

# Phys 230 Homework 3 with Final Modifications: Continuum Model of Liquid-Liquid Phase Separation

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March 28th, 2022

## 1 Scientific Background and Motivation

Living organisms rely on the organization of their numerous biochemical processes (or compartmentalization) to regulate their metabolism and responsiveness. It has been experimentally proven that membraneless organelles can assemble by intracellular phase separation, representing a novel approach of cellular organization. Liquid-liquid phase separation, which is especially relevant for biological systems, consists of a homogenous solution of some molecule spontaneously separating into two coexisting liquid phases. In separating the system one phase is of high density corresponding to the original molecule, while the other is sparsely populated. Between the two phases exists an interface, allowing for the selective passage of molecules, leading to the 'liquid droplets' functioning as compartments [1].

In modeling the compartmentalization of living organisms through liquid-liquid phase separation, we will consider a continuum model of the system's free energy. Our initial free energy density,  $f$ , consists of an effective interaction between molecules with the term  $|\nabla u|^2$ , where  $u$  is some normalized density order parameter (ranging from -1 to 1, where 1 represents the denser region in terms of our molecules), along with a double well term defining the interface.

$$f = \frac{k}{2} \left[ |\nabla u|^2 + \frac{1}{2\delta^2} (u^2 - 1)^2 \right] \quad (1)$$

The constant  $k$  is defined as the energy cost of having an interface between phases, while  $\delta$  defines the thickness of the interface.

From here we use the continuity relation for the normalized density to generate a partial differential equation, where  $\tau^{-1}$  is effectively a diffusion constant.

$$\frac{\partial u}{\partial t} = -\frac{k}{\tau} \nabla^2 \left[ \nabla^2 u + \frac{1}{\delta^2} (u - u^3) \right] \quad (2)$$

Now, we can use the finite difference method to determine the solution to the given partial differential equation. For the purposes of this model we will only consider a flat interface in two-dimensions.

## 2 Finite Difference Method

To numerically solve the partial differential equation through the finite difference method we will follow the brief steps below:

- Initialize spatial arrays: We will set up a 2D array, accounting for x and y coordinates, with each set of coordinates corresponding to a box. This array will be  $m \times m$ , with x and y both ranging from -1 and 1. The size of each box is  $\frac{2}{m}$ .
- Now we initialize the density on the spatial array according to our preferred initial conditions.
- From here we will translate the  $\nabla^2$  and  $\nabla^4$  terms into a finite difference form (this will most likely be done using the np.roll command shown in class).
- Next we evolve the system through time either using the forward Euler method for simplicity, or a Verlet algorithm for accuracy. This whole process will then be repeated.

### 3 Objective 1: Simplest Case

We will start by considering the partial differential equation in (2) for some initial  $u$  and its evolution across some box with periodic boundary conditions. The evolution of our system will be determined using the finite difference code described in section 2. We can try several different initial conditions in the density along with using different parameters:  $\tau, k, \delta$ .

Depending on the initial parameters the system will have the following possible behaviors; complete separation and the formation of droplets (as seen in Fig. 1), or no discernible separation.

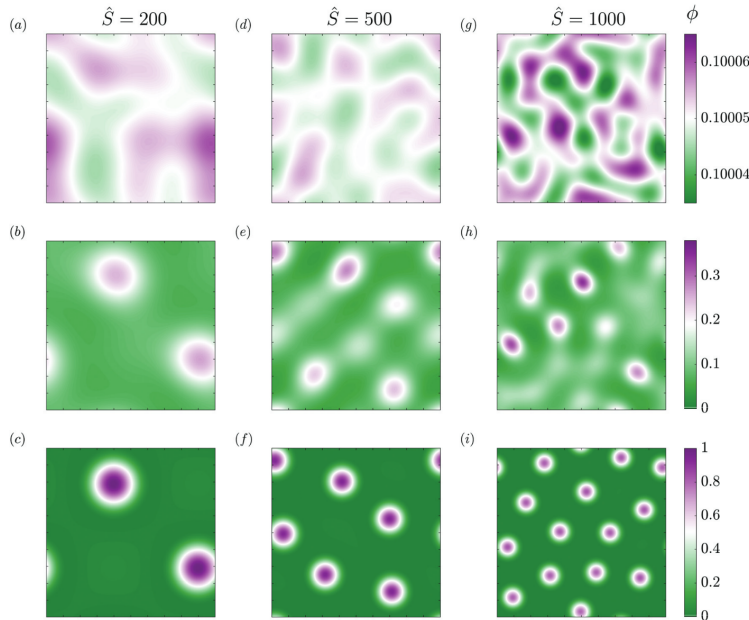


Figure 1: An example of the phase separation that we expect to see. Each row represents a different time, while  $\hat{S}$  represents the size of the molecule relative to the box. This graph is from the computational modeling of protein aggregation on a cell membrane using a continuum model, see [2].

### 4 Objective 2: Phase Separation Statistics

With the different parameter regimes tested above, we can determine the average size of the clusters along with the average distance between them over time (and the relationships each has with  $k, \delta, \tau$ ).

