Cylindrical biomolecule model based on experimental data

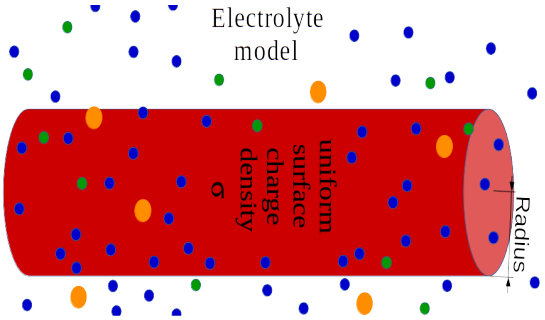

Figure 1: Cylindrical biomolecule model

Classical Solvation Density Functional Theory (CSDFT) is an efficient computational approach that describes electrical double layer properties of biomolecules of approximate cylindrical (or spherical) shape at infinite dilution. In the approach, the polyelectrolyte properties of the biomolecule are characterized by an effective molecular radius *R* and uniform bare surface charge density σ, whereas the biological environment is represented by an electrolyte (either alkaline or acid) solution comprised of ionic species (characterized by radius, charge and bulk concentration) and explicit water molecules (characterized by neutral ions at experimental size and bulk concentration) (Figure 1). Since CSDFT extends the capabilities of conventional mean-field (non linear Poisson Boltzmann) approaches, it captures a nontrivial balance and competition between the electrostatic screening ion correlations, electric potential and water crowding effects on the cytoskeleton polyelectrolyte properties (Figure 2). The formulation predicts a rich ionic layering formation arising from the high size asymmetry and concentration ratios between water molecules and ions. It also demonstrates a strong impact of pH level and salt concentration on the polyelectrolyte properties of F-actin, following the similar trends revealed for other cylindrical biomolecules (B-DNA). The biophysical principles underlying these phenomena are identified with: the formation of a strongly correlated and condensed ionic liquid which electrically screen the filament surface; the enhancement of the charge screening due to water crowding pushing more ions closer to the filament surface, and the changes on the bare filament surface charge by protonation / deprotonation reactions of the residues exposed to the liquid. Overall, the computational model has been shown to provide a good compromise between accuracy and computational cost.

