Finite Element Framework for Mechanics and Dynamics of Supramolecular Protein Assemblies

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FINITE ELEMENT FRAMEWORK FOR MECHANICS AND DYNAMICS OF SUPRAMOLECULAR PROTEIN ASSEMBLIES

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INTRODUCTION

The conformational dynamics and mechanical properties of supramolecular protein assemblies play a central role in a broad array of cellular functions ranging from migration and division to transcription and translation. The finite element method (FEM) provides a natural framework for the computation of protein normal modes and mechanical response based either on atomic coordinates or electron density maps [1]. Here, we present development of the finite element framework for the computation of actin filament mechanics and solvent damping effects. A new normal modes data bank for structures in the electron microscopy data bank (EMDB [2]) is also presented.

ACTIN FILAMENT MECHANICS

Recent molecular dynamics simulations [3] of ATP-bound and ADP-bound F-actin structures indicate that conformational changes involved in the DNAse-binding loop in subdomain two of G-actin are responsible for the nearly factor of two change in persistence length and associated effective bending stiffness measured experimentally [4]. This might be attributable principally to changes in atomic-level filament shape, which should be captured by a coarse-grained elastic model based on atomic-level molecular shape [1]. Also, it remains largely unknown how actin-binding proteins mediate F-actin equilibrium mechanical properties, despite their importance to understanding the mechanics and stability of actin-based cellular processes. Thus, it is important to study the equilibrium mechanical properties of F-actin examining the roles of bound nucleotide state and actin-binding proteins.

To illustrate, single filaments of more than 52 monomers (Figure 1A & B) are simulated using the coarse-grained elastic FE model to examine the effects of fimbrin ABD2 on filament mechanical stiffness in stretching, torsion, and bending (Figure 1A–D). We hypothesize that the filament elastic strain energy distribution is altered by actin-binding proteins, as shown in Figure 1, and that this leads directly to the observed differences in equilibrium, linear mechanical response properties, as well as to the alteration of nonequilibrium rupture/fracture strength under these different modes of loading. For example, bound actin-binding protein may alter the distribution and concentration of elastic strain energy, thereby altering the propensity for filament fracture.

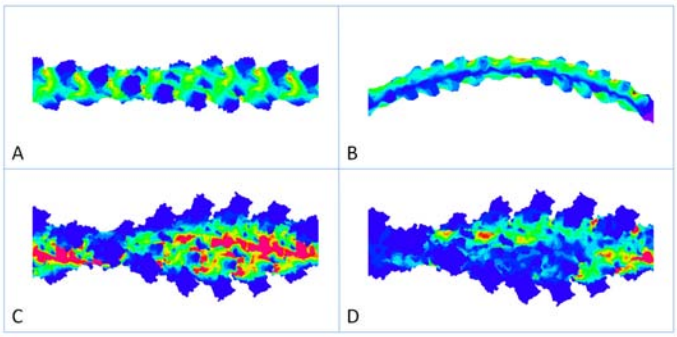

Figure 1. Elastic strain energy distribution in stretching **(A)** bare F-actin and **(C)** fimbrin ABD2-F-actin and in bending **(B)** bare F-actin and **(D)** fimbrin ABD2-F-actin.

SOLVENT DAMPING

Normal mode analyses are typically performed in the absence of solvent-damping. However, frequencies computed from the harmonic equations of motion are not related directly to the actual time-scales associated with dynamical protein motions in physiological solvent. Also, recent studies suggest that solvent-induced energy dissipation dominates internal protein dissipation for the slowest, large length-scale motions [5-6].

To model solvent damping effects on the relaxation response of large proteins, we start from the Langevin Dynamics formalism describing local protein dynamics well in

the solvent-dominated dissipation regime. In the solvent-dominated limit, this reduces to the overdamped equations of motion, which may be solved for the eigenmodes and eigenvalues that result from, $\mathbf{Z}\dot{\mathbf{x}}+\mathbf{K}\mathbf{x}=0$, where $\mathbf{Z}$ is the damping term associated with solvent-drag on the protein boundary. In the finite element framework, the elastic stiffness matrix remains unchanged by the addition of external solvent drag. Then, the solvent-damping term that includes hydrodynamic interactions may be computed directly by embedding the protein in a Stokes-fluid. The hydrodynamic drag matrix is calculated by imposing a unit velocity in each coordinate direction on the boundary of the protein and calculating the resultant forces on each FE boundary node (Figure 2), which yields the corresponding column in the drag matrix $\mathbf{Z}$.

