Continuum Model of Liquid-Liquid Phase Separation

Phys 230 Final Project, 5/3/22

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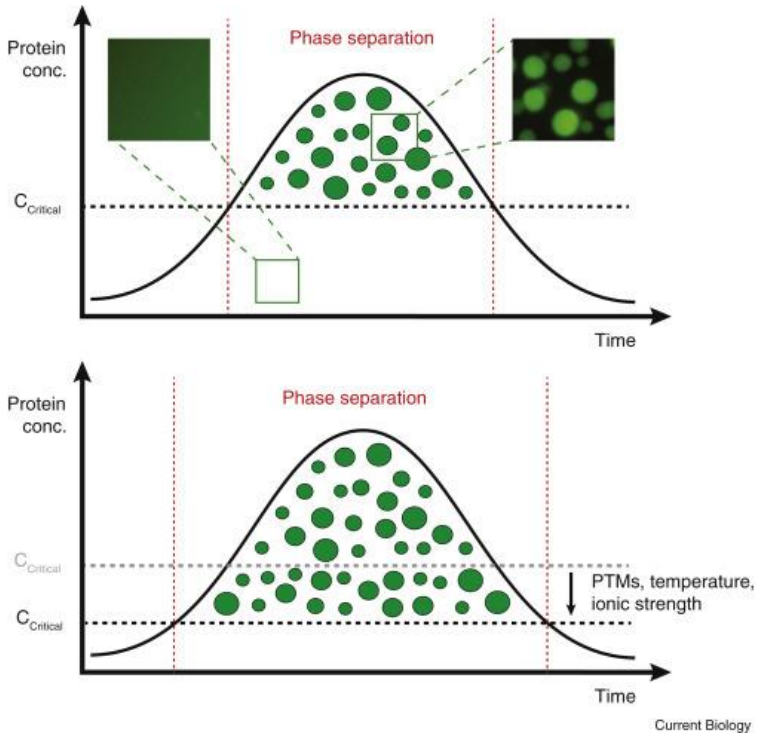
Biological Examples of Phase Separation

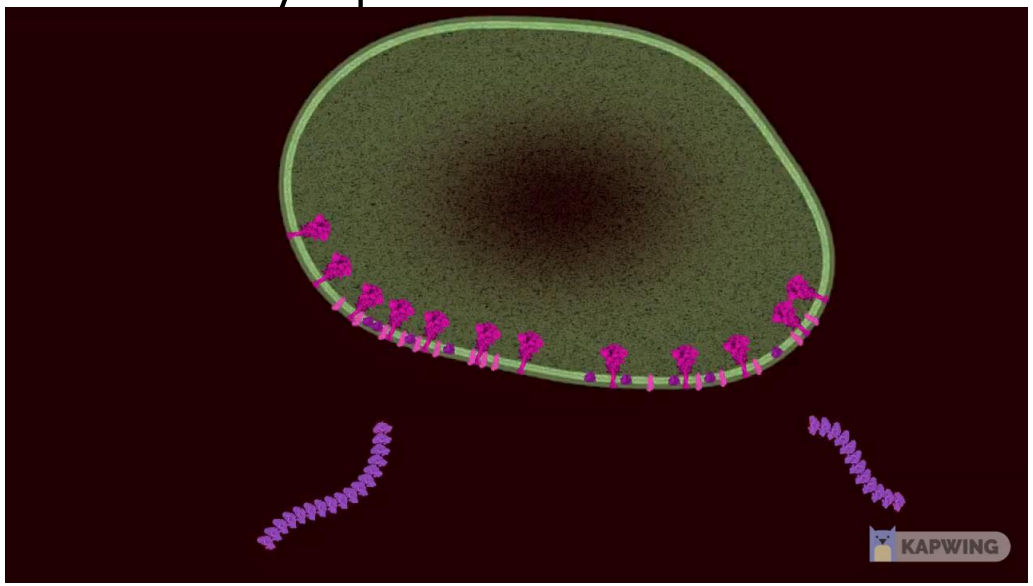
- Living organisms rely on organization of biochemical processes to regulate their metabolism and responsiveness
- Experiments have proven that membrane-less organelles can assemble through phase separation
- Phase separation can be particularly useful for the quantifying the replication of viruses



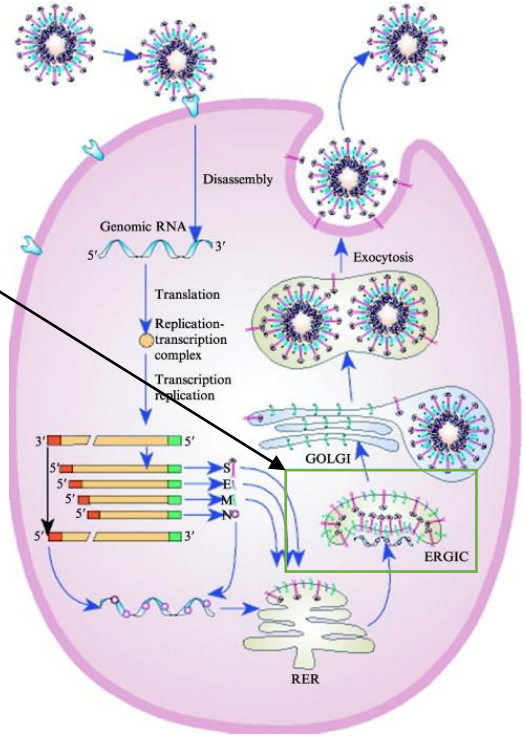
Alberti, S (2017).
DOI: https://doi.org/10.1016/j.cub.2017.08.069

