Dynamics of nonequilibrium self-assembly through reaction-diffusion simulations

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1. Abstract

In diverse cellular pathways including clathrin-mediated endocytosis (CME) and viral bud formation, cytosolic proteins must self-assemble and induce membrane deformation. To understand the mechanisms whereby assembly is triggered and how perturbations can lead to dysfunction requires dynamics of not just assembly components, but their coupling to active, force-responsive, and ATP-consuming structures in cells. Current computational tools for studying self-assembly dynamics are not feasible for simulating cellular dynamics due to the slow time-scales and the dependence on energy-consuming events such as phosphorylation. We recently developed novel reaction-diffusion algorithms and software that enable detailed computer simulations of nonequilibrium self-assembly over long time-scales [1]. Our simulations of clathrin-coat assembly in CME reveal how the formation of structured lattices impacts the kinetics of assembly, and how localization to the membrane can stabilize large, dynamic assemblies not observed in solution. We developed a relatively simple equilibrium theory to quantify how localization of protein binding partners to the membrane can dramatically enhance binding through dimensionality reduction, providing a trigger for assembly [2]. Tuning the speed and success of vesicle formation can be sensitively controlled by the stoichiometry of assembly components, particularly those that control membrane localization through lipid binding [3]. Our results suggest that stoichiometric balance and membrane localization can act as potent regulators of self-assembly, and our reaction-diffusion software provides a powerful tool to characterize dynamics within the cell.

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[3] Holland, D.O. Johnson, M.E.* Stoichiometric balance of protein copy numbers is measurable and functionally significant in a protein-protein interaction network for yeast endocytosis. *PLoS Comp Biol.* **14**, e1006022 (2018).