Dynamics of nonequilibrium self-assembly

through reaction-diffusion simulations

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Protein self-assembly is critical for life



Dayel.com

Biological motivation from clathrin-mediated endocytosis



Outside the cell

Biological motivation from clathrin-mediated endocytosis

Cytoplasm



Outside the cell

Coated structures nucleate on the plasma membrane



Sochacki et al, Nat Cell Biol 2017

A long-term question

• How is the transition from early clathrin-coated structures to productive vesicles controlled?



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Membrane Localization

• Stoichiometry

Current methods for simulating self-assembly have limitations

Limitations

Molecular Dynamics

- Cell-scale dynamics
- Non-equilibrium events

Strengths

- Molecular structure
- Steering





Grime et al, Nat Comm 2016







Add molecular structure



Algorithms for single-particle RD

Flexible



Readdy

Schoneberg, J & Noe, PLoS One 2013

Adding molecular structure to reaction-diffusion



```
p_{react}(\varDelta t | \mathbf{r} = \mathbf{c_1} - \mathbf{c_2}, \mathbf{l_1}, \mathbf{l_2})
```

Parameters: k_a , D_1 , D_2 , σ , D_{R1} , D_{R2} , l_1 , l_2

MEJ. J Phys Chem B (2018)

Adding molecular structure to reaction-diffusion



MEJ. J Phys Chem B (2018)

github.com/mjohn218/

NERDSS is a versatile software for non-equilibrium self-assembly simulations



MEJ, Hummer *Phys Rev X*Yogurtcu, MEJ, *J Chem Phys*MEJ *J Phys Chem B*Fu, Y., ...MEJ, *J Chem Phys*

Varga, Yogurtcu, Loggia, & MEJ In prep. 2019

github.com/mjohn218/NERDSS_beta

Assembly can be driven through multiple mechanisms



For clathrin assembly, relative copy numbers control success of assembly

Conc.=1.7 μM

K_D=100 μM



Clathrin localizes t adaptor proteins, populations







Membrane localization reduces the dimensionality of the search









Yogurtcu, O.N. MEJ. PLoS Comp Biol 2018









Concentration: A⁻¹



Significant increase in complex formation



Yogurtcu, O.N. MEJ. PLoS Comp Biol 2018

Conclusions

- Membrane localization can control timing and success of self-assembly via dimensionality reduction
- Many proteins, particularly involved in membrane remodeling, can exploit localization to drive protein-protein binding
- NERDSS simulates self-assembly models previously inaccessible to existing software tools

Thanks!

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Graduate & postdoc positions available!



COLLABORATORS

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National Institute of General Medical Sciences