Biological Example Cont.: SARS-CoV-2

- Can attempt to model the assembly stage of coronavirus in the Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC) with phase separation
- Will be done by quantifying the free energy of the system largely defined by two different phases: regions with or without proteins
- The occurrence of phase separation can define regimes in which budding, and ultimately replication occurs



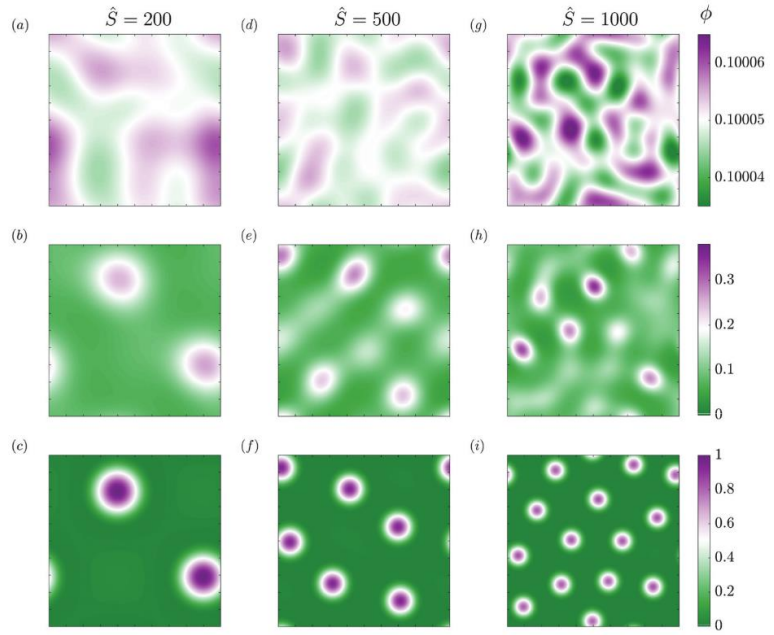
Maastricht Science Program NanoBiology Course 2020, https://www.youtube.com/watch?v=PXNi3iR9Ae4



de Haan et al. (2005, 10.1016/S0065-3527(05)64006-7)

Two Component Phase Separation Model

- Start by defining a free energy for the system based off some density u:
  - Consider two different phases on a flat surface
  - Classify an interface between the two phases with some typical thickness
- With this model we hope to determine regimes in which phase separation occurs, along with the average cluster size and distance between clusters



Mahapatra, A. (2021). https://doi.org/10.1039/d1sm00502b

Two Component Model Formalism

- We have the free energy, with u=-1 representing one phase and u=1 the other:

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

Where k is the interfacial energy cost, and δ defines the thickness of the interface.

- From conserving the density;

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

$\frac{1}{\tau}$ is a diffusion constant.

Numerical Process

- We use a gaussian distribution with a slight bias towards one of the phases to initialize the density array on the specified lattice
- We then perform the following operations for each time step, where its size is determined by the system parameters
  - Evolve the system through time using the Fourth Order Runge Kutta method
  - Use a discrete Laplacian up to fourth order to determine spatial derivatives of the density array
- In the case of animations, we saved an image of the density plot for each 10,000 time steps
  - However I was not able to get this to work properly in time

