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Governing Principles of Multiprotein Complex Formation on The Cell Membranes: Insights from Theory and Reaction-Diffusion Simulation[1] OSMAN N. YOGURTCU, MARGARET E. JOHNSON, Johns Hopkins University — A significant number of the cellular protein interaction networks, such as receptor-mediated signaling and vesicle trafficking pathways, includes reactions that involve membranes as a molecular assembly platform. Membranes both reduce the search space and induce a cooperative binding effect for stabilizing complexes with multiple membrane recruiter molecule binding sites. Mathematical models along with computer simulations provide insight into the dynamics of complex formation and help identify general principles that govern successful recruitment and assembly on membranes. Here, using a very efficient in-lab developed single-molecule scale stochastic simulation software, we show that the magnitude of complex formation enhancement has a simple functional form that applies whenever membrane recruiter concentrations are sufficiently high, and surprisingly, is independent of the protein binding strength. We propose that membrane localization works as a mechanism that ensures assembly only at specific times (after recruitment to surfaces) but does not precisely regulate the proteins involved since they benefit equally from surface restriction. This robust strategy is employed by adaptor proteins involved in clathrin-mediated endocytosis in both yeast and mammalian cells, where their relatively weak binding interactions with one another prevents protein coat assembly in solution, but transitions to a rapid assembly on the plasma membrane.

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