure (1) (i.e. sphere or cylinder) where only the polar head-groups are exposed to the solution ***Figure 1a and 1b***. Because their cores are non-polar while the outside surface remains water soluble, micelles are ideal for encapsulating other non-polar molecules. For example, artificial amphiphilic (lipid-like) copolymers are designed to assemble into micelles for the encapsulation of Single Wall Carbon Nanotubes (2) ***Figure 1c***. This encapsulation is found to change the fluorescent properties of the nano particles. It is also important to note that the reverse structure can assemble inside non-polar solutions (i.e. oil) and are know as reverse-micelles. In reverse micelles, the hydrophilic head group associates interiorly resulting in the exposition of the hydrophobic tails.

In vesicles, the lipids stack in two reflecting layers, in a head-tail-tail-head manner, such that only the head groups are exposed to the water molecules on both sides of the dual-layer ***Figure 1d***. Because the hydrophobic tails are sandwiched between sheets of polar head groups, vesicles are ideal for the encapsulation of various solvents. This is the primary structure of animal cells where both the interior and exterior of the cells are aqueous. The lipid membranes in the vesicles exhibit emergent properties that we will explore more in detail in this paper.

Membrane phases

New collective behaviors emerge once the lipids assemble in the vesicle membrane. This membrane undergoes a phase transition around a critical

temperature. For homogeneous membranes (where all the lipids are identical) this temperature is known as the melting temperature of the lipid and noted as T_m. Although by convention T_m is attributed to the lipid, it only makes sense to refer to the phase transition when talking about the membrane (group of severally interacting lipids).

The transition temperature of a membrane depends on the length and saturation (3) of the carbon chain that makes up the tail group, and the electrostatic properties of the head group in the composite lipids. Additional charge screening at higher salt concentrations may also affect the value of this melting temperature.

Above T_m, the membrane is fluidic. The lipids can diffuse freely inside the dual layer of the membrane. Although the lipids are mobile in this phase, they still do escape from the membrane surface to the solution because of the hydrophobicity of the tail group. This is evidenced through the detection of individual fluorescent lipids randomly, and laterally diffusing on a lipid membrane within a length scale of 100nM (4). On the other hand, below Tm, the membrane is in gel phase. In the gel phase, the lipids are packed more orderly and remain relatively immobile. Such a phase can be evidenced using Atomic Force Microscopes as the membrane thickness can change by as much as 1 nanometer, ***Figure 2***, because of the increased order in the lipid stacking (5).

Around the transition temperature (6), the two phases co-exist (5) resulting in newer properties for the vesicle. In the next part we will look at various studies exploiting those emergent properties in a vesicle with membrane transition around room temperature.

Emergent properties of vesicles around the transition temperature

DMPC (1,2-dimyristoyl-d54-sn-glycero-3-phosphocholine) is a lipid with a transition temperature Tm =23 C. At room temperature, heterogeneities arise on the membranes of DMPC vesicles from the coexistence of the lipid and gel phases (5). These heterogeneities, which can be understood as a local variation in the lipid stacking inside the membrane, result in cross-membrane pores allowing solvents of finite sizes to leak in or out of the vesicles. The exact sizes of such pores are not known but recent studies suggest that only molecules smaller than two nucleotides (approximately 7 angstroms or 1 Dalton) may pass through the pores(7, 8).

With this unique ability to permeate ions and ATP without losing large macromolecules (such as proteins and nucleic acids), DMPC vesicles are

becoming popular in biochemical experiments where a chemical exchange must occur at room temperature (8). One such use is in the design of temperature sensitive, nano-scale, bioreactors where two neighboring chemicals only mix at a desired temperature (7). A potential application would be in the design of a drug that will only be activated at the targeted cancerous site, thereby reducing the risk of contamination or misdelivery in the patient.

Additionally, because the phase transitions of the membrane can be understood by looking at the lipid stacking, more exotic vesicles can be designed by mixing different types of lipids and varying the temperature. For instance, various shapes of vesicles have been reported at different ratios of DMPC and DHPC(9) (10). These vesicles were observed using cryo-Transmission Electron Microscopy (11). A carton representation of the various shapes is given in ***Figure 3***.