Fourth Order Runge Kutta

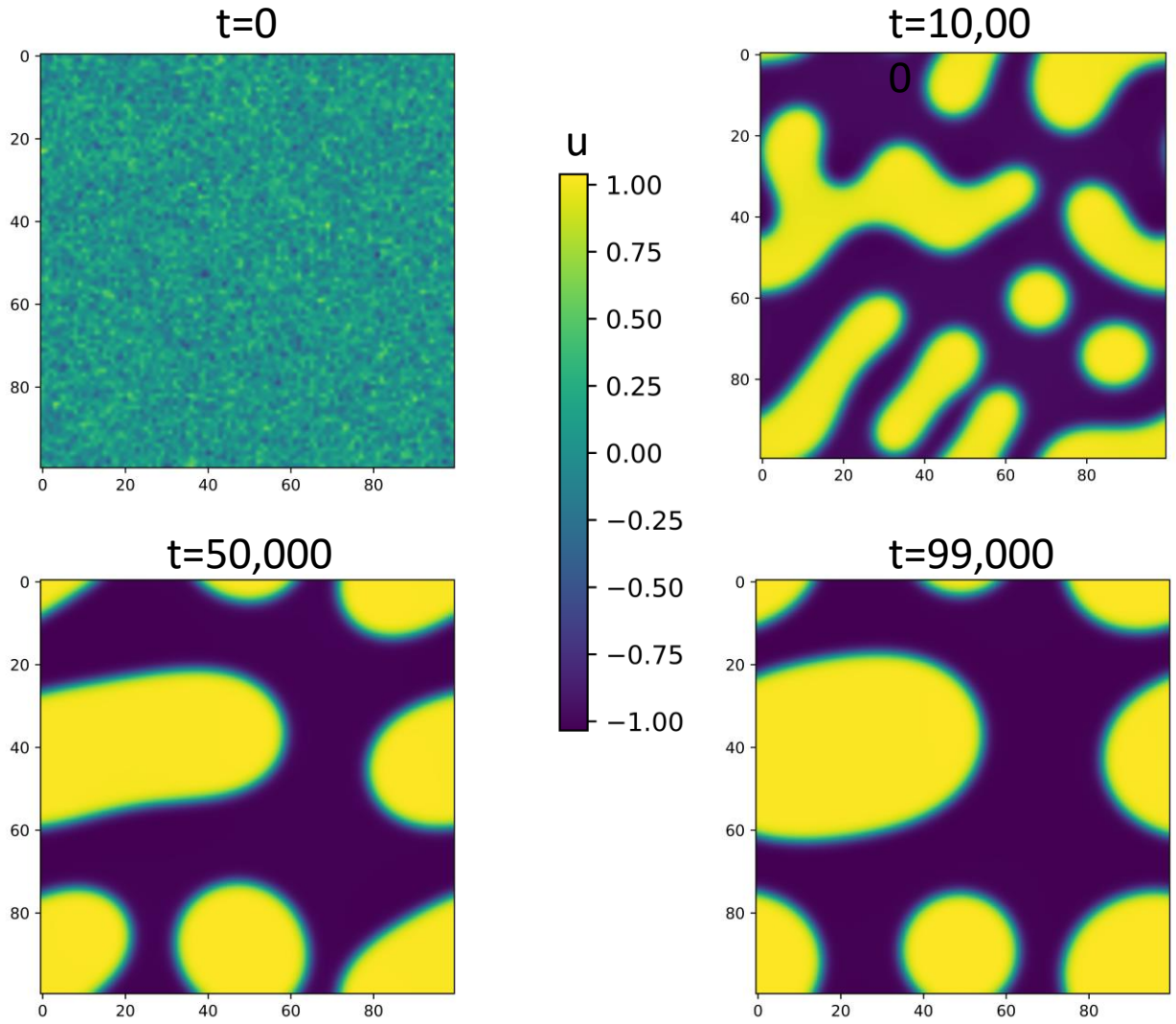
- Acts as a higher order expansion of Forward Euler algorithm, allowing the use of larger time steps
- Finds the time derivative at various locations between t and t+dt and effectively averages them

$$
\begin{aligned}
k_1 &= f(t_n, y_n), \\
k_2 &= f\left(t_n + \frac{h}{2}, y_n + h\frac{k_1}{2}\right), \\
k_3 &= f\left(t_n + \frac{h}{2}, y_n + h\frac{k_2}{2}\right), \\
k_4 &= f\left(t_n + h, y_n + hk_3\right).
\end{aligned}
$$

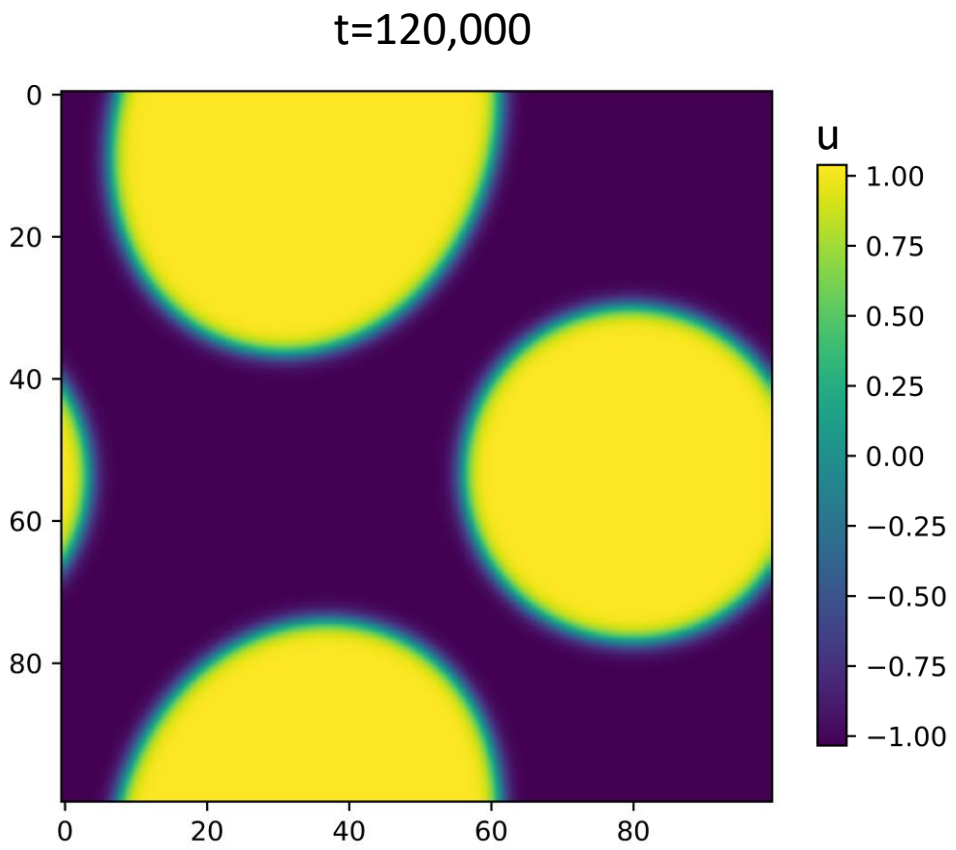
$$
y_{n+1} = y_n + \frac{1}{6}h\left(k_1 + 2k_2 + 2k_3 + k_4\right)
$$

Density Evolution Time Frames

With the parameters: $\frac{k}{\tau} = .1$, $u_i = -.1$, and $\delta = 1$.



