Phy 230 Project: Continuum Modelling of LLPS

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1 Scientific Background and Motivation

Cellular organization is essential for living organisms rely to regulate their metabolism and responsiveness. Experiments have already shown 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 homogeneous solution of some molecule spontaneously separating into two coexisting liquid phases where one phase of high density separates out as droplet from the low density phase surrounding it. There exists an interface which allows selective passage of molecules thereby leading to the formation of 'liquid droplets' that can function 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.

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

The constant k is defined as the energy cost of having an interface between phases, while δ defines the thickness of the interface.
From here we use the continuity relation for the normalized density to generate a partial differential equation, where τ^{-1} is effectively a diffusion constant.

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

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 Numerical Solution pseudocode

We can solve the system of partial differential equations for our model system through Finite Difference method. The brief steps are as following:

- Spatial discretization: We will set up a 2D array, U, over a square box domain (-1,1)x(-1,1). The box is split into m x m cells, where m is an integer. The size of each cell is 2/m.
- Next we will write the Cahn-Hilliard equation in Finite difference form. Here, we will convert laplacian terms i.e. ∇^2 and ∇^4 terms into a finite difference form. We are using np.roll command shown in class for this.
- Initialization:We initialize the density on our spatial array by using numpy RNG(Random Number Generator) np.random.normal or any other python way of introducing random number between -1 and 1 (with slight bias towards -1).
- Time Evolution: We evolve our system through time and find the value of the density and forward time. Here we update our finite differenced equation in time using Forward Euler time stepping at first and then we can use other methods like Runge-Kutta 4th-order(RK4) time stepping method to compare the speed between the two methods.At the later phase of our simulation, to make it more efficient, we can also use useful python package like 'numba' in our code to speed up our computation.

3 Objectives

- Part 1: **Simple Cahn Hilliard simulation to form droplets**
  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(u) along with using different parameters: τ,k,δ. A sample standard result of droplet formation that we are trying to get in part 1 is shown below in Figure 1.
- Part 2: **Droplet Statistics**
  We will try to write a script for calculating the statistics for size distribution of the droplets i.e. we will measure radius of droplet(R),calculate average radius and how that changes with time.Ideally, droplets should grow with time by two way - a) brownian motion: droplets coalesce or merge and become one big droplet at steady state, b) Ostwald ripening: smaller particles dissolve and deposit onto larger particle to form much bigger droplet, this happens due to diffusive flux between the droplets. If we can find some scaling behaviour of this radius dynamics with time, we will have idea about how the droplet size changes with time. Then we can calculate size distribution of the droplets.

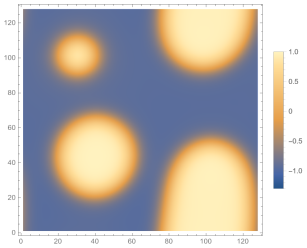

Figure 1: droplets in (-1,1) box

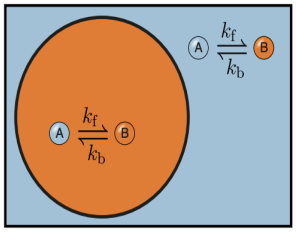

Figure 2: droplets with first order reactions

- Part 3: **Droplet dynamics with multivalent interactions**
  Biological droplets(e.g. protein-RNA droplets) can undergo chemical reactions in their interior involving multivalent interactions.This can be part 3 of increasing complexity. At the beginning we are trying to introduce a simple two component first order chemical reaction scheme $A \rightarrow B$ and the reverse $B \leftarrow A$ (where B is the droplet material and A is soluble building block)through a reactive flux component s(t).[2]
  We assume the forward reaction $A \rightarrow B$ proceeds with rate k_f and the backward reaction $B \leftarrow A$ occurs with rate k_b. Here s will govern how many B particles are created ($s > 0$) or destroyed ($s < 0$).Therefore our modified system of equation will be:

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

  where,

$$s = k_f\frac{(1-u)}{2} - k_b\frac{(1+u)}{2}$$

  (since density of the droplet material(B) is u and total density is 1, so density of A is 1-u)
  In this reaction-diffusion coupled system, our goal would be to see if droplets are forming or not. We can play with the initial density value (u_0) to see how the steady state behaves, it reaches to a single large droplet or something else. The goal of including these chemical reactions is to suppress Ostwald ripening so that the droplets can not grow in time to ultilately form large droplet. This reactive flux will help in that coarsening. Further if time permits, we will go to multiple reactions and autocatalytic droplets scheme as proposed in the paper [2]. Here also in the reaction-diffusion coupled droplet dynamics, we can calculate how size(radius) changes with time and ultimately find statistics of size distribution.
  Note: This brief write-up will be continuously modified as the project becomes developed gradually.

4 Modifications and Summary

All the changes to the project after the last assignment submission is discussed in this section. No changes are made to any previous section.
First, we started with the same initial model shown in Section 1, we showed effect of parameters on time scale of phase separation. Then we tried to create the most efficient code possible with the numba package in python keeping both Forward Euler and RK4 method in one combined code. I was trying to find an adaptive time stepping if possible,but due to non-linear complexity it was not possible. While analyzing the two component model from Section 1, I compared the computational speed using a 4th order Runge Kutta (RK) method to a simpler Forward Euler (FE) method. 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.

Next I played with the chemical reaction scheme to see it's effect on the dynamics of the model. I tried different random initialization of the model with varying reaction rates of different magnitude. Then, I tried single droplet initialization with the reactions. When the reaction rate is too high, it shrinks the droplet too fast ,but when the rates are very small the single droplet grows. In the presentation, I talked about finding a critical radius (Rcrit) above which droplet grows and below which droplet shrinks, but due to time limitation and complexity I couldn't fully able to analyze that. I also tried to modify my code to create a movie or animation of the dynamics of the droplet and it was almost about to be working and yet not worked fully(updates didn't happen properly in the movie).
Possible next steps would be to understand the effect of reactions on single or preferably two droplet initial configuration and see how it relates to suppression of Ostwald ripening. I tried the two droplet initialization scenario with the same tanh function but I am having trouble getting stable droplets as initial state.In the computational point of view, I would try to apply the numba and other decorators to multiple droplet initialization too and also try to make a movie.

5 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] Zwicker, D.,Hyman A.A.,Jülicher, F. (2015).*Suppression of Ostwald ripening in active emulsions* PRE 92, 012317 http://dx.doi.org/10.1103/PhysRevE.92.012317