Protein condensates by liquid-liquid phase separation using lattice-based Monte Carlo simulations

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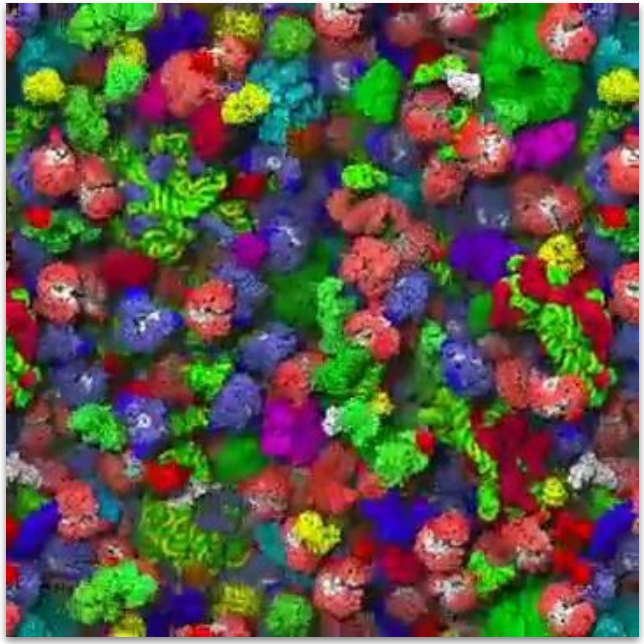
Cells have a densely packed cellular environment

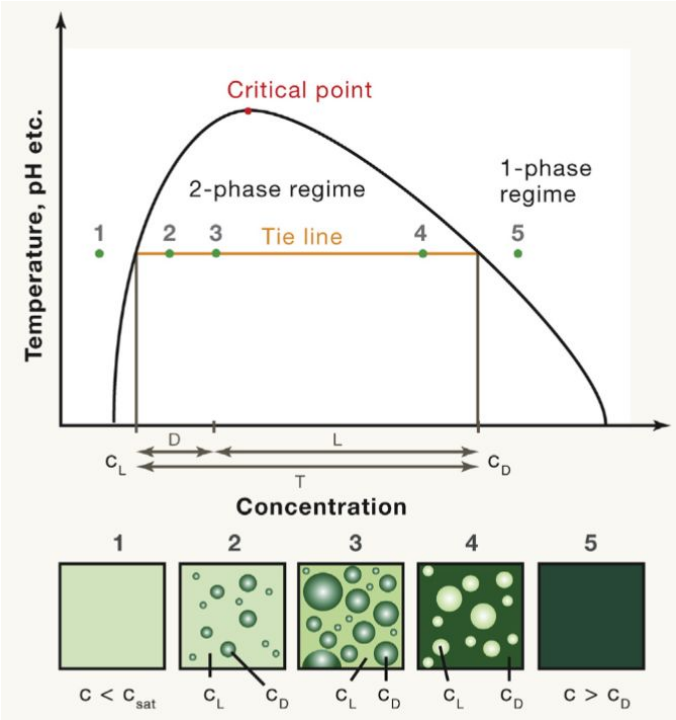
- An organized space enables control over complex biochemical reactions
- Localization of reaction components
- Membrane-bound organelles
  - Regulate flux of molecules through membrane transport machineries
- Biomolecular condensates
  - Driven by phase separation
  - Phase-separated liquid compartments
  - Multivalency-driven phase separation



McGuffee SR, Elcock AH; *PLoS Comput. Biol.*, 2010

What is liquid-liquid phase separation?