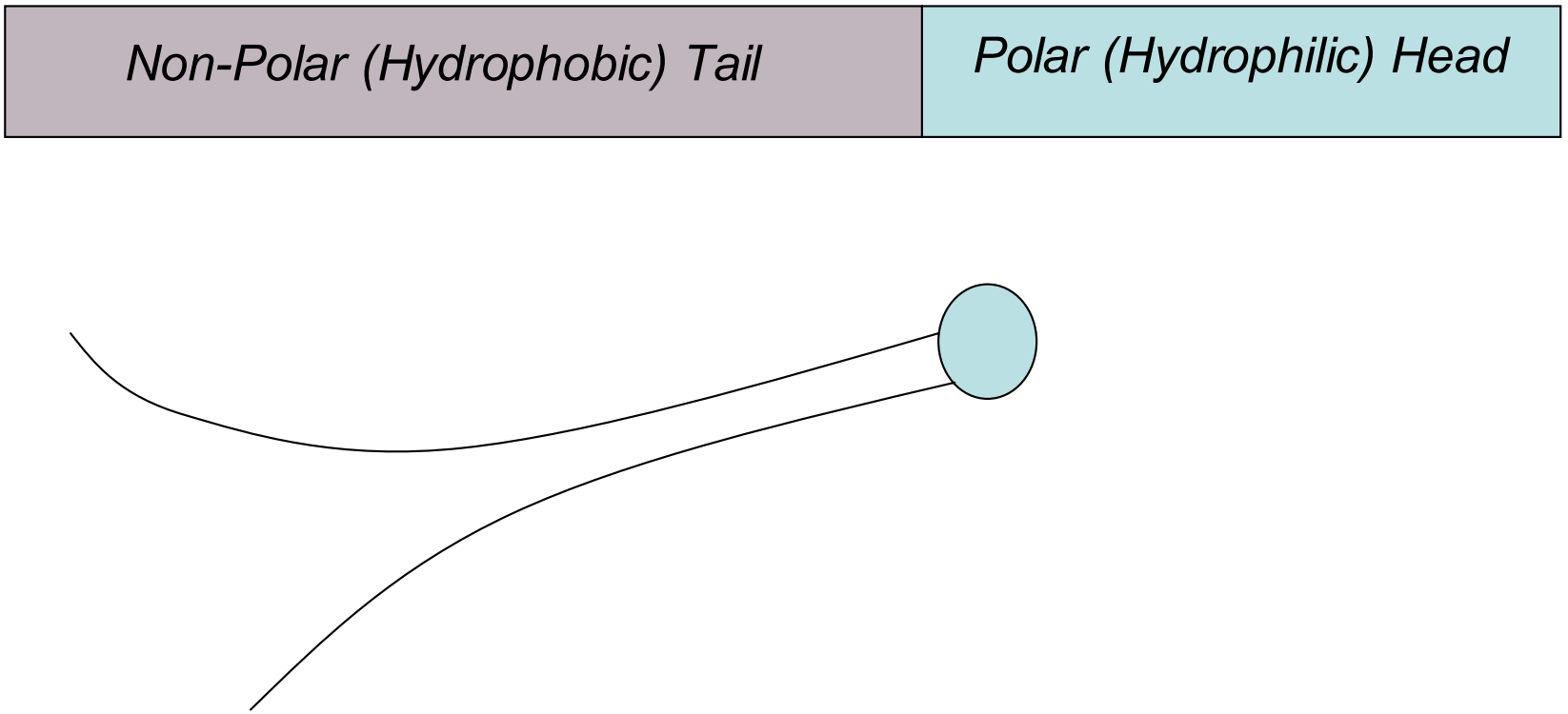
Conclusion

The properties of lipids in vesicle membranes are studied. The membrane undergoes a fluid to gel phase transition at a critical temperature (Tm). This critical temperature can be changed by altering the staking interactions between lipids. However, alterations in the membrane properties can translate to new properties for the vesicles. As an illustration, we surveyed how varying the temperature or lipid mixtures would result in vesicles or unusual shapes and porosity and discussed potential application in targeted drug delivery.

