Computational Models of Protein Phase Separation on Curved Surfaces

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Introduction

Biological liquid-liquid phase-separation plays an important role in the formation of cellular microstructures and protein organization. Experiments have shown that proteins (SynGAP and PSD-95) exhibit liquid-liquid phase transitions in neuronal structures and may influence the formation of postsynaptic densities (PSD) [1]:

- SynGAP and PSD-95 bind with high affinity.
- SynGAP trimer form a 3:2 complex with two PSD-95.
- 3:2 complex undergoes phase transitions.

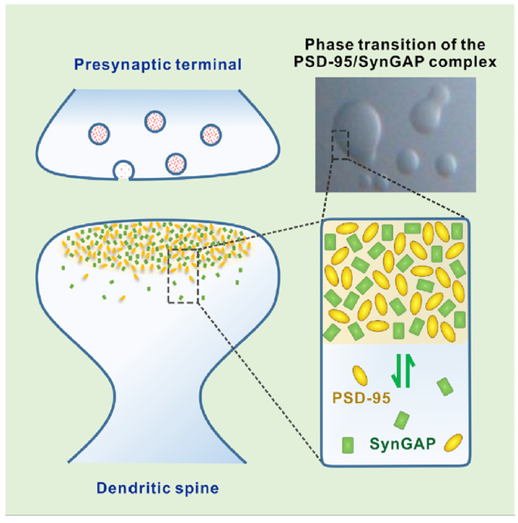

Figure 1: Phase separation of SynGAP and PSD-95 [1].

Objectives

- Model drift-diffusion at particle and ensemble scales that incorporates geometry.
- Include intermolecular and external forces on proteins.
- Phase separation model coupled to proteins.

Drift-Diffusion Markov Chain

Transition Probabilities:

$$M_{ij} \propto \overbrace{\exp\left(-\frac{|x_i - x_j|^2}{4D\Delta t}\right)}^{\text{Drift-Diffusion}} \times \overbrace{\exp\left(-\frac{u_i - u_j}{2k_BT}\right)}^{\text{Gibbs-Boltzmann}} \times \overbrace{\exp\left(-\frac{\log A_i - \log A_j}{2}\right)}^{\text{Area Correction}} \quad (1)$$

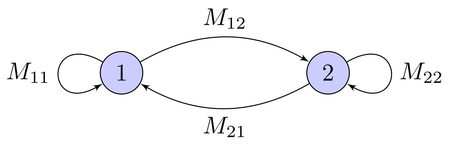

Figure 2: Simplified Markov Chain

Ginzburg-Landau Field

Potential Energy:

$$V[q] = \overbrace{\alpha_1 \sum_i \sum_{j \neq i} W_{ij}(q_i - q_j)^2}^{\text{Nearest Neighbors Similar}} + \overbrace{\alpha_2 \sum_i (1 - q_i^2)^2}^{\text{Phase Collapses to } \pm 1} . \quad (2)$$

Figure 3: Ginzburg-Landau Field. Click here for animation.

Results

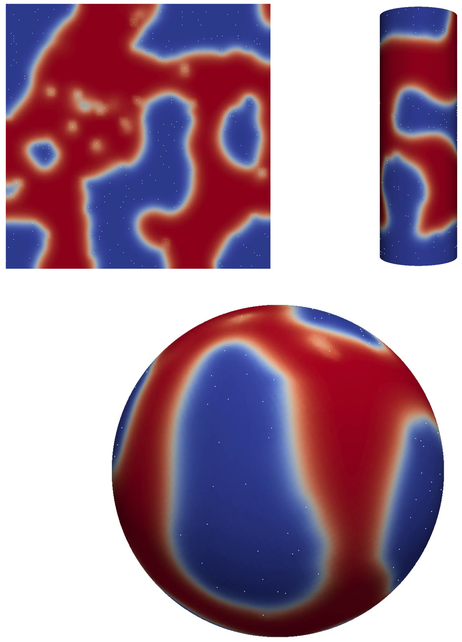

Figure 4: SynGAP/PSD95 clustering simulations on planar, cylindrical, and spherical surfaces. Click here for animations.

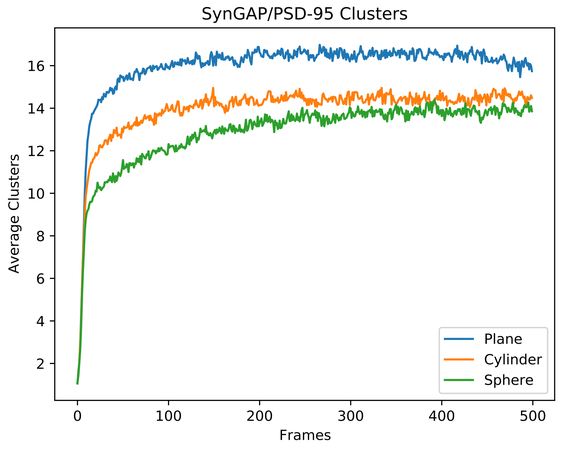

Figure 5: Number of protein clusters on different surfaces, averaged over ~ 50 simulations.

Conclusion

- Developed model incorporating geometry and protein dynamics at continuum and particle level dynamics.
- Analyzed the role of geometry in clustering of proteins.
- Applied to protein phase separation of SynGAP and PSD-95 clustering in neuronal dendritic spines.

References

[1] M. Zeng et al. Phase transition in postsynaptic densities underlies formation of synaptic complexes and synaptic plasticity. *Cell*, 166:1163–1175, 2016.

Acknowledgements

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