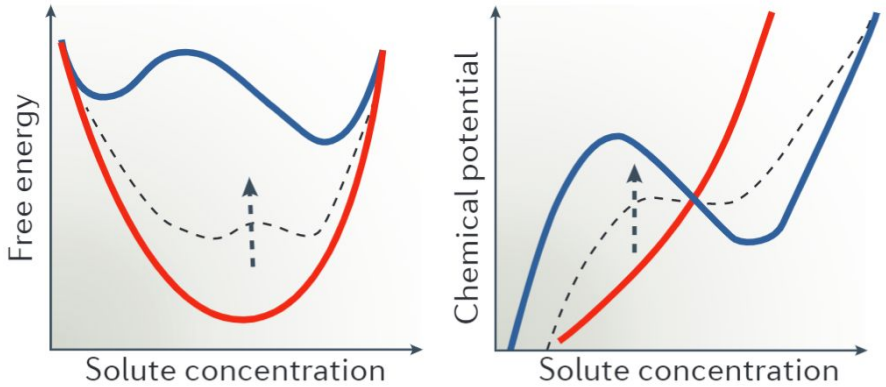
- Solution condenses into a dense and light phase
- Driving forces:
  - molecule/solvent interactions
  - molecule/molecule interactions
  - solvent/solvent interactions
- Phase separation depends strongly on:
  - Solution and environmental conditions
  - Molecule concentration and identity



Alberti,S., Gladfelter, A., and Mittag,T.; *Cell.*, 2019

Multivalency promotes phase separation

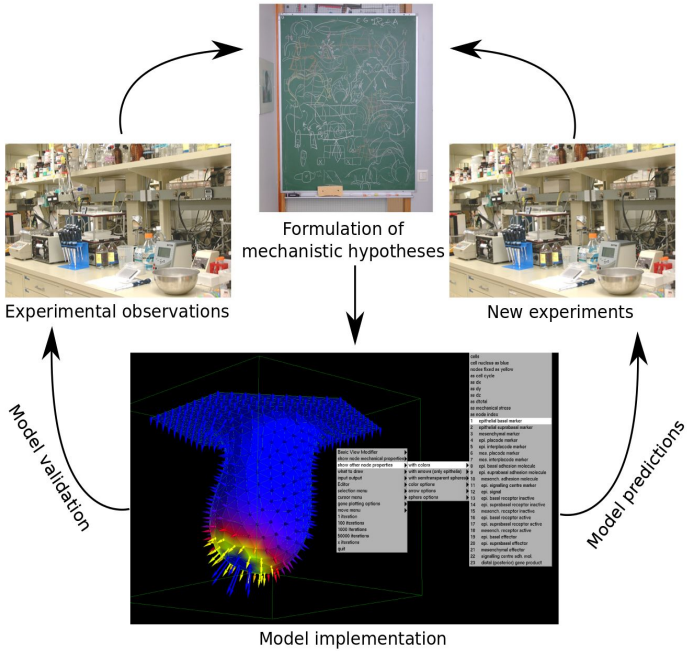
- Macromolecules assemble into large polymers
  - Higher affinity → larger complexes
- Polymeric complex formation is thermodynamically coupled
  - Complex solubility decreases as size increases
  - Complex size increase → weak, non-specific interactions between molecules are enhanced
  - Enhanced interactions → decreases complex solubility



Banani,S., Lee,H., Hyman.A, and Rosen,M.; *Nat. Rev. Mol. Cell Biol.*, 2017

Simulation and theory provide insights on the forces that drive phase separation

- Valency and physical properties of the biomolecules play a role in governing phase separation
- **Quantitative understanding of phase separation within living organisms is challenging due to incomplete knowledge of the components and their interactions**

