Physics of Formin Regulated Actin Growth

Daniel Reeves[1], Keith Cheveralls[1], and Jané Kondev[1]

Short Abstract — **The formin family of proteins persistently cap growing ends of actin filaments and regulate elongation. We analyze the mechanism by which binding sites on flexible protein tethers recruit actin monomers to the growing end via a generic two step process. The binding sites capture freely diffusing actin monomers, which are then transferred to the growing end. We develop computational and analytic models that predict how the kinetics of the diffusion-to-capture process can be regulated by parameters such as tether length and number. This general mechanism plays roles in systems as diverse as cell adhesion and viral assembly.**

Keywords **— formin, actin dynamics, diffusion-to-capture**

I. Introduction

FORMINS are a widely expressed family of proteins that play active roles in the regulation and growth of cytoskeletal structures. They are responsible for rapid nucleation and assembly of actin filaments and networks. By capping the fast-growing barbed end of actin filaments, while allowing on-going insertion of actin subunits, they exclude other capping proteins from halting the growth of the filament [1]. The formin homology 1 (FH1) domain is critical for this function, in that it restores or improves growth of the capped actin filament; in some cases the FH1 domain increases the rate beyond that of actin alone [2]. It is thought to act as a flexible tether between multiple profilin-actin binding sites and the capping domain.

We analyze a general mechanism by which cells may regulate the diffusion-limited step of ligand binding by utilizing tethered binding sites. Specifically, the flexible FH1 domain recruits actin monomers to the growing end via a generic two step dynamic process. First, tethered binding sites collide with diffusing profilin-actin monomers. Second, the tethered receptor/ligand complex diffuses until the actin is transferred to the growing end. We focus on the first process, by which a freely diffusing ligand is captured by a tethered binding site. Previous work [3, 4] has explored equilibrium statistics such as occupancy, whereas we investigate the kinetics of binding as a function of parameters such as tether length, number of binding sites, and number of tethers.

Similar mechanisms are implicated in other biological systems. Virus capsid assembly is accelerated and stabilized by the coulombic interaction between tether-like RNA and capsomers [5]. Some scaffold proteins improve self-assembly of multi-domain proteins by providing a flexible scaffold. This process is also pertinent to cell adhesion in which tethered ligands form bridges to surface receptors on neighboring membranes [6].

II. Approaches

We analyze the dynamics of the diffusion process using analytic, simulational and experimental approaches. Specifically, we calculate capture rates as a function of length and number of the tethers, binding radius, and diffusion constant. We treat the diffusion to capture problem with Smuluchowskii type diffusion-reaction equations, utilizing the local equilibrium approximation [7, 8] for the dynamics of the tether. We find numerical and analytical solutions to the equations. Simulations are performed in three dimensions using the bond-fluctuation model for the tether and a random walk for the free ligands.

Experiments are underway in collaboration with the Goode and Dogic labs at Brandeis University. They will measure the effect of tether length and number of tethers on formin capped actin polymerization using formin constructs with synthetic tethers.

III. Results & conclusions

From the analytic and simulation results, we estimate that capture rates vary by a factor of two or more over a range of FH1 domains. Therefore, we expect the experiments to yield measurable changes in growth rate with tether length that will indicate the relative importance of the two steps in the capture/transfer process. Furthermore, we find a non-linear relationship between capture rate and tether number, which we expect to be borne out by experiments.

References

[1] Goode, B.L., and M.J. Eck (2007). Mechanism and function of formins in the control of actin assembly. Annual Review of Biochemistry 76:593-627.

[2] Kovar, D.R., et al. (2006). Control of the assembly of ATP- and ADP-actin by formins and profilin. Cell 124(2):423-435.

[3] Longo, G., and I. Szleifer (2005). Ligand-receptor interactions in tethered polymer layers. Langmuir 21(24).

[4] Zhang, C.Z., and Z.G. Wang. (2007). Polymer-tethered ligand-receptor interactions between surfaces II. Langmuir 23(26).

[5] Hu, T., and B.I. Shklovskii. (2007). Kinetics of viral self-assembly: Role of the single-stranded RNA antenna. Physical Review E 75(5)

[6] Jeppesen, C., et al. (2001). Impact of polymer tether length on multiple ligand-receptor bond formation. Science 293.

[7] Szabo, A., K. Schulten, and Z. Schulten (1980). 1st Passage Time Approach to Diffusion Controlled Reactions. Journal of Chemical Physics 72(8).

[8] Hyeon, C., and D. Thirumalai (2006). Kinetics of interior loop formation in semiflexible chains. J Chem Phys 124(10):104905.

[1]Department of Physics and Program in Quantitative Biology, Brandeis University, Waltham, MA. E-mail: dreeves@brandeis.edu