

Novel Single-Molecule Resolution Method for Spatio-Temporal Simulations of Protein Binding and Recruitment on the Membrane

Osman N. Yagurtcu, Margaret E. Johnson. Department of Biophysics, Johns Hopkins University, Baltimore, MD, USA.

In the early stages of clathrin-mediated endocytosis (CME), a variety of distinct proteins can bind to the membrane and engage in further interactions with proteins on the membrane and in solution. Understanding the dynamics of this process requires correctly accounting for the behavior of protein interactions while restricted to the 2D membrane surface, as it is fundamentally distinct from binding in solution due to changes in the dynamics of the proteins. Here we introduce the 2D Free-Propagator Reweighting (2D-FPR) method that accurately models the spatial and temporal dynamics of proteins as they are recruited to the membrane surface and as they interact with one another while bound to the membrane. In this method the position of each diffusing protein is tracked, and reactions between binding partners can occur upon collisions. Reaction probabilities are determined by the solution to the 2D Smoluchowski diffusion equation with reactive boundary conditions, allowing us to take large time steps. Molecule positions are propagated by free diffusion, but by using a trajectory reweighting approach we can recover the exact association rates for all reactive pairs. This approach is uniquely able to capture the changes in protein binding dynamics that can occur upon membrane binding because it accounts for both the diffusional motion of proteins and their binding reactions. These important details are absent from models that lack spatial resolution. We present our simulation results on modeling adaptor protein interaction dynamics, and discuss the effects of varying local protein concentration on both recruitment to the membrane and complex formation in the confined 2D geometry.