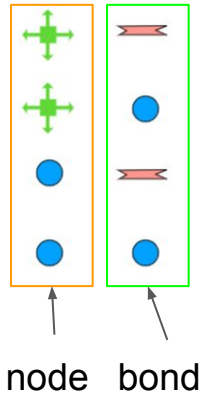


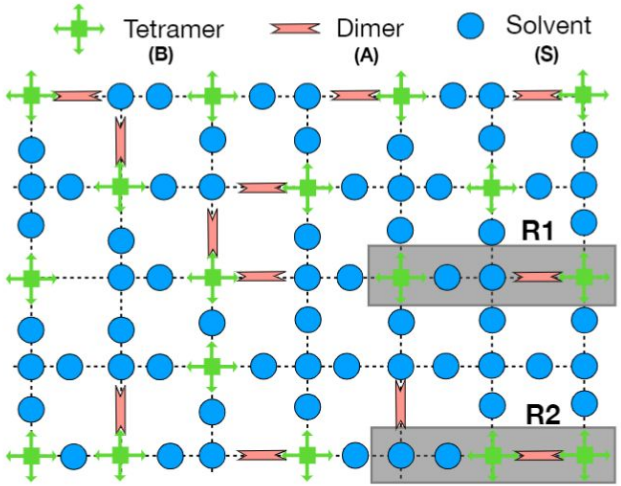
Metropolis monte carlo simulations of multivalency effects on liquid-liquid phase separation

- **Problem:** The process that leads to phase separation depends on the system and is mainly driven by thermodynamics. Biomolecular condensates often comprise biomolecules with a fixed valence whose structures allow for specific bonding interactions with a fixed number of other molecules.
- **Goals/objectives:**
  - To find and classify energetically favorable configurations of a lattice based 2D system consisting of tetramers, dimers and solvent
  - To find the tetramer-dimer concentrations that lead to molecule condensate phase separation
- **Approach:** Inside isolated system, we consider an aqueous 3-component environment including solvent, tetramer, and dimer molecules in which components are allowed to diffuse

Simulation method

- Lattice based simulation
  - 2 separate 2D lattices
  - First represents nodes: **Tetramers or Solvent**
  - Second represents bonds: **Dimers or Solvent**
- Use **random numbers** to fill the lattice
  - presence of tetramer on nodes
  - presence of dimer in bonds
- Each configuration is assigned **energy** values
  - BA (-2)
  - BS (+1)
  - SA (+1)
  - SS (-1)

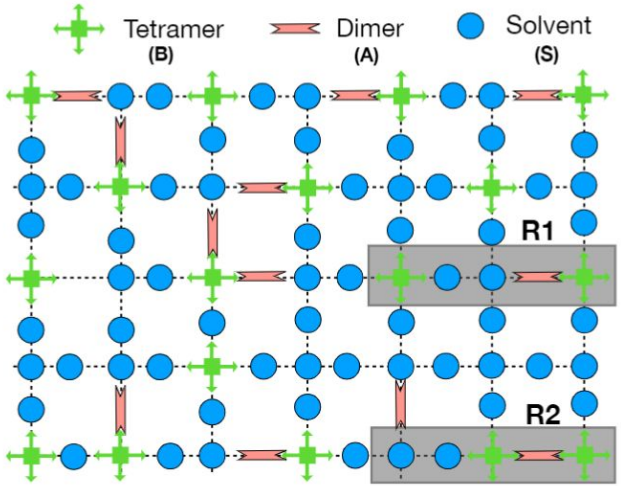




Nandii,S.,et al..; *arXic.*, 2019

Simulation method

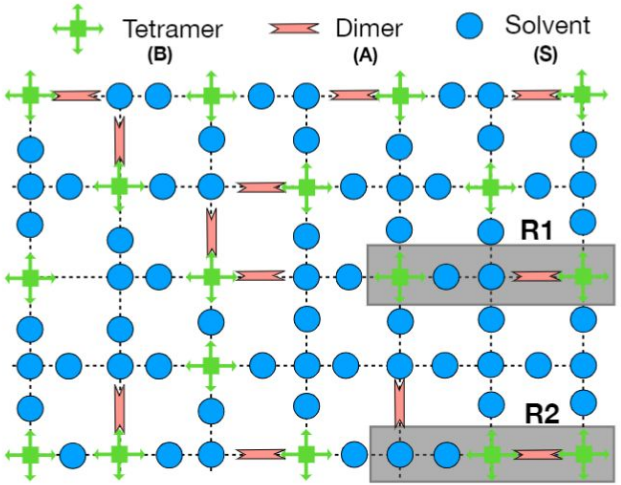
- Use **Metropolis monte carlo** simulation
  - Evaluate total energy of the initial state
  - Swap random node
  - Calculate total energy again
- Measure cluster sizes of **tetramers** that are bonded by **dimers**
- Plot average cluster size vs. **tetramer:dimer** ratio



