On the thermodynamics of lipid mixtures on curved substrates

Piermarco Fonda

Hydrodynamics at All Length Scales: From High-Energy to Hard and Soft Matter
November 20th 2019
Self-assembled lipid membranes

**Structural DOFs**

- (a) Spherical micelle
- (b) Cylindrical micelle
- (c) Lamellar phase
- (d) Reversed micelle
- (e) Continuous lattice
- (f) Vesicle

**Thermodynamical DOFs**

- Homogeneous
- Liposome Dispersion

- LIQUID
- SOLID

Sackman (1983)
Multicomponent artificial lipid membranes

Ternary mixtures on a vesicle

Saturated
Unsaturated
Sterol

Liquid disordered phase (LD or $L_{\alpha}$): “liquid heads” “disordered tails”

Liquid ordered phase (LO or $L_{\beta}$): “liquid heads” “ordered tails”

Single 2D liquid (mixed)

changing $T, \phi_i, \ldots$

2D Liquid/Liquid coexistence (phase separated)
Multicomponent artificial lipid membranes

Ternary mixtures on a vesicle

2D Liquid/Liquid phase coexistence on a curved surface

Shape effects on mixed states

Pulling out a tube from a spherical vesicle:

Curvature-driven lipid sorting needs proximity to a demixing point and is aided by proteins

Benoit Sorre\textsuperscript{a,b,1}, Andrew Callan-Jones\textsuperscript{a,1}, Jean-Baptiste Manneville\textsuperscript{b}, Pierre Nasso\textsuperscript{a}, Jean-François Joanny\textsuperscript{a}, Jacques Prost\textsuperscript{a,c}, Bruno Goud\textsuperscript{b}, and Patricia Bassereau\textsuperscript{a,2}

\textit{Sorre et al. (PNAS, 2009)}
Degrees of freedom

Two *liquid* phases with different *mechanical* properties

**Geometry**
- Shape
- Area & volume
- Membrane topology

**Thermodynamics**
(at equilibrium)
- Local composition
- Domain size, shape & number
- Interface topology

**Degrees of freedom**

Two *liquid* phases with different *mechanical* properties
Two *liquid* phases with different *mechanical* properties

**Geometry**
- Shape
- Area & volume
- Membrane topology

**Thermodynamics** (at equilibrium)
- Local composition
- Domain size, shape & number
- Interface topology

Degrees of freedom
Scaffolded Lipid Vesicles (SLVs)

Rinaldin, P.F., Kraft, Giomi (arXiv 1804.08596, under review)
The JL sharp interface model

\[ F = \sigma \int_{\Gamma} ds + \sum_{\alpha = \pm} k_{\alpha} \int_{\Sigma_\alpha} dAH^2 + \bar{k}_\alpha \int_{\Sigma_\alpha} dAK \]

Jülicher, Lipowsky (PRL, 1993)

- \( k_{\pm} \) bending moduli
- \( \bar{k}_\alpha \) saddle splay moduli
- \( \sigma \) line tension
- \( \text{Area}(\Sigma_{\pm}) \) fixed
- \( \lambda_{\pm} \) Lagrange multipliers

\[ H = \frac{1}{2} \left( \frac{1}{R_1} + \frac{1}{R_2} \right) \]
Mean curvature

\[ K = \frac{1}{R_1 R_2} \]
Gaussian curvature
Shape equations

2D Bulk:

$$\lambda_\pm H = k_\pm \left( \nabla^2 H + 2H(H^2 - K) \right)$$

1D Interface:

$$\sigma \kappa_n = \Delta \bar{k} \dot{\gamma}_g + \Delta k_\alpha \nabla_N H$$

$$\sigma \kappa_g = \Delta k H^2 + \Delta \bar{k} K + \Delta \lambda$$

$$0 = 2\Delta k H + \Delta \bar{k} \kappa_n$$
Shape equations

2D Bulk:

\[ \lambda_\pm H = k_\pm \left( \nabla^2 H + 2H(H^2 - K) \right) \]

1D Interface:

\[ \sigma \kappa_n = \Delta \bar{k} \dot{t}_g + \Delta k_\alpha \nabla N H \]

\[ \sigma \kappa_g = \Delta k H^2 + \Delta \bar{k} K + \Delta \lambda \]

\[ 0 = 2\Delta k H + \Delta \bar{k} \kappa_n \]
The JL energy is geometric, and as such can be studied with tools from surface theory (see PF et al. Phys. Rev. E 98, 032801).

The JL sharp interface model has two independent parameters:

\[
\frac{\Delta k}{\sigma}, \quad \frac{\Delta \bar{k}}{\sigma}
\]

Agreement with results from free vesicles

Baumgart, Das, Webb, Jenkins (Biophysical Journal, 2005)

Semrau, Schmidt (Soft Matter, 2009)

Agreement with results from free vesicles
Area fraction diagrams

From JL model we get:

Is this phase separation?

