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An explicitly solvated full atomistic model of the cardiac thin filament and application on the calcium binding affinity effects from familial hypertrophic cardiomyopathy linked mutations MICHAEL WILLIAMS, STEVEN SCHWARTZ, Dept. of Chemistry and Biochemistry, The University of Arizona — The previous version of our cardiac thin filament (CTF) model consisted of the troponin complex (cTn), two coiled-coil dimers of tropomyosin (Tm), and 29 actin units. We now present the newest revision of the model to include explicit solvation. The model was developed to continue our study of genetic mutations in the CTF proteins which are linked to familial hypertrophic cardiomyopathies. Binding of calcium to the cTnC subunit causes subtle conformational changes to propagate through the cTnC to the cTnI subunit which then detaches from actin. Conformational changes propagate through to the cTnT subunit, which allows Tm to move into the open position along actin, leading to muscle contraction. Calcium disassociation allows for the reverse to occur, which results in muscle relaxation. The inclusion of explicit TIP3 water solvation allows for the model to get better individual local solvent to protein interactions; which are important when observing the N-lobe calcium binding pocket of the cTnC. We are able to compare in silica and in vitro experimental results to better understand the physiological effects from mutants, such as the R92L/W and F110V/I of the cTnT, on the calcium binding affinity compared to the wild type.

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