Nandii,S.,et al..; *arXiv.*, 2019

Metropolis Monte Carlo Method

- Based on **random numbers**
- **Calculate the energy** of the system
- **Randomly choose a particle in the system to move**, and save its coordinates (the old coordinates)
- Randomly move this particle (new coordinates)
- **Calculate the energy** of the system
- Use the **difference between the new and old energies** in a Monte Carlo test. If this test passes, then keep the new coordinates, else, restore the old coordinates

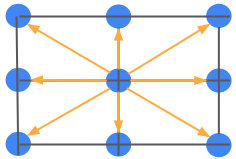


Nandii,S.,et al..; *arXic.*, 2019

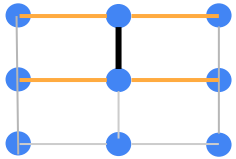
$$exp(-(E_{new} - E_{old})/kT) >= random(0,1)$$

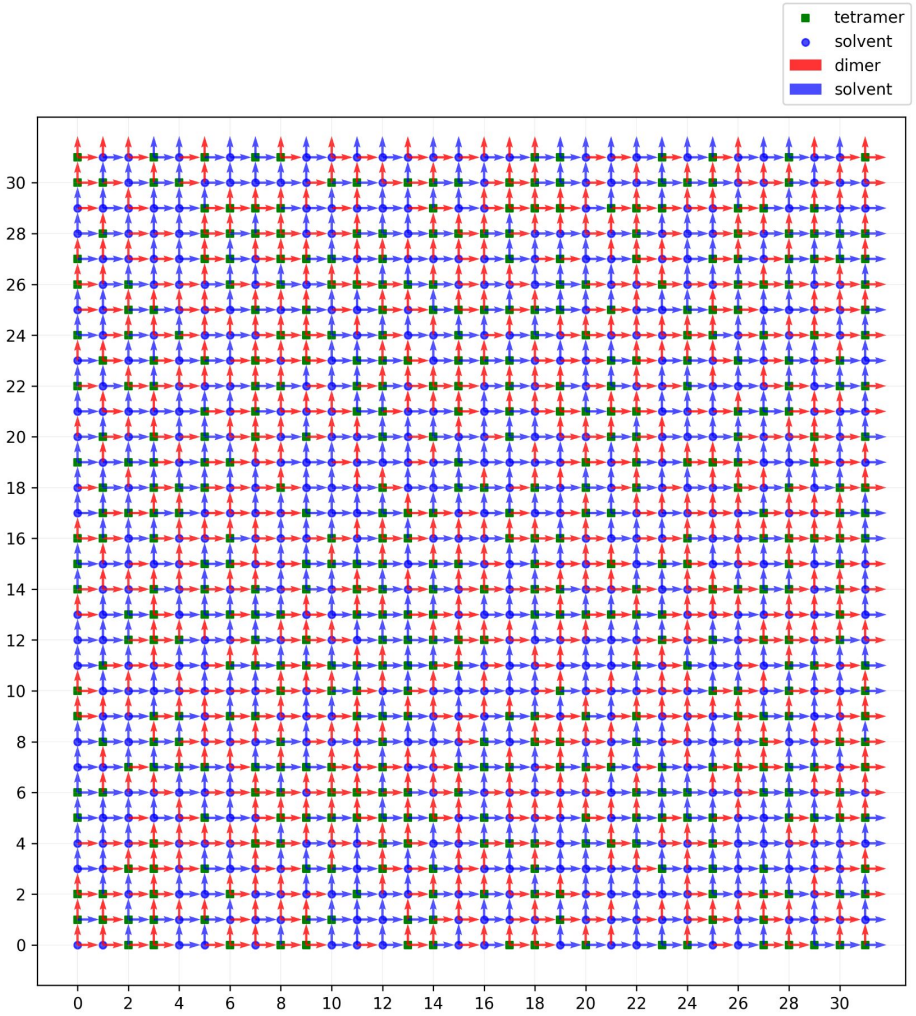
Simulation

Node movement

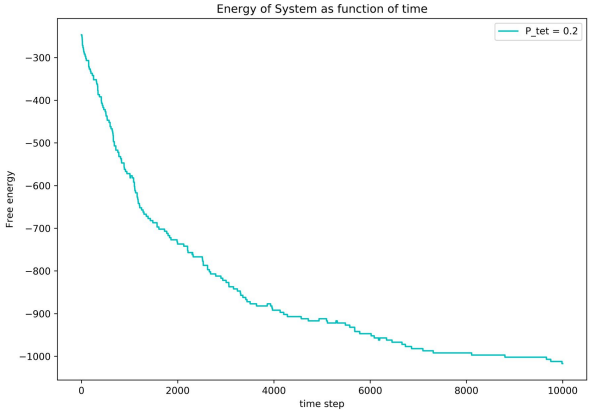


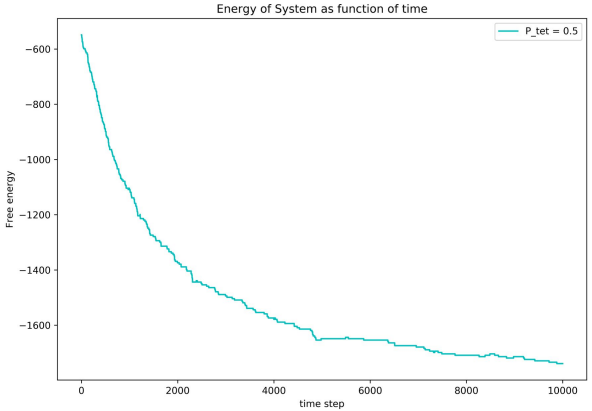
Bond movement

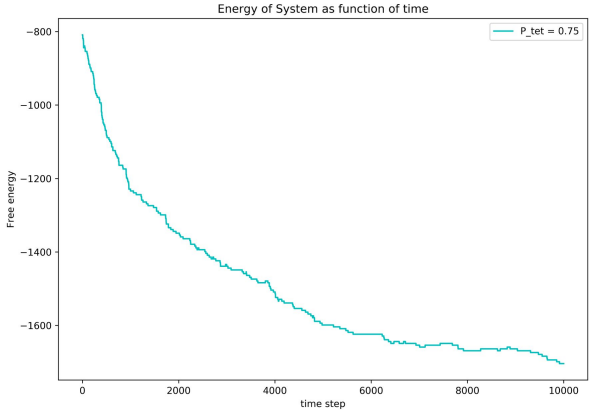




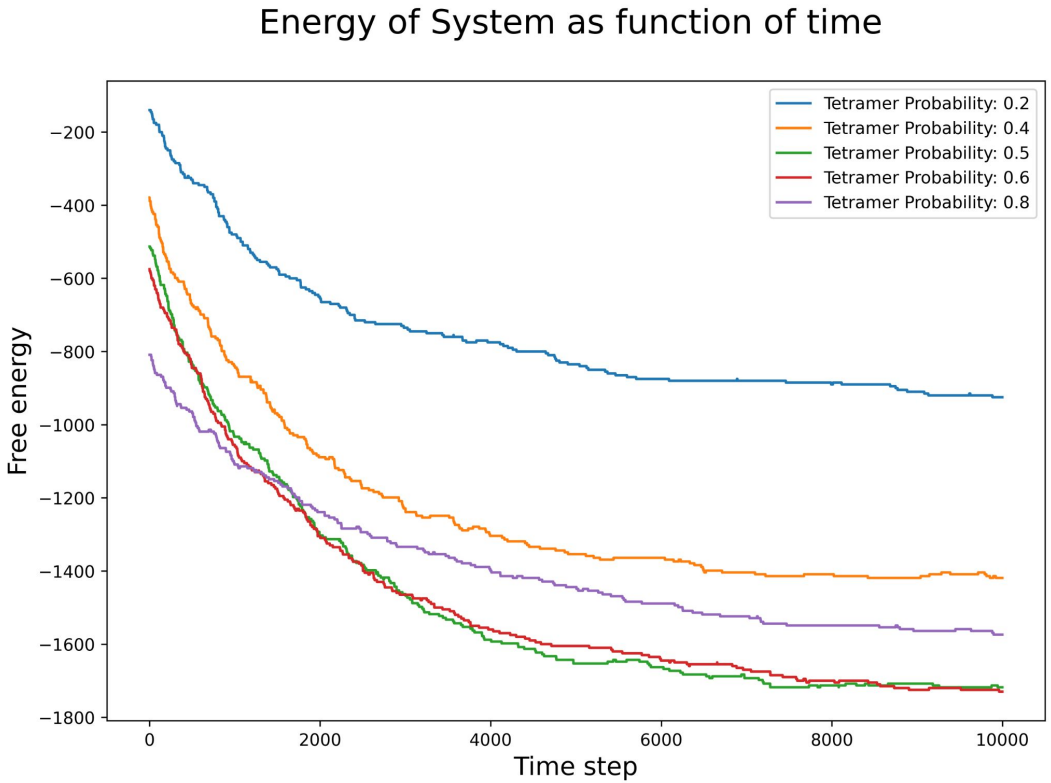
Preliminary Results







$$exp(-(E_{new} - E_{old})/kT) >= random(0,1)$$



Dimer probability: 0.5

Conclusion

- What we've done so far
  - Nodes can swap with neighbors
  - The energy is always **negative**
  - Energy of the lattice **decreases** with increasing time steps

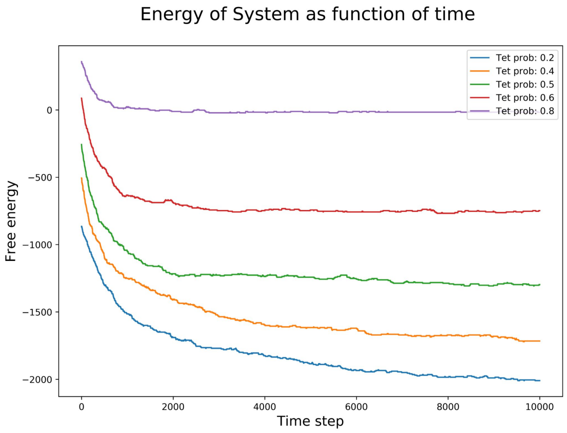