Completely Separated System

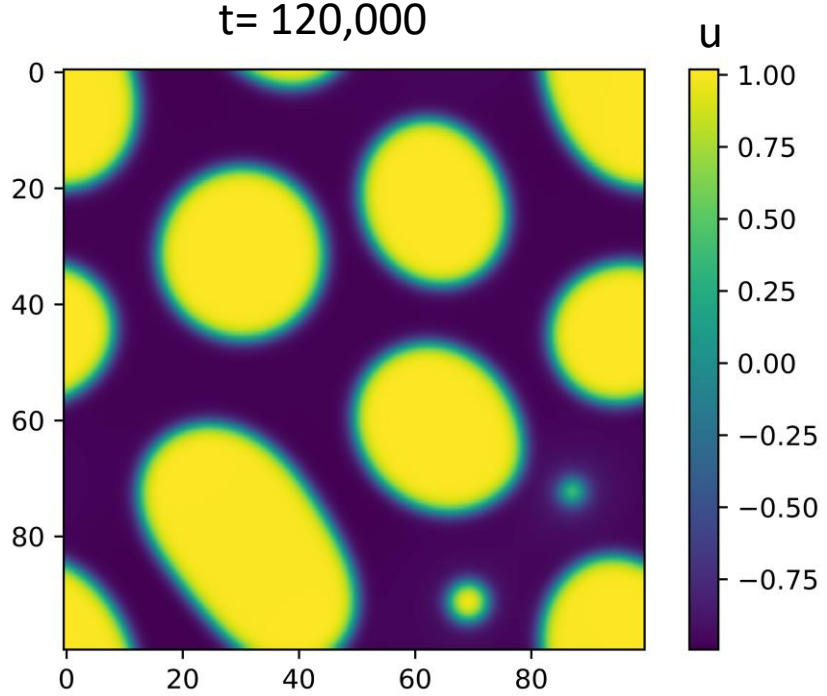


With the parameters: $\frac{k}{\tau} = .1$, $u_i = -.1$, and $\delta = 1$.

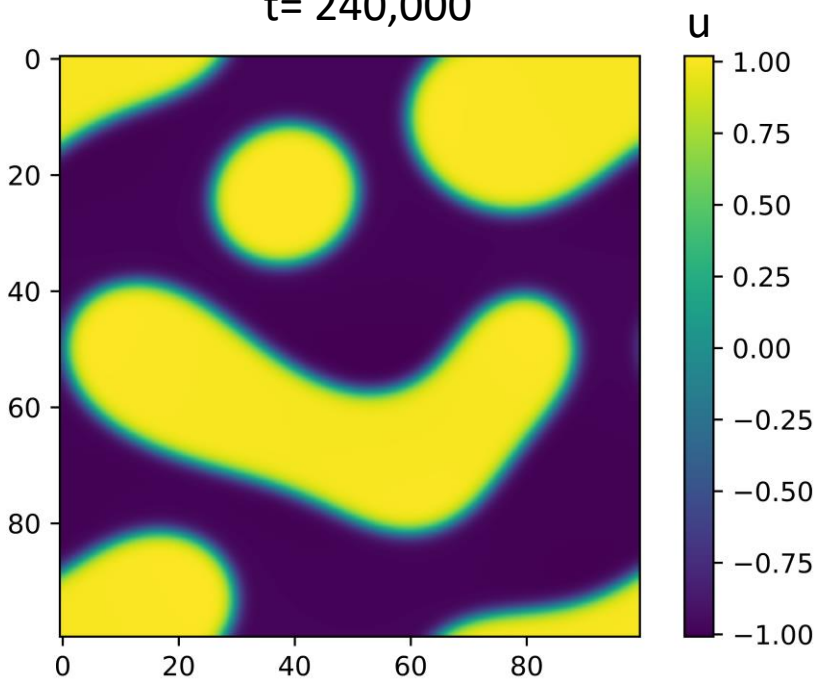
Effect of Parameters on Separation Time Scale

- Decreasing k/τ makes the phase separation occur at a slower rate
- Each figure below is for a different run with the parameters: $\frac{k}{\tau} = .01,\ u_i = -.1,\ \text{and}\ \delta = 1$

