

Spatially-explicit modeling framework for predicting the dose-dependent effects on contraction of myotropes

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Introduction

- Myotropes are a new kind of calcium-independent therapeutic drugs that bind to sarcomeric proteins
- Their clinical development has reinforced the need for new quantitative understanding of sarcomere-level function
- Mathematical models can be used to produce *in silico* predictions regarding the impact of myotropes on contractility

Methods

- FiberSim (1) is a spatially explicit computer model of half-sarcomere contraction
- FiberSim can be used to evaluate sarcomere contractility as a function of a mytrope dose, specifically mavacamten in this study
- It was hypothesized that mavacamten stabilizes the SRX (super-relaxed state) of myosin (2)
- K_D of mavacamten and myosin was determined from previously published ATPase data (3) and used to calculate the proportion of SRX myosin associated with mavacamten
- Isometric force was then calculated for different mavacamten concentrations

Key results

- Isometric force decreases with increasing mavacamten concentrations, consistent with experimental data showing a decrease in ATPase activity of isolated actomyosin assays
- IC_{50} (mavacamten dose for 50% isometric force) is ~40% lower than K_D .
- This implies that contractile force is more sensitive to mavacamten than the ATPase of isolated myosins.
- Simulations suggest that mavacamten inhibiting a myosin head's force-generating ability also reduces recruitment of additional myosin heads due to the force-dependency of the SRX to DRX transition
- FiberSim can be used to investigate the effects of other myotropes and help accelerate the development of myotrope-based therapies for muscle disease

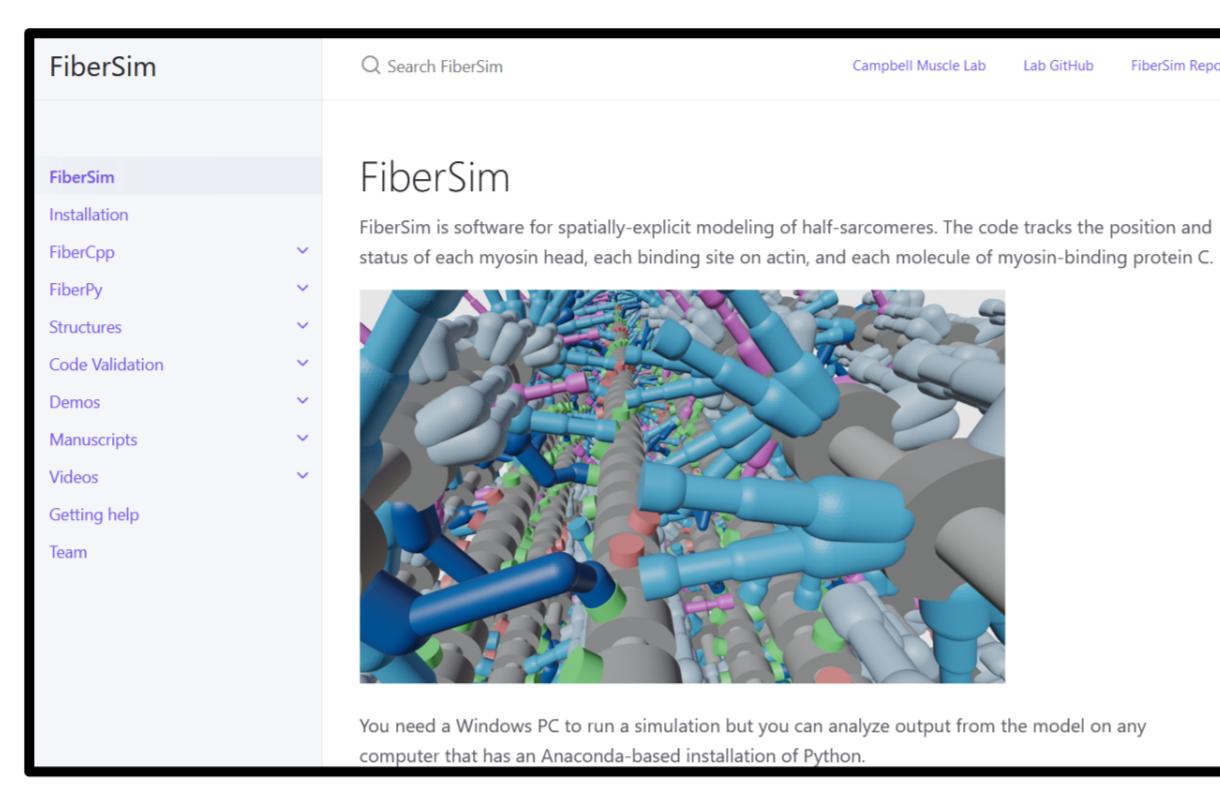
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Acknowledgements: Funding from NIH HL146676 (KSC), HL148785 (KSC) and TR0001998 (KSC). Funding from AHA TP135689 (KSC) and 929744 (SK).