- How does the energy decrease with respect to tetramer-dimer ratio?
  - Energy **decreases faster** when we increase tetramer ratio while keeping dimer probability fixed up to a **saturation point**, after which it reverses the trend
  - For all probabilities, the energy **decreases fast** at the beginning and then the **rate of decrease slows down**

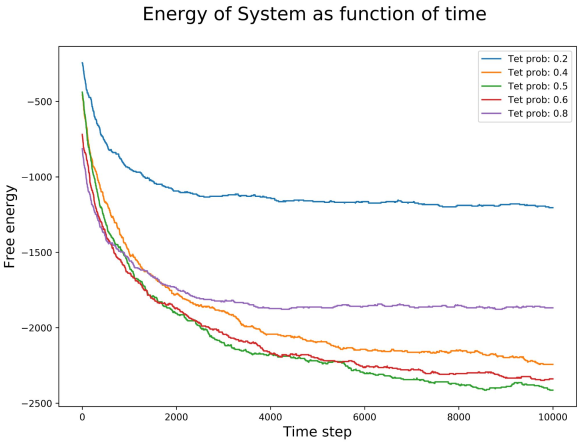
- Future plans
  - Allow bonds to swap
  - Study the impact of tetramer-dimer ratio on **rate of energy decrease**
  - Study the impact of tetramer-dimer ratio on **size of clusters** of tetramers bounded by dimers