t= 120,000

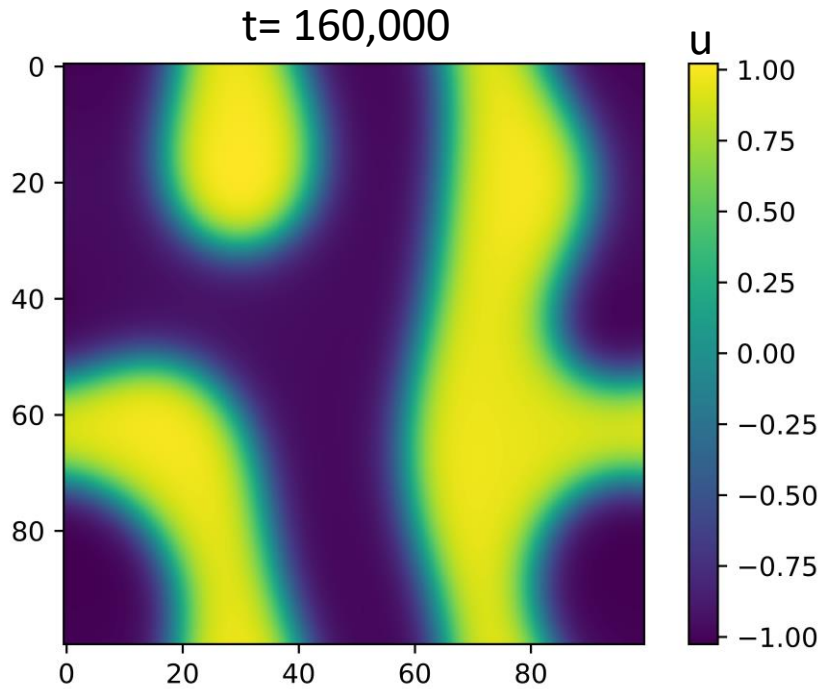


t= 240,000

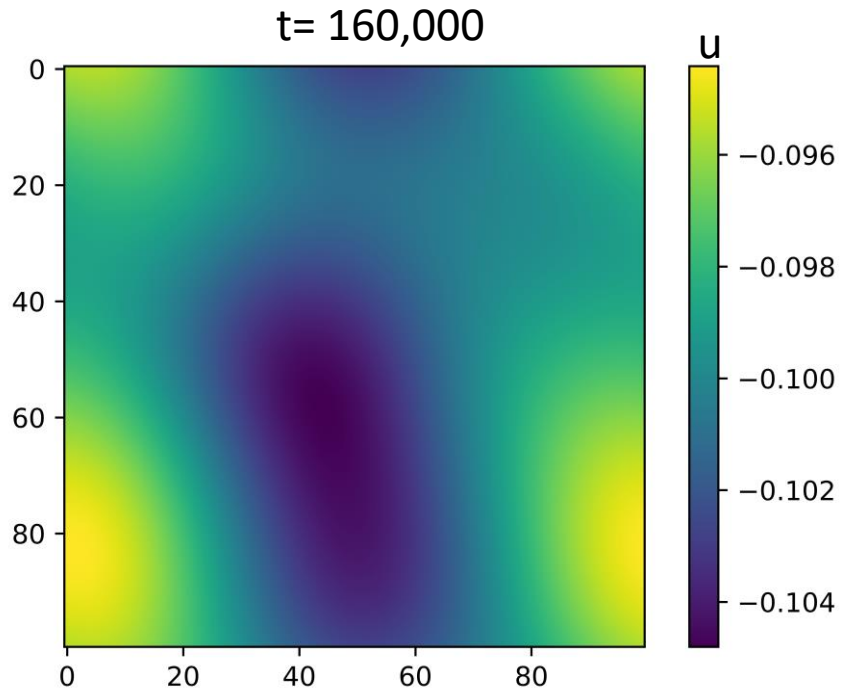


Separation Time Scale Cont.

- Increasing δ ultimately makes phase separation more difficult



With the parameters: $\frac{k}{\tau} = .1$, $u_i = -.1$, and $\delta = 3$.



With the parameters: $\frac{k}{\tau} = .1$, $u_i = -.1$, and $\delta = 10$.

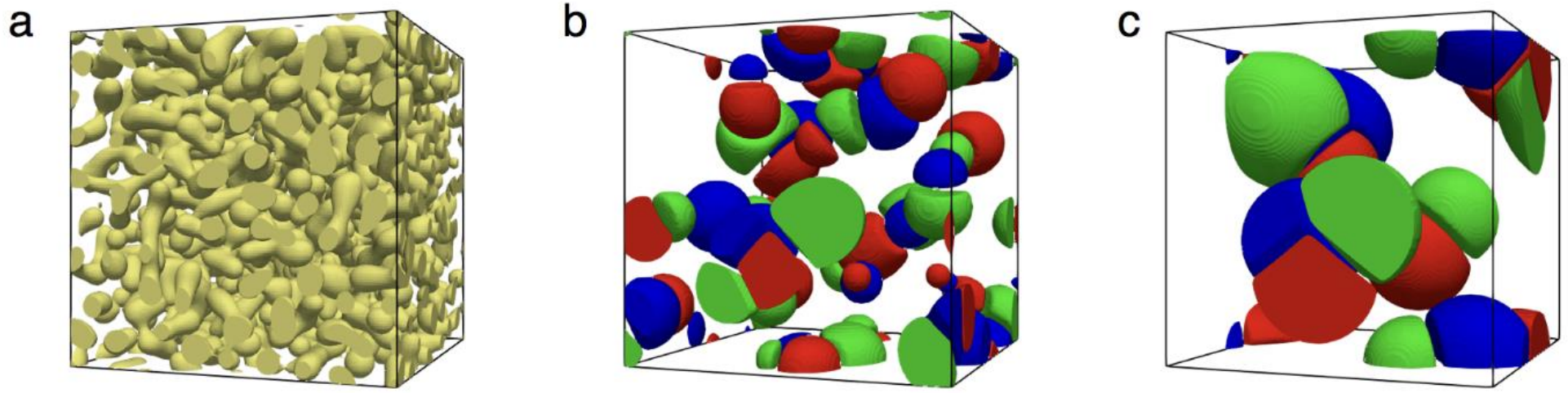
- Is there a δ such that phase separation does not occur?