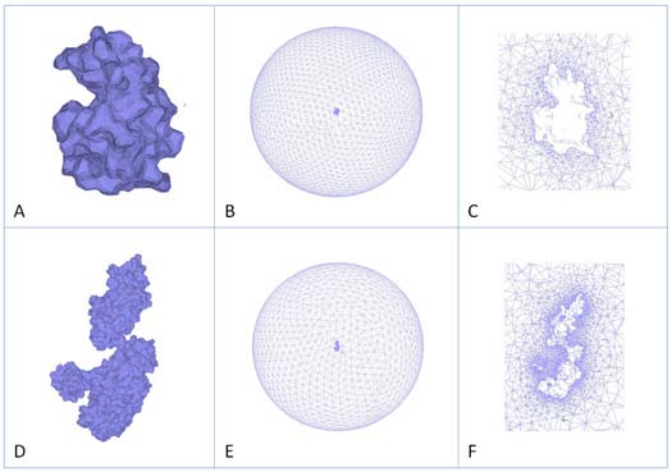

Figure 2. FE models for **(A–C)** lysozyme (PDB ID 193L) and **(D–F)** Taq polymerase (PDB ID 1TAQ). **A** & **D** show the FE mesh for the protein model, **B** & **E** show the spherical fluid volume mesh employed to model the suspending solvent, and **C** & **F** show close-ups of the fluid mesh surrounding the proteins (in cross-section).

EM-NMDB

The FE-based approach is well suited to compute the normal modes and relaxation time-scales of EM-based structures that lack atomic coordinates. We have established and maintained the Electron Microscopy Normal Modes Database (EM-NMDB) where the lowest normal modes for the majority of structures in the EMDB are computed through the automated FE-based normal mode analysis procedure and stored publically. Figure 3 shows the classification of EM-NMDB structures according to biological function, which covering a broad range of proteins. The lowest normal modes of these structures may provide insight into biologically relevant motions or suggest alternate conformations that may be used in multi-reference refinement of single-particle reconstructions. For example, distant domains correlated in their motions can be predicted from normal modes (Figure 4). These correlations are computed using hierarchical clustering and a linearized mutual information metric computed from the normal modes.

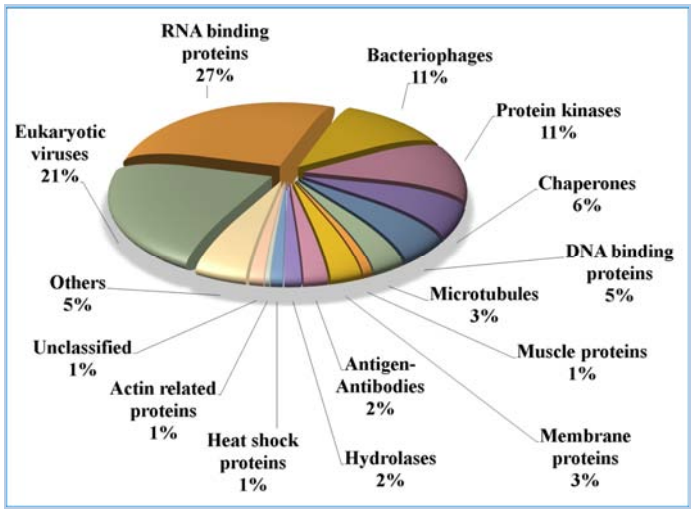

Figure 3. Classified EM-NMDB structures based on biological function

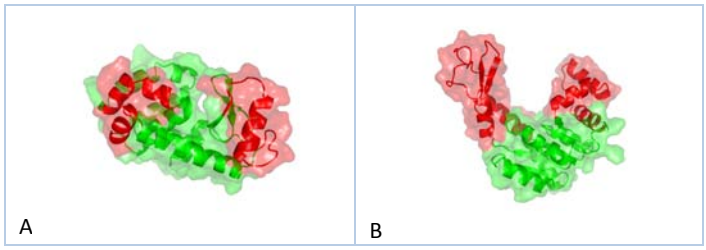

Figure 4. Maximally correlated distant domains. **(A)** T4 lysozyme (PDB ID 3LZM) and **(B)** Adenylate kinase (PDB ID 4AKE)

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