References

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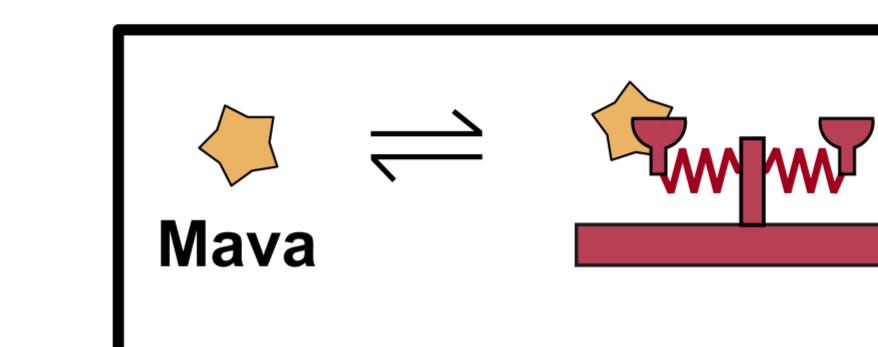
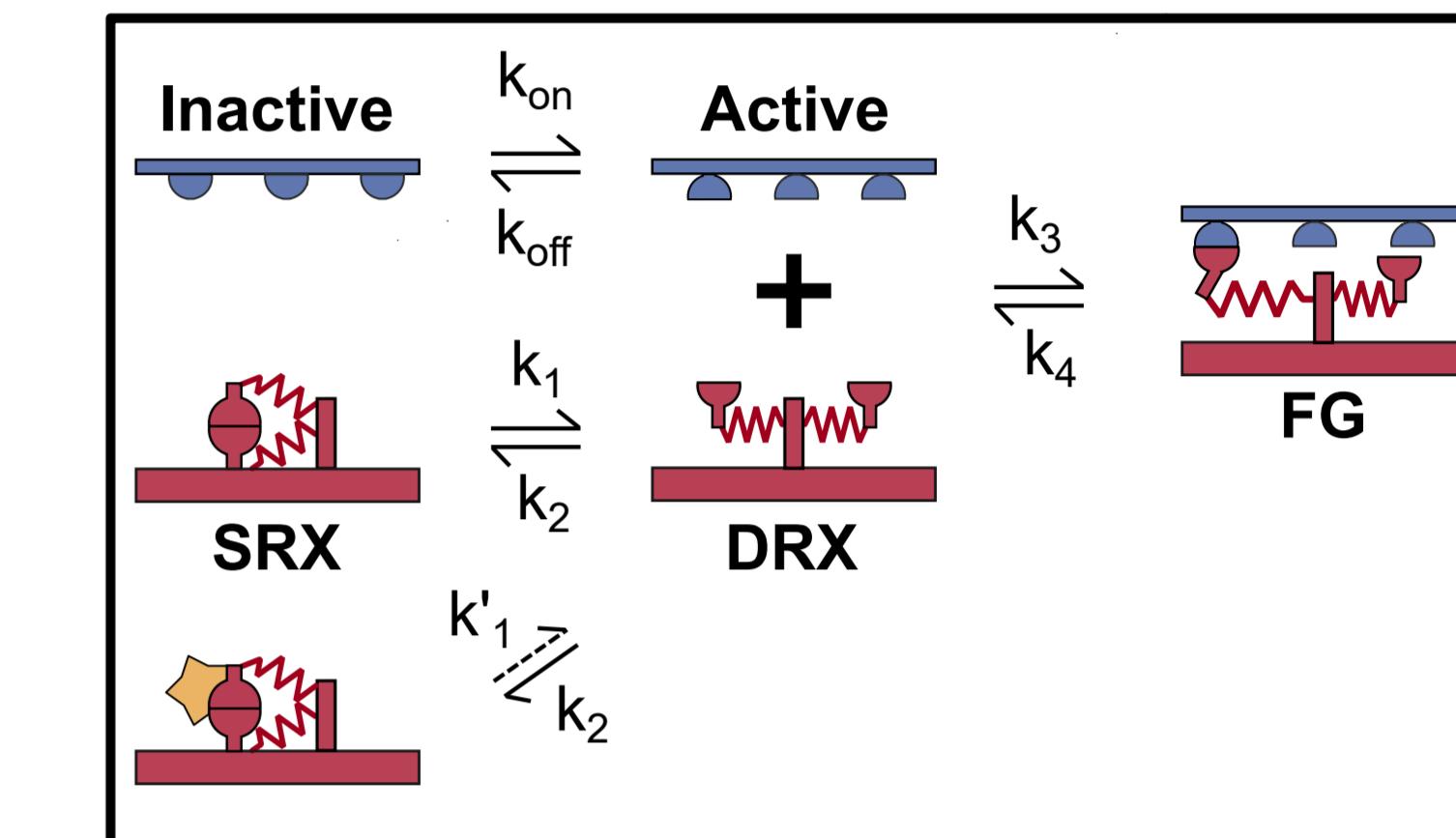
FiberSim = model of half-sarcomere contraction<https://campbell-muscle-lab.github.io/FiberSim/>