Two Component Model Results

- Successfully showed phase separation for a specific parameter regime when only accounting for two phases on a flat surface
- Decreasing k/τ increases the phase separation time scale
- Similarly, increasing δ makes phase separation more difficult, especially in our relatively small lattice

Three Component Model

- To ramp up our model, we will consider three different phases, where the density of each phase ranges from 0 to 1
  - We consider each phase's entropic and interaction free energies



Mao, S. (2019). https://doi.org/10.1039/c8sm02045k

Three Component Analytics

- The generalized free energy for an N component mixture:

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

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

Where χ_{ij} are the phase interaction parameters, λ defines the interfacial width, and M_{ij} is a mobility coefficient.

Numerical Modifications

- We initialize two different density arrays, and confirm that the sum is less than 1
- Stick with same Runge Kutta formalism, except we evolve both differential equations simultaneously
- Taking the derivative is much more complex: need to account for dot products between gradients, along with additional Laplacian terms
  - Still working on this portion

Next Steps

- Two component model:
  - Possibly find critical interface thickness where phase separation no longer occurs
  - Planned to include statistics of average cluster size for various parameters; not enough data to do so yet
    - Want to generate analytic form for time steps, so I don’t need to guess and check various values
    - Adaptive time scaling (smaller time steps initially)
  - See effects of larger lattice size and different initial densities
- Three component model:
  - Need to fix way in which I numerically approximate the divergence in the evolution equation
  - See effects of modifying interaction parameters between each of the phases

Conclusion

- In terms of the two component model, we;
  - Showed a regime in which phase separation occurs
  - Determined how modifying parameters impacts the phase separation time scale

- For the three component model; I still need to correctly represent the divergence term in the evolution equation

Final Results and Modifications

Phys 230 Final Project, 5/13/22

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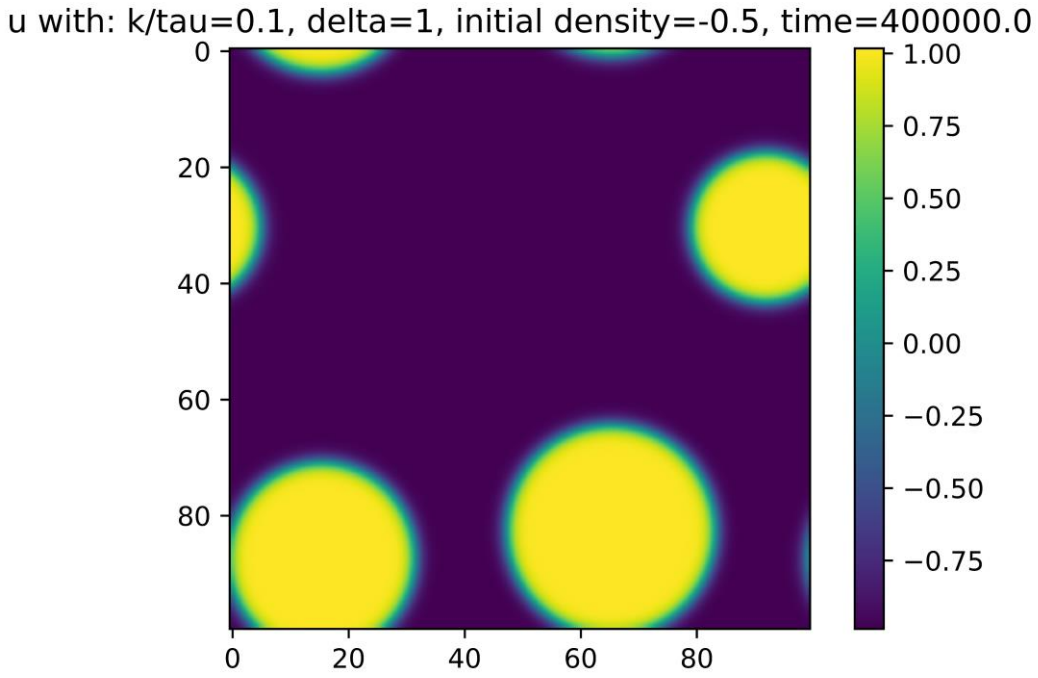
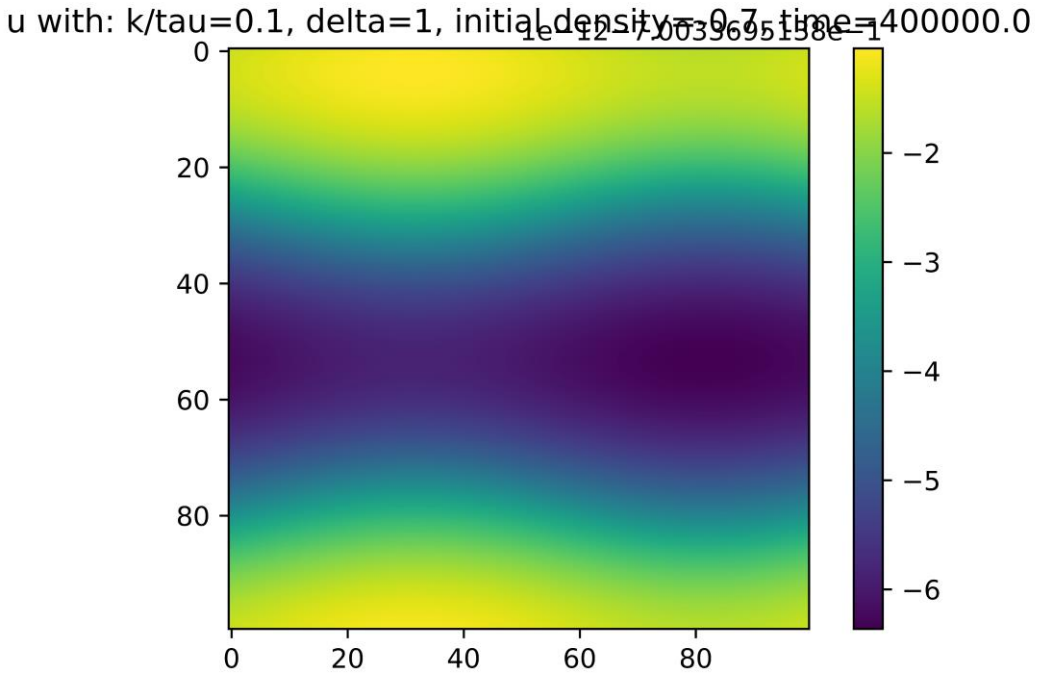
Modifications to Project