Reference and Notes:

1. Dill, K. A. & Flory, P. J. (1981) *Proc Natl Acad Sci U S A* **78,** 676-680.
2. Kang, Y. & Taton, T. A. (2003) *J Am Chem Soc* **125,** 5650-1.
3. The carbon chain is saturated when there is abundance of hydrogen and all the carbon-carbon linkage are through a single bonding. Double (and triple) carbon=carbon linkage would change the rigidity and the shape of the tail thereby disrupting the packing mode.
4. Schmidt, T., Schutz, G. J., Baumgartner, W., Gruber, H. J. & Schindler, H. (1996) *Proc Natl Acad Sci U S A* **93,** 2926-9.
5. Tokumasu, F., Jin, A. J. & Dvorak, J. A. (2002) *J Electron Microsc (Tokyo)* **51,** 1-9.
6. Tm +/- 5C is the accepted region in recent literature.
7. Monnard, P. A. (2003) *J Membr Biol* **191,** 87-97.
8. Cisse, I., Okumus, B., Joo, C. & Ha, T. (2006) *Proc Natl Acad Sci U S A*. *Under Review*
9. DHPC is also a lipid and stand for DihexanoyPhosphoChloline
10. Dam, L., Karlsson, G. & Edwards, K. (2004) *Biochim Biophys Acta* **1664,** 241-256.
11. Cryo-TEM is an Electron Microscopy where the sample is frozen for achieving higher imaging resolution

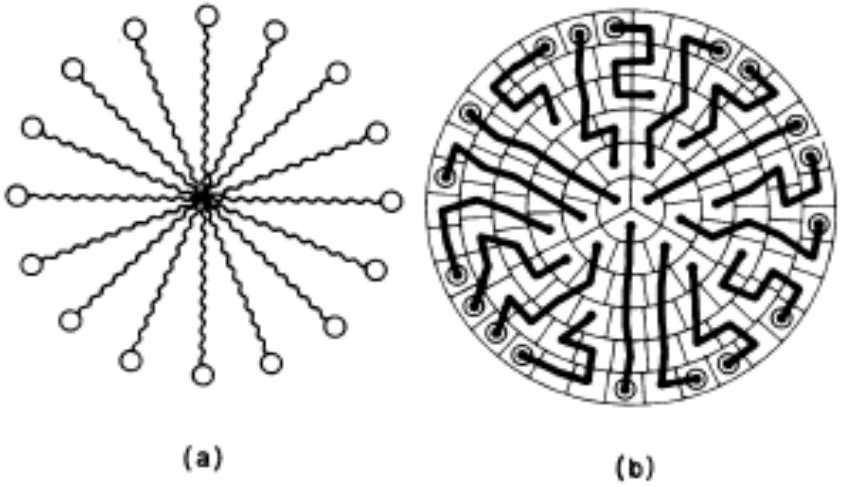
Scheme 1



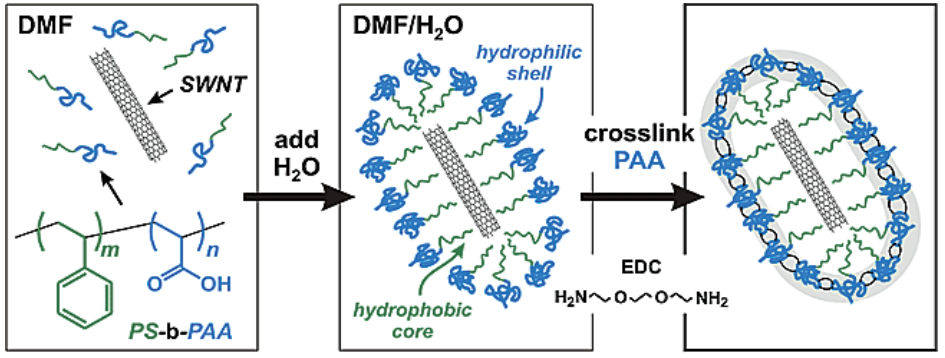
Scheme1: Conventional representation of a lipid with a tail group of 2 carbon chains

Cartoon originally made for PHY569 term paper by I.Cisse

Figure 1



(a) Conventional representation of a micelle.
(b) Lattice model representation. Because the diagrams are two-dimensional, they most nearly resemble the cross section of a cylindrical micelle.



