Modeling framework for predicting the dose-dependent effects on contraction of myotropes

Authors: C. Zhu, S. Kosta, K.S. Campbell

Myotropes, such as omecamtiv mecarbil and mavacamten, are new therapeutics that bind to sarcomeric proteins. Their clinical development has reinforced the need for new quantitative understanding of sarcomere-level function.

FiberSim (<https://campbell-muscle-lab.github.io/FiberSim/>) is a spatially-explicit computer model that simulates myofilament-level mechanics. The code tracks the position and status of each contractile protein within the half-sarcomere lattice. It can predict how modulating the function of a sarcomeric protein (e.g., due to a bound myotrope) will impact contractility. In particular, it can quantify sarcomere function modulation as a function of myotrope dose.

In this study, we assessed the mavacamten dose-dependence of maximal isometric force. As suggested by experimental data (PMID: 32960449), we assume that mavacamten stabilizes the super-relaxed state of myosin dimers. The steady-state proportion of myosin heads bound by mavacamten can be calculated as a function of the mavacamten concentration using ATPase dose-dependent curve from the literature (PMID: 28808052).This prediction can then be integrated into FiberSim to predict a dose-response curve for maximum isometric force, which qualitatively compares to the experimental ATPase dose-dependent curve.

FiberSim is a flexible and open-source software that can be used to study myofilament contraction. It is possible to evaluate a myotrope effect on force (or any other metrics, such as shortening velocity, or rate of force development) based on the target protein function modulation by the myotrope. Dose-dependent curves can be predicted. Combining this modeling approach with experimental data might to help develop new therapeutics and improve clinical care.