- Focused on generating a faster two component code with the numba package rather than exploring the parameter space
- Tested two component form of Flory-Huggins free energy density to compare with the original model
- With the success of our modified two component model, we created a model for a three component mixture
- See a more in depth explanation towards the end of the Phys_230_project.pdf file

Two Component Results (rk_fe_numba_combined.py)

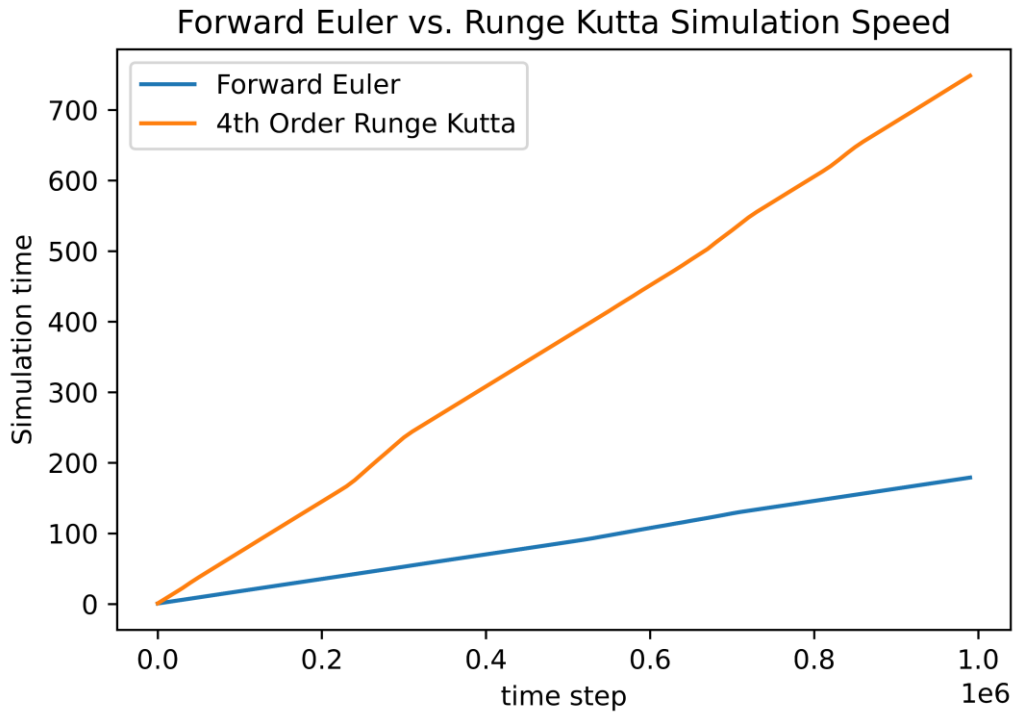




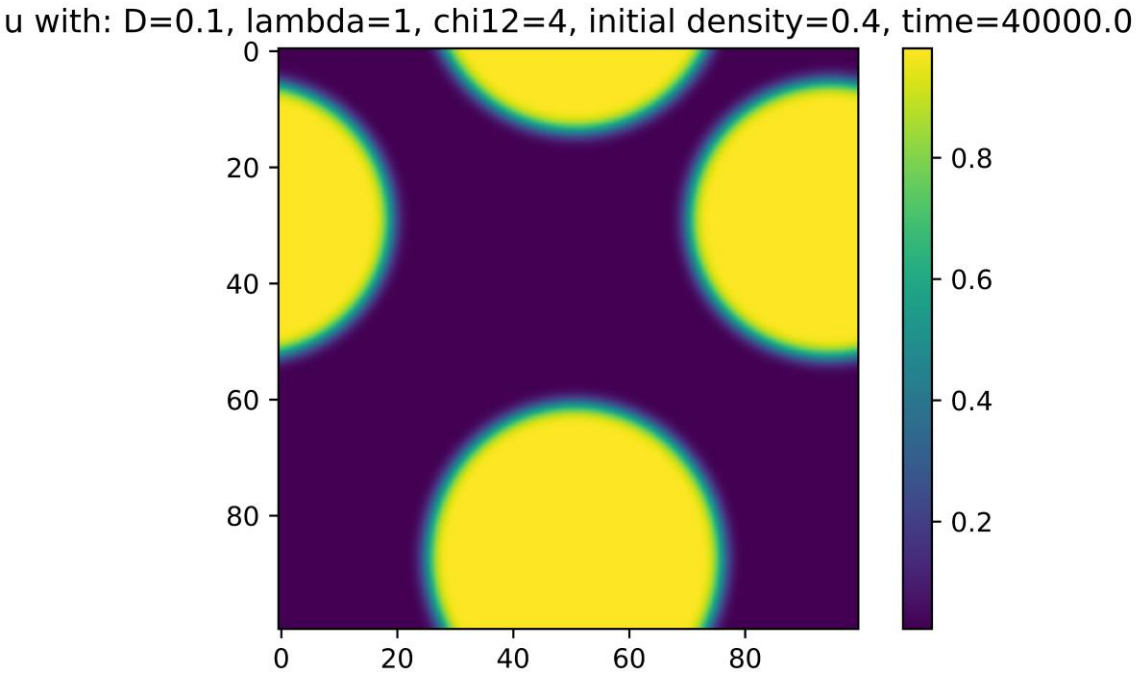
- The above graphs show a regime in which we see phase separation, and one in which we do not

Speed Comparison: Runge Kutta and Forward Euler (rk_fe_numba_combined.py, time_graph_gen.py)

- Compared simulation speeds using two component model
- Based off the parameter regimes simulated, the time step size difference is not large enough for Runge Kutta to be more efficient than Forward Euler

