

503c Exploring the Allostery of Actin Filaments Via Molecular Dynamics Simulations and Coarse-Grained Analysis

Jhih-Wei Chu and GREGORY A. Voth

The structural and mechanical properties of monomeric actin, the trimer nucleus, and actin filaments are determined as a function of the conformation of the DNase I binding loop (DB-loop) using all-atom molecular dynamics (MD) simulations and coarse-grained (CG) analysis. The simulations of the actin filament contain a total of 575,000 atoms. Recent X-ray structures of monomeric actin in the ADP state (G-ADP) by Otterbein et al. (Science, 293, 5530, 2001) and in the ATP state (G-ATP) by Greceffa and Dominguez (Journal of Biological Chemistry, 278, 34172, 2003) indicate that the DB-loop of actin does not have a well-defined secondary structure in the ATP state but folds into an alpha helix in the ADP state. MD simulations and CG analysis indicate that such a helical DB-loop significantly weakens the inter-monomer interactions of actin assemblies, and thus leads to a wider, shorter and more disordered filament. The computed persistence lengths of actin filament composed of G-ATP, F-ATP (16 micrometer), and of G-ADP, F-ADP (8.5 micrometer) agree well with the experimental values for the two states. Therefore, the changes of structure and mechanically properties of actin filament after ATP hydrolysis can be attributed to a loop-to-helix transition of the DB-loop. This may provide a direct connection between the conformational changes of an actin monomer and the structural and mechanical properties of the cytoskeleton. The information provided by MD simulations also helps to understand the possible origin of the special features of actin dynamics such as faster growth/dissociation rates at the + end, the higher ATPase activity after polymerization, and fragmentation.