Why something like is never observed?
Effective free energy density with a *single* scalar order parameter (binary system)

\[ F = \int_{\Sigma} dA \mathcal{F}(\phi, \nabla_i \phi, \Sigma) \]

Gradients and curvatures are small compared to microscopical scales

\[ \mathcal{F} \simeq \frac{D(\phi)}{2} \nabla_i \phi \nabla^i \phi + f(\phi) + k(\phi) H^2 + \bar{k}(\phi) K + \ldots \]

**Fixed concentration**

\[ \Phi = \frac{1}{A \Sigma} \int_{\Sigma} dA \phi(x) \]

\[ G = F - \mu \Phi \]

- \( D(\phi) \) compressibility
- \( f(\phi) \) homogeneous free energy density
- \( k(\phi) \) bending modulus
- \( \bar{k}(\phi) \) saddle splay modulus

*What is a *reasonable* choice of these coefficients? How does this choice affect the phase diagram?*

It has long history:
- Markin (1981)
- Leibler (1986)
- Leibler, Andelman (1986)

However: the vast majority of literature focuses on local behavior and open systems.
A simple model

We still need a way to choose the concentration (and temperature!) dependence of the coefficients. A seemingly natural starting point: mean field approximation of a 2D lattice-gas model with curvature-dependent NN interactions:

\[ \mathcal{H} = -\frac{1}{4} \sum_{\langle i,j \rangle} J_{ij} s_i s_j + \sum_i h_i s_i \]

\[ J_i = a^2 \left( J + L_\kappa H^2_{(i)} + L_\kappa K_{(i)} \right) \]

\[ h_i = a^2 \left( M_\kappa H^2_{(i)} + M_\kappa K_{(i)} \right) \]

After evaluation of \( Z \) and in the continuum limit:

Local mixing entropy

\[ S(\phi) = -\phi \ln \phi - (1 - \phi) \ln(1 - \phi) \]

\[ f(\phi) = -k_B T S(\phi) + J \phi (1 - \phi) \]

\[ \kappa(\phi) = L_\kappa \phi (1 - \phi) + M_\kappa \phi \]

\[ \bar{\kappa}(\phi) = L_\bar{\kappa} \phi (1 - \phi) + M_\bar{\kappa} \phi \]

4 new coupling constants which reduce to 2 for spheres:

now we can compute phase diagrams
Classical homogeneous phase separation

To understand bulk phases (far from interfaces), we **neglect gradients** for now. Thermodynamic equilibrium is given by minima of the free energy density:

\[ f'(\phi) = \mu \]

The local order parameter is a constant everywhere. **Mixed** phase always stable.

**Demixed** phase for

\[ \phi_- < \Phi < \phi_+ \]
Minimal inhomogeneous systems: two spheres

A *crude* approximation: two spheres isolated from the environment but freely exchanging order parameter with each other.

**Equilibrium:**

\[
\frac{f'(\phi_1)}{R_1^2} + \frac{k'(\phi_1)}{R_1^2} = \mu = f'(\phi_2) + \frac{k'(\phi_2)}{R_2^2}
\]

**Total concentration constraint**

\[
\frac{R_1^2}{R_1^2 + R_2^2} \phi_1 + \frac{R_2^2}{R_1^2 + R_2^2} \phi_2 = \Phi
\]

With concave potentials, **check stability against demixing** on each sphere.

---

With concave potentials, **check stability against demixing** on each sphere.

---

With concave potentials, **check stability against demixing** on each sphere.

---

With concave potentials, **check stability against demixing** on each sphere.
Inhomogeneous thermodynamic potentials

The phase diagram of \( \Delta \phi = \phi_2 - \phi_1 \) for \( M_\kappa = 0 \)

\[
F = f(\phi) + M_\kappa \phi \frac{1}{R^2}
\]
Inhomogeneous thermodynamic potentials

The phase diagram of for\* $M_K \sim O(0.01)$

$$\mathcal{F} = f(\phi) + M_k \phi \frac{1}{R^2}$$

$\Delta \phi \neq 0$

\( \text{Inhomogeneous mixing} \)