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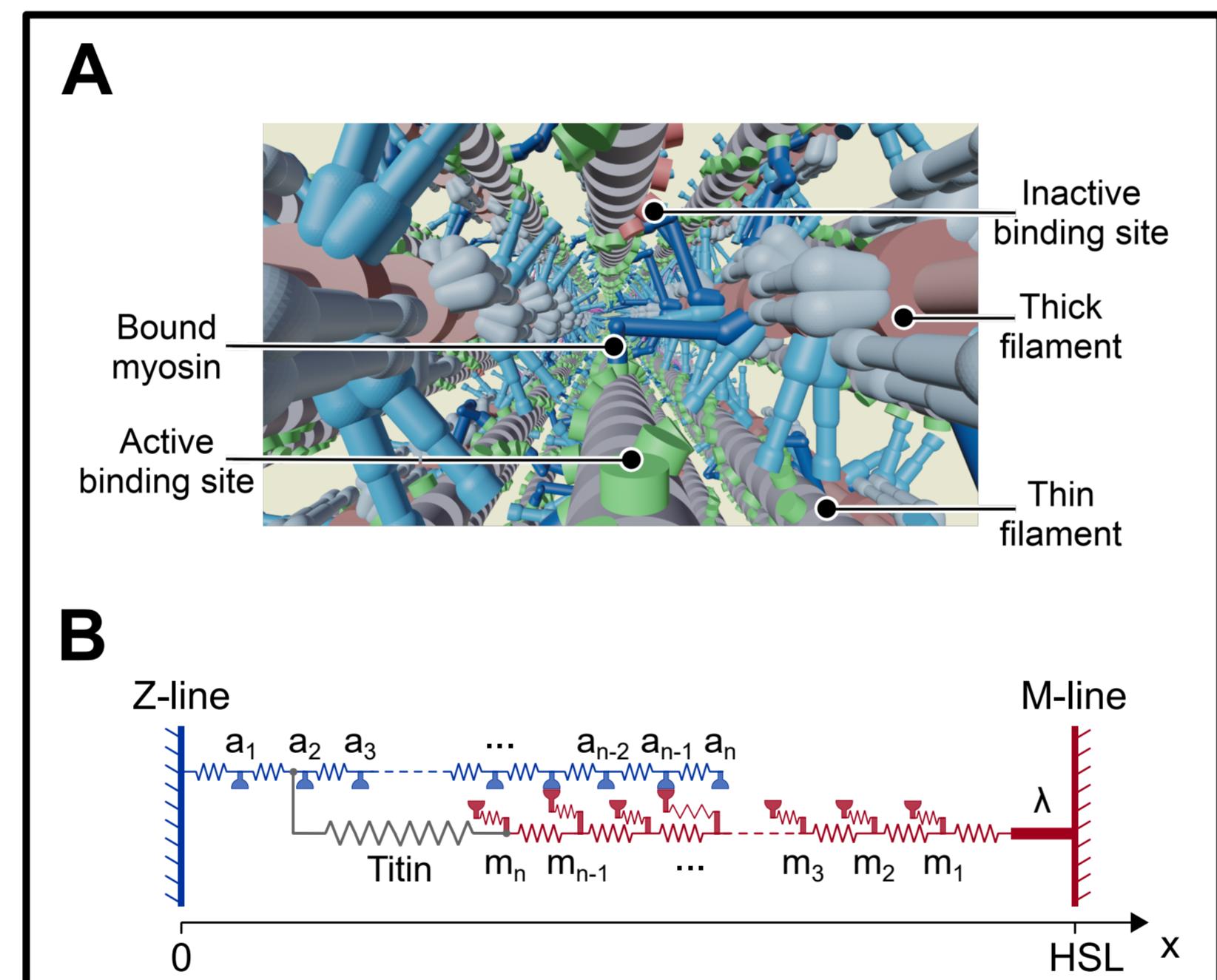
Myotrope = drug that targets contractile protein

