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Methods

Simulations were performed using the FiberSim framework (PMID 34932957). As previously described, myosin heads cycled between a super-relaxed OFF state (SRX), a disordered relaxed state (DRX), and a single attached force-generating state (PMID 34932957, 30054031). The rate at which myosin heads transitioned between the SRX and DRX heads increased linearly with force (PMID 30054031).

Crit simulations were identical to the control case except that the DRX to SRX rate constant was increased 3-fold so that myosin heads in the calculations were biased towards the SRX state. The Drug was simulated by increasing the kon­ rate for binding sites on the thin filament 3-fold to increase the Ca2+-dependence of contraction.

Simulations for electrically-excitable muscle were identical to those for permeabilized muscle except that the basal value of the kon rate was doubled to account for the increased Ca2+-sensitivity of intact muscle.

The FiberSim software is open-source. A workflow that reproduces the simulations is available at <https://campbell-muscle-lab.github.io/FiberSim/>