*in units where $f \sim O(1), R_1 = 1$
Inhomogeneous thermodynamic potentials

The phase diagram of for* $M_K \sim O(0.1)$

$$\mathcal{F} = f(\phi) + M_k \phi \frac{1}{R^2}$$

$$\Delta \phi \neq 0$$

Inhomogeneous mixing

$\Delta \phi = \phi_2 - \phi_1$

*in units where $f \sim O(1), R_1 = 1$
Inhomogeneous thermodynamic potentials

The phase diagram of $\Delta \phi = \phi_2 - \phi_1$ for $M_\kappa \sim O(1)$

$$\mathcal{F} = f(\phi) + M_\kappa \phi \frac{1}{R^2}$$

$\Delta \phi \neq 0$

Inhomogeneous mixing

*in units where $f \sim O(1), R_1 = 1$
Inhomogeneous thermodynamic potentials

The phase diagram of for $M_\kappa \sim O(1)$

$$\mathcal{F} = f(\phi) + M_\kappa \phi \frac{1}{R^2}$$

$\Delta \phi \neq 0$

Inhomogeneous mixing

*in units where $f \sim O(1), R_1 = 1$
Inhomogeneous thermodynamic potentials

The phase diagram of for $M_K \sim O(1)$

$$\mathcal{F} = f(\phi) + M_k\phi \frac{1}{R^2}$$

$\Delta \phi \neq 0$ Inhomogeneous mixing

*in units where $f \sim O(1), R_1 = 1$
A new framework

Is this phase separation? No*

*Dumbbell ≠ Two spheres
More realistic surfaces

How good of an approximation are two disjoint spheres? Our colloids are dumbbells:

P.F. et al. (arXiv 1812.11563, under review @ PRE)
More realistic surfaces

How good of an approximation are two disjoint spheres? Our colloids are dumbbells:

The antimixed state survives for large enough bending modulus!

P.F. et al. (arXiv 1812.11563, under review @ PRE)
Are there quadratic curvature interactions?

\[ \mathcal{F} \simeq J \frac{\xi^2}{2} \nabla_i \phi \nabla^i \phi + f(\phi) + k(\phi)H^2 + \bar{k}(\phi)K + \ldots \]

If the full free energy has location-dependent binodal points we find – through boundary layer analysis of the gradient term – corrections to the line tension due to curvature

\[ \tilde{\sigma} \simeq \sigma + \delta_k H^2 + \delta_{\bar{k}} K + \ldots \]

Where

\[
\sigma = \xi \int_{\phi_-}^{\phi_+} \mathrm{d}\varphi \sqrt{2 \tilde{f}(\varphi)} \\
\delta_k = \xi \int_{\phi_-}^{\phi_+} \mathrm{d}\varphi \frac{\tilde{k}(\varphi)}{\sqrt{2 \tilde{f}(\varphi)}}
\]

with

\[ \tilde{f}(\varphi) = f(\varphi) + \frac{f(\phi_-)(\varphi - \phi_-) + f(\phi_+)(\phi_+ - \varphi)}{\phi_+ - \phi_-} \]

\[ \delta_k, \bar{k}/\sigma \text{ are the 1D analogues of the Tolman lengths} \]

For our MFT lattice gas model we find

\[ \tilde{\delta}_k, \tilde{\bar{k}}/\sigma = \frac{3q}{4} L_{k,\bar{k}} (T_c - T)^{-1} \]
Are there quadratic curvature interactions?

Actual MFT compressibility

\[ D = \xi^2 \left( J + L_k H^2 + L_{\tilde{K}} K \right) \]

\[ D_{flat} = 0.679 \left[ \frac{\mu m^2}{s} \right] \]
\[ \alpha = 25.96 \left[ \frac{\mu m^4}{s} \right] \]

\[ D_s = D_{flat} + \frac{\alpha}{R^2} \]
\[ \alpha \propto L_k + L_{\tilde{K}} \]

Since NN interaction modulates both diffusion and reaction forces, we infer that, in bilayer membranes, there should be a **quadratic interaction** and a curvature dependent critical temperature

\[ T_c = \frac{q}{2} \left( J + L_{\kappa} H^2 + L_{\tilde{K}} K \right) \]

P.F. et al. (arXiv 1812.11563, under review @ PRE)
Summary

- SLVs are **closed** thermodynamical systems
- Sharp interface models have **limited** applicability
- **Curvature-composition** interactions are essential to get the full picture
- **Non-spherical** shapes are necessary to make this effect evident

- New equilibrium states can emerge: **antimixing**
- Different couplings (**linear** vs. **quadratic**) produce very different phenomenologies
Future directions

• Extend the model to n-nary mixtures
• Is critical temperature affected by curvature? And line tension?
• In Leiden, we can 3D print \textit{any surface} and coat it with lipids: we want to engineer the right surface to highlight specific curvature effects:

\textit{Rinaldin, Doherty (unpublished)}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure}
\caption{A micron-sized version of the Academiegebouw in Leiden}
\end{figure}

\textbf{Measuring membrane Gaussian rigidity using curved substrates, \textit{PF et al. (in preparation)}}

\textit{Honerkamp-Smith et al. (BJ, 2008)}

A collaboration with:

- Luca Giomi
- Melissa Rinaldin
- Daniela Kraft
End of presentation