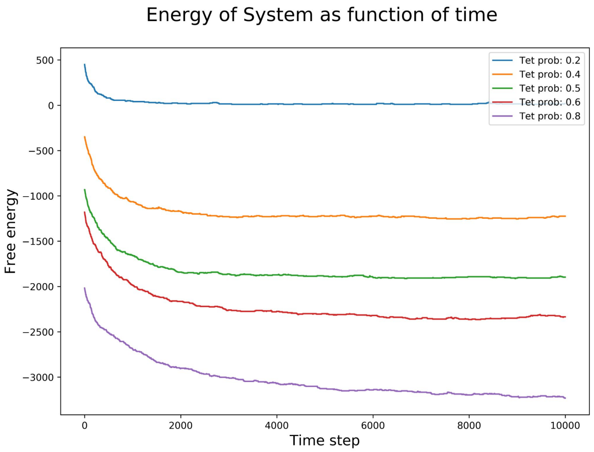
New Implementations

- Bonds are now diffusing
- Redundant swaps were removed

Energy Plots with Bonds allowed to diffuse

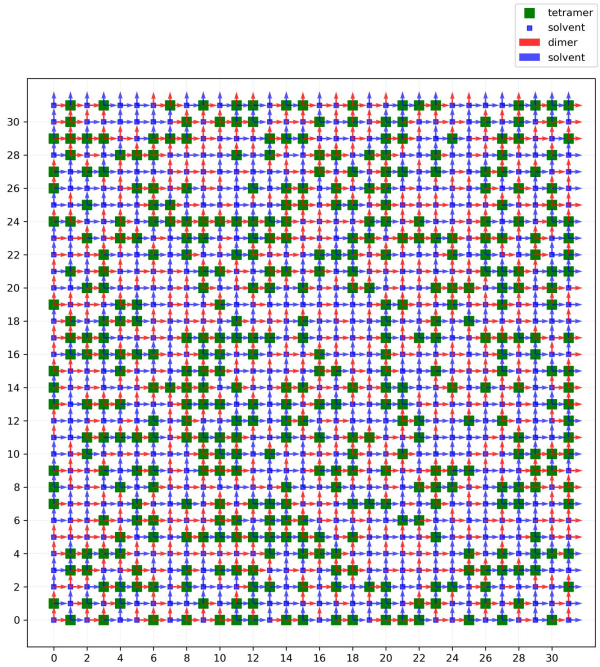


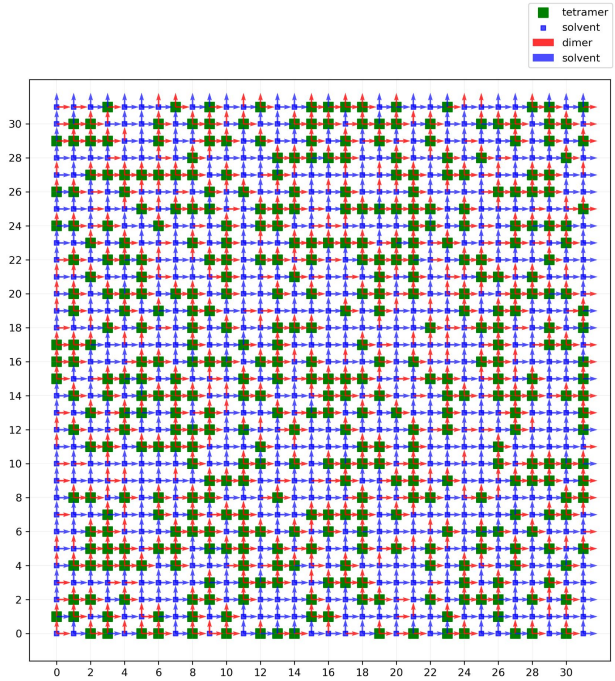




From left to right: dim_prob=0.2, dim_prob=0.5

Step 0 vs Step 10,000





Tet=0.4 and dim = 0.5

Cluster density change with simulation steps