(c)

(c) Scheme for encapsulation of Single-walled carbon nano-tube (SWNT) using “lipid-like” co-polymers

(d) Conventional representation of a vesicle

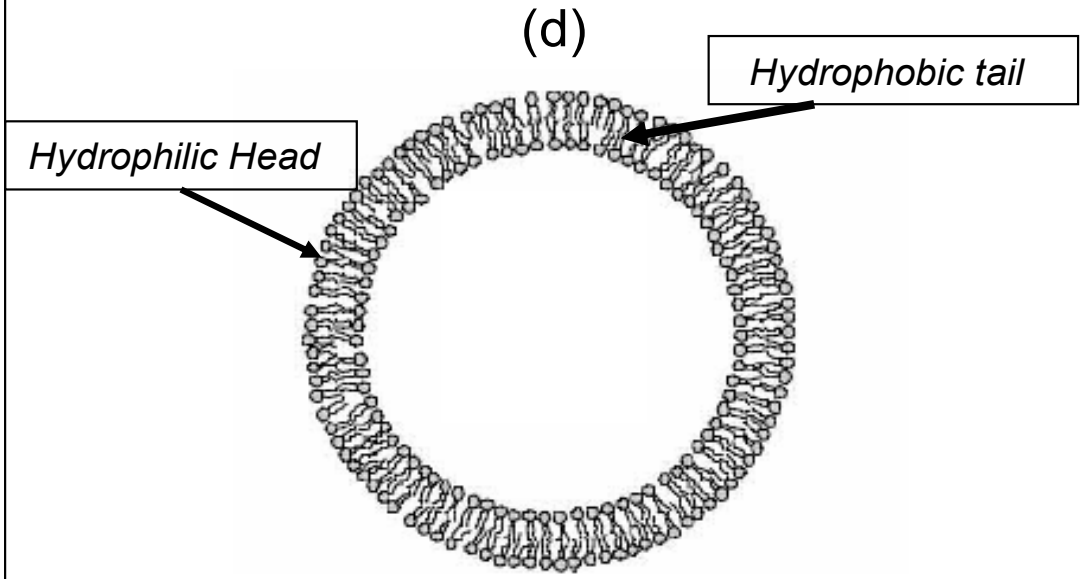
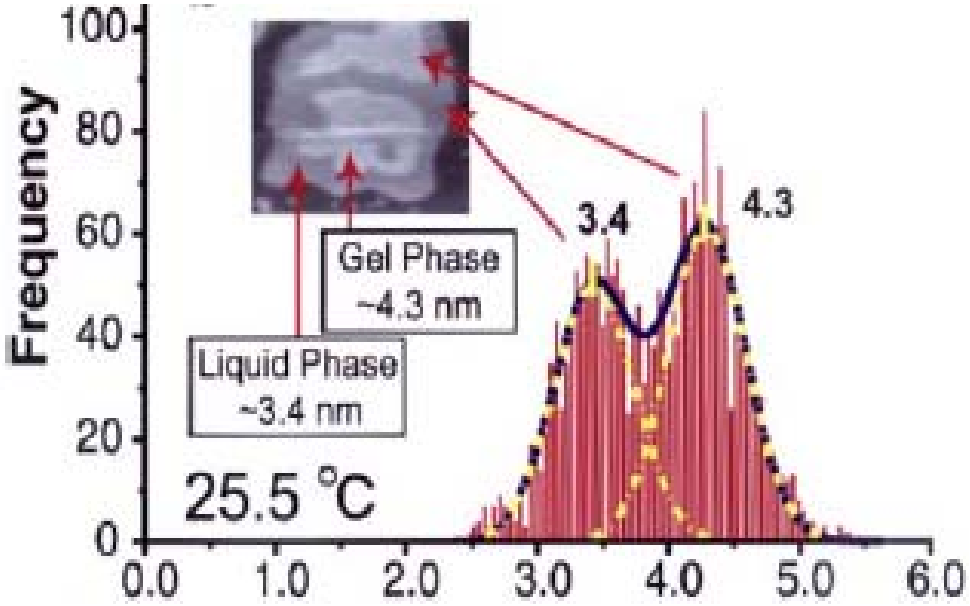


Figure 1 (a) And (b) are from Dill and Flory Proc. Natl. Acad. Sci. USA 78 (1981)
(c) Is from Kang and Taton J. Am. Chem. Soc., 125 (19), 5650 -5651, 2003 And (d) is original

Figure 2



AFM-derived height profiles during a temperature-induced phase transition of a DMPC membrane can be represented as Gaussian distributions. A 1.4 × 1.4 μm area was analysed from three consecutive 10 × 10 μm images collected at a heating rate of 0.11°C.

