**A computational model demonstrates how a cardiac myosin binding protein-C mutation impacts calcium sensitivity and power output in a mutant mice model**S. Kosta1, S. Harris2, K.S. Campbell1

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Cardiac myosin binding protein-C (cMyBP-C) is a sarcomeric protein that is essential for cardiac contraction regulation. Mutations in MyBP-C’s cardiac-specific gene (MYBPC3) are a leading cause of hypertrophic cardiomyopathy (HCM). In particular, the L348P substitution (L352P in humans) is an HCM-associated missense mutation that increases binding of cMyBP-C’s M-domain to actin. A CRISPR-gene edited mouse model was previously developed, with a ~40% expression of the L348P mutant protein. Permeabilized cardiomyocytes from these L348P-CR heterozygous mice (HET) showed increased Ca2+ sensitivity of tension and slowed shortening velocities compared to wild type (WT) mice.

Since cMyBP-C is exclusively located in the C-zone of the sarcomere and interacts with both the thick and thin filaments, spatially-explicit models can help gain insights about its role in cardiac contraction regulation. FiberSim (<https://campbell-muscle-lab.github.io/FiberSim/>) is a spatially-explicit model of myofilament-level contraction that simulates contractile properties. In this work, FiberSim was used to compare tension-pCa and force-velocity curves for two models, called WT and HET. For the WT model, cMyBP-C could either stabilizes the super-relaxed state of myosin dimers, or bind to actin. For the HET model, 40% of the cMyBP-C had an increased attachment rate for actin compared to the WT model. Finally, a HOM model was generated where 100% of the cMyBP-C had an increased attachment rate for actin compared to the WT model.

The simulation results for WT and HET were in good agreement with the experimental data. The HET model showed an increase in calcium sensitivity compared to WT. This can be explained by the increased number of bound cMyBP-Cs, which sustains thin filament activation and allows for more cross-bridges to bind to actin. The HET model also showed a decrease in shortening velocities compared to WT, suggesting that bound MyBP-Cs act like a drag that reduces maximal power output. The HOM model (for which no experimental data were available, as homozygosity is lethal prior to postnatal day 7) showed an even bigger increase in calcium sensitivity and a greater decrease in power output compared to WT. Finally, isometric twitch contractions showed decreased relaxation rates in the HET and HOM models compared to WT. This supports the hypothesis that increased binding of cardiac MyBP-C to actin inhibits normal cardiomyocyte relaxation, and suggests that the L348P missense mutation is incompatible with survival when inherited in the homozygous state.

Category: Models of Contraction/Regulation OR Thick/Thin Filament Regulation in Striated Muscle