In the case of an initially nearly uniform density, we can use linear stability analysis to determine the regimes in which we have global separation, generating a phase diagram. The distance between the formation of droplets can also be determined, and how it depends on the relevant parameters. We can then compare these results to our numerically determined system.

The code in determining these quantities is largely unknown as of now, since it will require greater understanding of the finite difference method used for the simulation.

### 5 Objective 3: Modification of Free Energy Density or Dynamics

To see how the system responds to the introduction of another component (which is often needed for biological systems), we can modify the free energy as seen in Section 5.1. With this modification we expect to see slight changes to the separation regimes, where we now have additional droplet types. In case this method does not work, we can also modify the continuity equation (used to find the PDE) to account for a flow, which could possibly change the shape of the droplets. In both cases the process will be the same as Objective 1 and 2, outside of the need to solve more than one differential equation for the finite difference code.

## 5.1 Multi-Component Free Energy

In including the free energy of multiple components, our model completely changes according to the Flory-Huggins free energy density. We now have the following free energy for an N component liquid mixture where  $u_i$  ranges from 0 to 1 [3]:

$$f_{FH} = c_0 RT \left[ \sum_{i=1}^N u_i \ln u_i + \frac{1}{2} \sum_{i,j=1}^N \chi_{ij} u_i u_j - \frac{\lambda^2}{2} \sum_{i,j=1}^N \chi_{ij} \nabla u_i \nabla u_j \right] \quad (3)$$

We also have the new continuity equation [3]: (I have not taken the variational derivative yet)

$$c_0^2 \frac{\partial u_i}{\partial t} = \nabla \cdot \sum_j M_{ij} \nabla \left( \frac{\delta f}{\delta u_j} \right) \quad (4)$$

With the following constants: T is the temperature of the system,  $c_0$  represents the total concentration of solvents,  $\chi_{ij}$  represents the Flory interaction parameters,  $\lambda$  defines the characteristic width of the interface, and  $M_{ij}$  are the Onsager mobility coefficients.

## 6 Final Modifications and Summary

Any changes made to the project since the submission of this assignment are discussed in this section. No changes were made to any previous section.

### 6.1 Summary of Project

First, we started with the same initial model shown in Section 1, although rather than focusing on statistics based off the parameters  $\frac{k}{\tau}$  and  $\delta$  we tried to create the most efficient code possible with the numba package in python. During my final presentation, I also mentioned how I would like to find an analytic form corresponding to the time step. Unfortunately, due to the non-linearity of the various models used, I was unable to do so. This fact also invalidated my idea of using an adaptive time step.

In analyzing the two component model from Section 1, I compared the speed using a 4th order Runge Kutta (RK) method to a simpler Forward Euler (FE) method. Although I did not have the time to explore the entire parameter space using this model, it appears the FE method is more efficient (the more efficient method depends on the relative sizes of the time steps, which depends on the parameters chosen). Along with the speed analysis, I also found regimes in which phase separation occurs, and in which it does not occur within the time frame of our simulation (based off the initial density of the system). For an initial density that is too high, the two phases never separate. Finding the critical density in which this occurs would be an interesting next step (and confirming it with linear stability analysis; which reports  $u_{ini,crit} = \sqrt{1/3}$ ).

We also compare our original two component model with one generated from a Flory-Huggins free energy term, as seen in Section 6.2. Eventually, in simulating this system, we determine that the behavior is very similar to the previous two component model (where we see a regime in which phase separation does/does not occur within our time frame). Confirming that this model gives us the behavior we want for two components, we attempted to use it to model a three component system. Using the Flory-Huggins free energy density with three components, represented in Section 6.3, I was able to simulate the system. Unfortunately, I did not have enough time to explore its parameter space sufficiently.

Possible next steps involve; improving the three component model (whether  $M_{ij}$  should be diagonalized), along with exploring parameter spaces for each model (while possibly finding separation regimes).

### 6.2 Math for Two Component Mixture

We have the following free energy for a two component system: (Note  $\chi_{ij} = \chi_{ji}$  and  $\chi_{ii} = 0$ )

$$f_{FH} = c_0 RT \left[ u \ln u + (1 - u) \ln (1 - u) + \chi_{12} u (1 - u) + \lambda^2 \chi_{12} |\nabla u|^2 \right] \quad (5)$$

With the given free energy, our variational derivative is:

$$\frac{\delta f_{FH}}{\delta u} = c_0 RT \left[ \ln u - \ln (1 - u) + \chi_{12} (1 - 2u) - 2\lambda^2 \chi_{12} \nabla^2 u \right] \quad (6)$$

We will assume  $M_{ij}$  is a diagonal matrix with the same constant along each diagonal. Since we assumed  $u_2 = 1 - u_1$ , we only need to consider one differential equation, with  $M_{11} = \frac{Dc_0}{RT}$  where  $D$  is a diffusion constant. Thus, our continuity equation is:

$$\frac{\partial u}{\partial t} = D\nabla^2 [\ln u - \ln(1 - u) + \chi_{12}(1 - 2u) - 2\lambda^2\chi_{12}\nabla^2 u] \quad (7)$$