At 25.5°C, two overlapping Gaussian distributions with peaks at 3.4 and 4.3 nm were present, indicating the coexistence of both gel and liquid crystalline phases.

From Tokumasu et. al. J. Electron Micr.,51,1, 2002

Figure 3

Cartoon showing the aggregate structures encountered in DMPC/DHPC mixtures either as a function of the lipid ration (q) or T

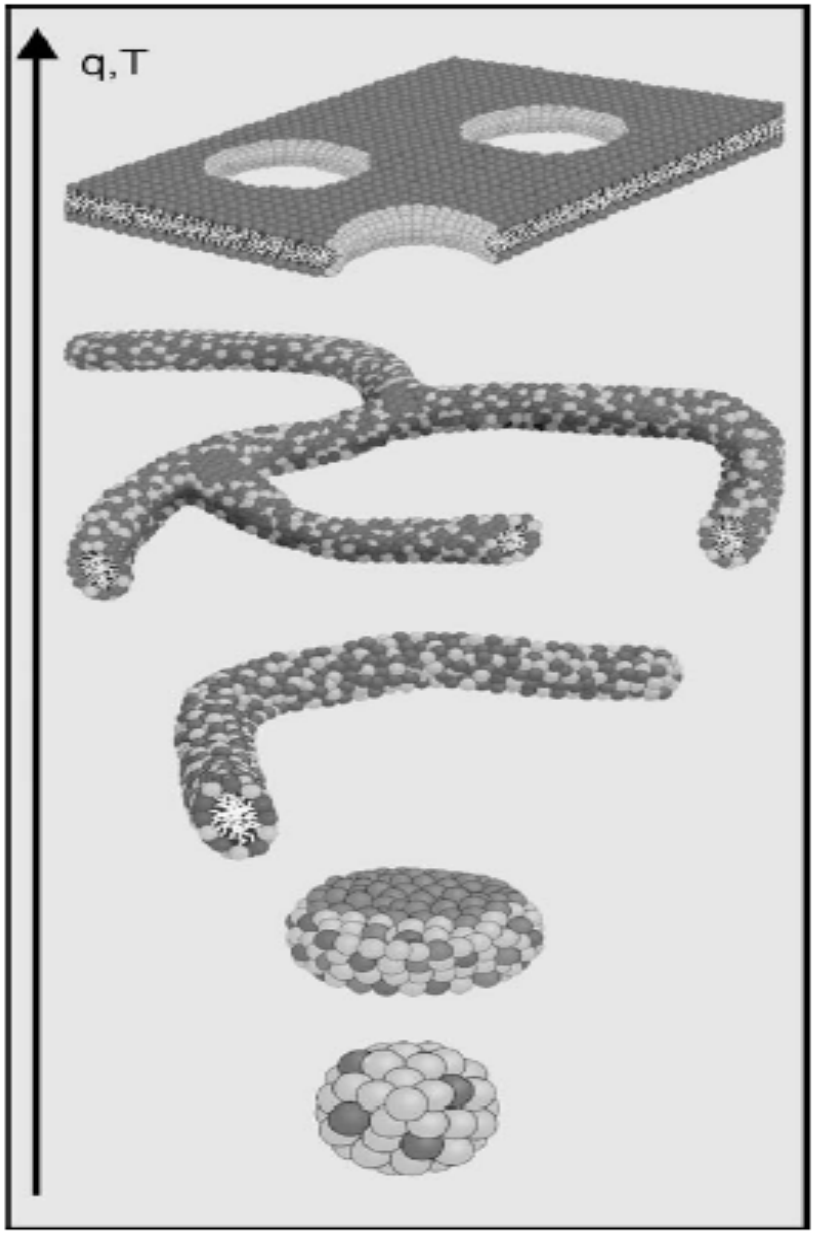


Figure 3 is from Dam, L et. al. *Biochim Biophys Acta* 1664, 2004