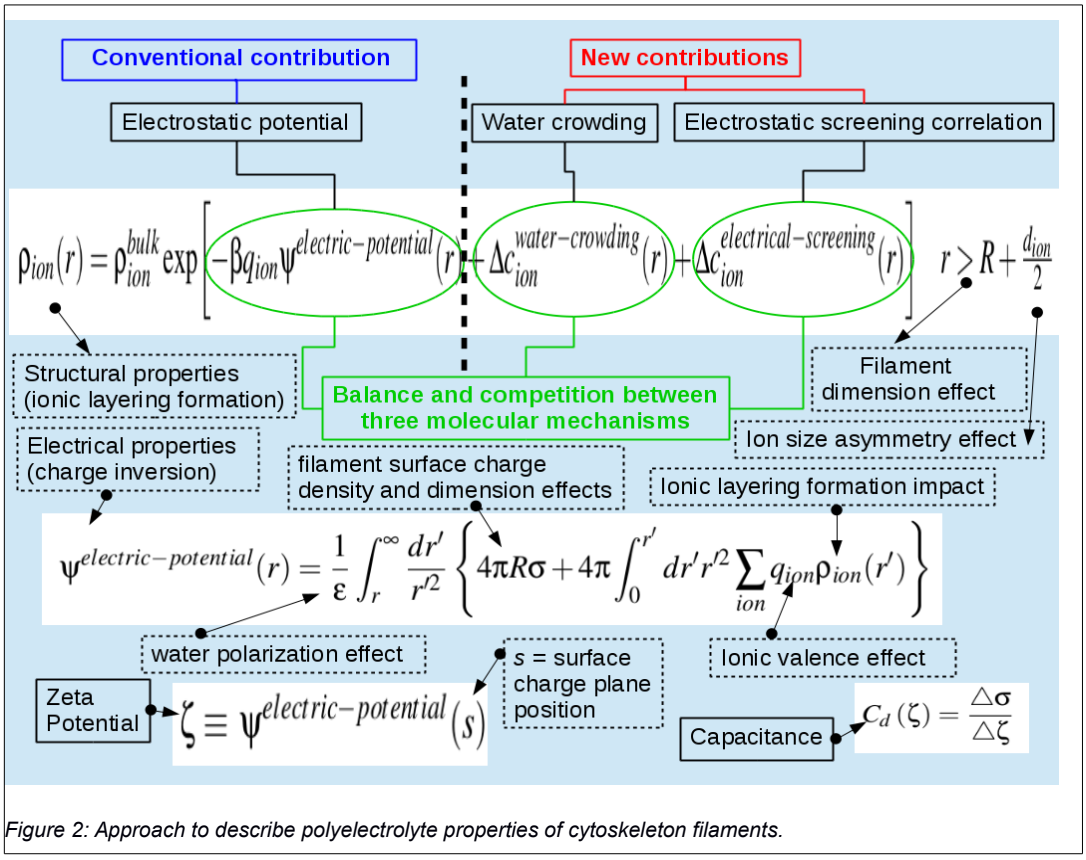

Figure 2: Approach to describe polyelectrolyte properties of cytoskeleton filaments.

Cylindrical biomolecule model based on Molecular structure data (Multi-scale approach)

Unless experimental data is available, an effective molecular radius *R* and uniform bare surface charge density σ for the cylindrical model can be estimated by using one of the most recent 13 monomers, biologically assembled Actin filaments posted on the protein data bank: (http://www.rcsb.org/): 3B5U (Cong [41]), 3B63 (refined Holmes [41]), 3MFP (Namba[42]), 2ZWH (Oda[43]), and 3J8I (Egelman[44]). They provide different molecular characterization including the amino acids sequence, the number and type of residues exposed to the electrolyte, and accessible surface. These (uncharged) molecular structures (in pdb format) and the application pdb2pqr (http://sourceforge.net/projects/pdb2pqr/) are are used to assign atomic charges and sizes, add hydrogens, optimize the hydrogen bonding network, and renormalize atomic charges of the residues exposed to the surface due to pH effects (protonation/deprotonation process). The resulting charged molecular structures (in pqr format) are used to extract information on the effective filament length $L=Z_{max}-Z_{min}$ and total charge $Q=\sum q_i$. The length and total charge are used to estimate the protein linear charge density $\lambda=Q/L$. Additionally, these molecular structures and the application "3v: voss volume voxelator" (http://3vee.molmovdb.org/volumeCalc.php) are used to estimate the total protein volume V*p* from where the effective radius *R* of each of molecular structure model is calculated as $R\simeq\sqrt{Vp/L\pi}$. The linear charge density and radius are subsequently used to calculate the filament surface charge density $\sigma=\lambda/2\pi R$ (Figure 3).

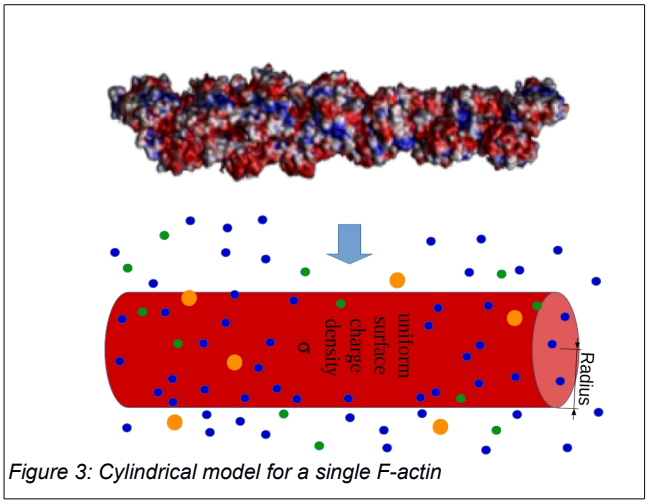

Figure 3: Cylindrical model for a single F-actin

As a first approach, these filament models and theory may be used to determine the impact of alterations in the intracellular environment and variations in the filament charge (produced by polymerization states, isoforms and mutations) on their stability (Zeta potential) and bundling formation (charge inversion) properties.