### 6.3 Math for Three Component Mixture

For simplicity we assume  $\chi_{12} = \chi_{21}, \chi_{13} = \chi_{31}, \chi_{23} = \chi_{32}$ . Where we ignore interactions between like states by setting  $\chi_{ii} = 0$ .

$$f_{FH} = c_0 RT \left[ u_1 \ln(u_1) + u_2 \ln(u_2) + u_3 \ln(u_3) + [\chi_{12}u_1u_2 + \chi_{13}u_1u_3 + \chi_{23}u_2u_3] - \lambda^2 (\chi_{12}\nabla u_1\nabla u_2 + \chi_{13}\nabla u_1\nabla u_3 + \chi_{23}\nabla u_2\nabla u_3) \right] \quad (8)$$

Without explicitly representing  $u_3$  as a function of  $u_1$  and  $u_2$ , the system above has the following variational derivatives:

$$\frac{\delta f_{FH}}{\delta u_1} = c_0 RT \left[ \ln(u_1) + \chi_{12}u_2 + \chi_{13}u_3 + \lambda^2\chi_{12}\nabla^2 u_2 + \lambda^2\chi_{13}\nabla^2 u_3 \right] \quad (9)$$

$$\frac{\delta f_{FH}}{\delta u_2} = c_0 RT \left[ \ln(u_2) + \chi_{12}u_1 + \chi_{23}u_3 + \lambda^2\chi_{12}\nabla^2 u_1 + \lambda^2\chi_{23}\nabla^2 u_3 \right] \quad (10)$$

$$\frac{\delta f_{FH}}{\delta u_3} = c_0 RT \left[ \ln(u_3) + \chi_{13}u_1 + \chi_{23}u_2 + \lambda^2\chi_{13}\nabla^2 u_1 + \lambda^2\chi_{23}\nabla^2 u_2 \right] \quad (11)$$

Were we to explicitly represent  $u_3 = 1 - u_1 - u_2$ , these would change to:

$$\frac{\delta f_{FH}}{\delta u_1} = c_0 RT [\ln u_1 - \ln(1 - u_1 - u_2) - 2\chi_{13}u_1 + (\chi_{12} - \chi_{13} - \chi_{23})u_2 + \lambda^2 [-2\chi_{13}\nabla^2 u_1 + (\chi_{12} - \chi_{13} - \chi_{23})\nabla^2 u_2]] \quad (12)$$

$$\frac{\delta f_{FH}}{\delta u_2} = c_0 RT [\ln u_2 - \ln(1 - u_1 - u_2) + (\chi_{12} - \chi_{13} - \chi_{23})u_1 - 2\chi_{23}u_2 + \lambda^2 [(\chi_{12} - \chi_{13} - \chi_{23})\nabla^2 u_1 - 2\chi_{23}\nabla^2 u_2]] \quad (13)$$

As mentioned in the two component modified model, we are assuming  $M_{ij}$  is a diagonal matrix, with each component corresponding to  $M_{ii} = \frac{Dc_0}{RT}$  with  $D$  a diffusion constant. Thus, our dynamics equations follow:

$$\frac{\partial u_1}{\partial t} = D\nabla^2 [\ln u_1 - \ln(1 - u_1 - u_2) - 2\chi_{13}u_1 + (\chi_{12} - \chi_{13} - \chi_{23})u_2 + \lambda^2 [-2\chi_{13}\nabla^2 u_1 + (\chi_{12} - \chi_{13} - \chi_{23})\nabla^2 u_2]] \quad (14)$$

$$\frac{\partial u_1}{\partial t} = D\nabla^2 [\ln u_2 - \ln(1 - u_1 - u_2) + (\chi_{12} - \chi_{13} - \chi_{23})u_1 - 2\chi_{23}u_2 + \lambda^2 [(\chi_{12} - \chi_{13} - \chi_{23})\nabla^2 u_1 - 2\chi_{23}\nabla^2 u_2]] \quad (15)$$

## 7 Relevant Articles

### References

- [1] Alberti, S. (2017). Phase separation in biology. In *Current Biology* (Vol. 27, Issue 20, pp. R1097–R1102). Elsevier BV. <https://doi.org/10.1016/j.cub.2017.08.069>
- [2] Mahapatra, A., Saintillan, D., Rangamani, P. (2021). Curvature-driven feedback on aggregation–diffusion of proteins in lipid bilayers. In *Soft Matter* (Vol. 17, Issue 36, pp. 8373–8386). Royal Society of Chemistry (RSC). <https://doi.org/10.1039/d1sm00502b>
- [3] Mao, S., Kuldinow, D., Haataja, M. P., Košmrlj, A. (2019). Phase behavior and morphology of multicomponent liquid mixtures. In *Soft Matter* (Vol. 15, Issue 6, pp. 1297–1311). Royal Society of Chemistry (RSC). <https://doi.org/10.1039/c8sm02045k>