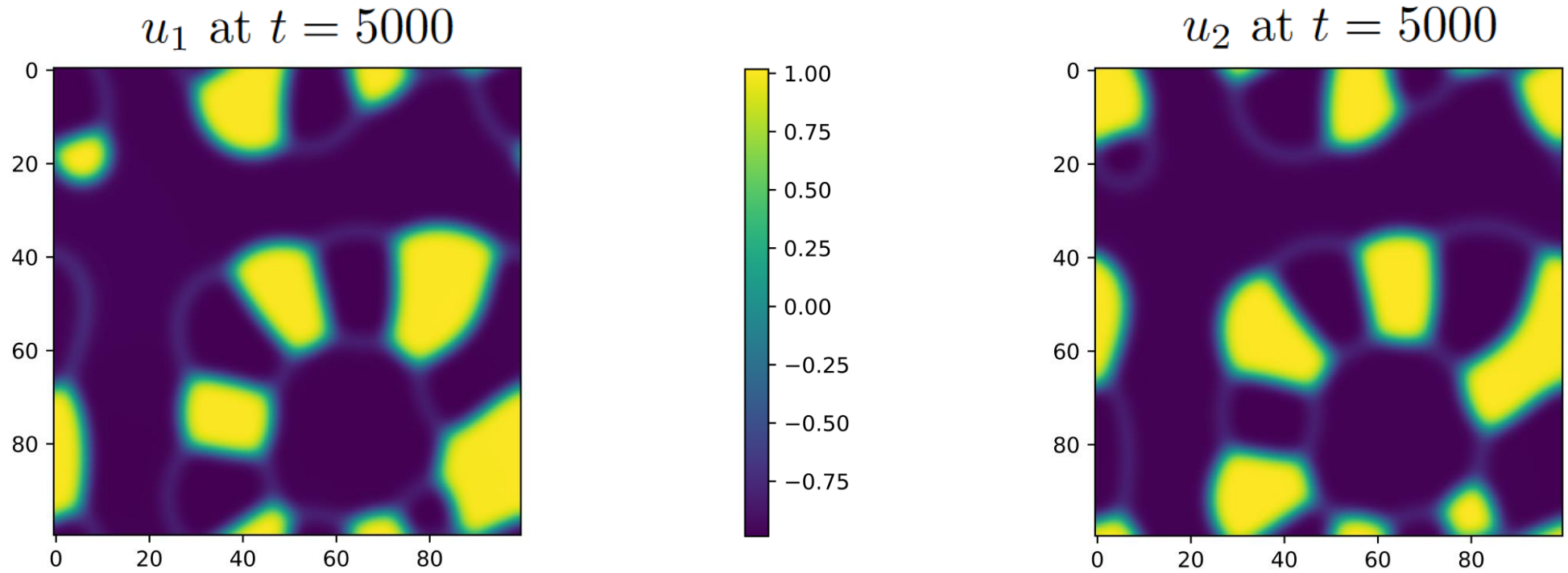


Results from Modified Two Component Model (modified2_final.py)



- Since we get similar behavior with this modified two component model we can use the same convention to generate a three component version

Three Component Model Results (three_component.py)



With parameters: $D = .1, \lambda = 1, \chi_{12} = \chi_{13} = \chi_{23} = 4, u_1$ initial $= .25, u_2$ initial $= .25$

Conclusions and Possible Next Steps

- Were able to show phase separation using both two component models
  - Can see regimes in which phase separation does and does not occur within our time frame
- Succeeded in simulating the three component system
  - However, we need to explore the parameter regimes more to see typical phase separation
- Our possible next steps include exploring parameter regimes of each model type, along with possibly modifying the Onsager coefficients in the three component model