Mavacamten (Mava):

- Targets myosin
- Has been shown to stabilize SRX

SRX myosin dimers associated with Mava have a decreased k_1 

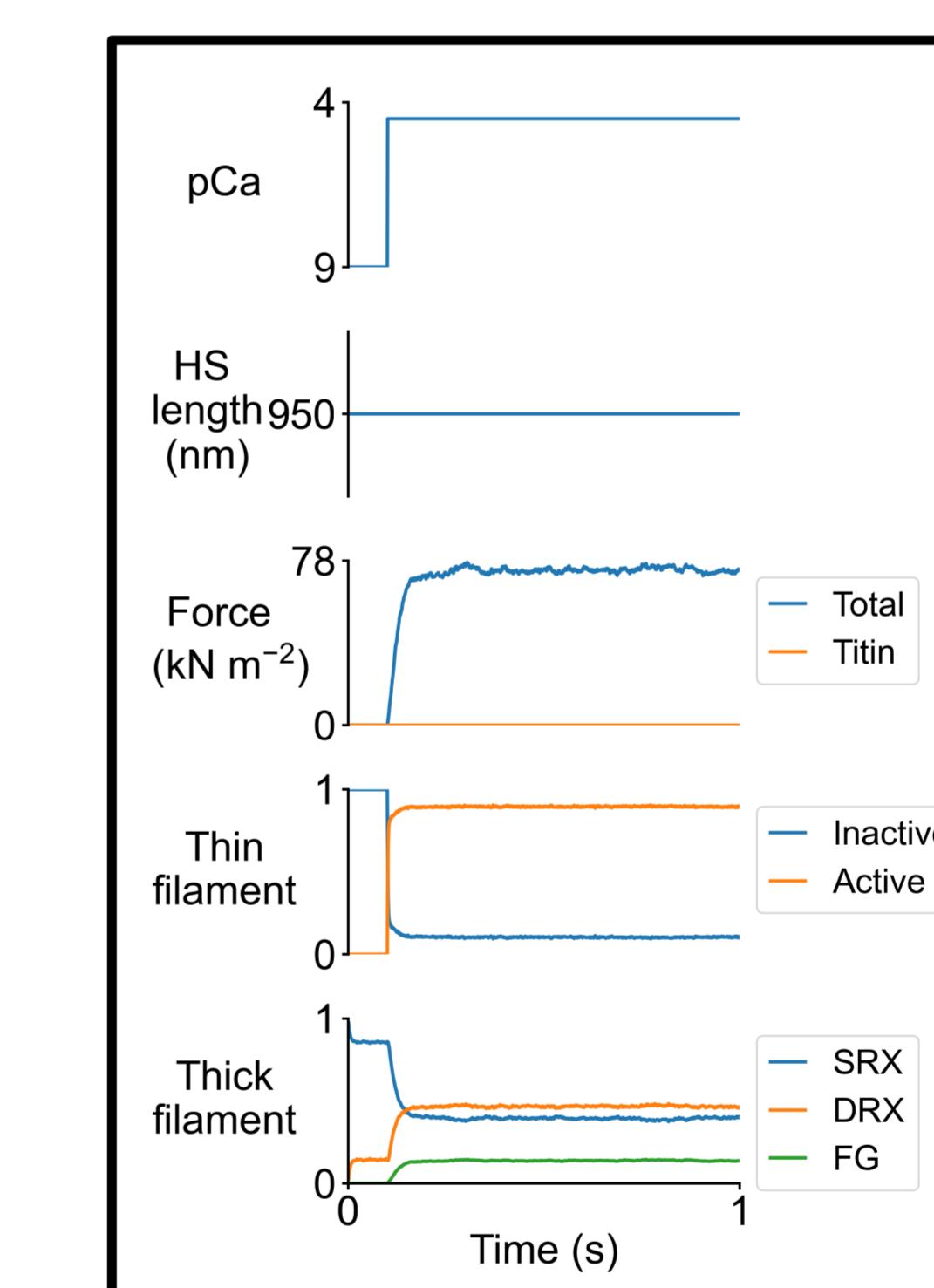
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Half-sarcomere model = hexagonal lattice of compliant thick and thin filaments

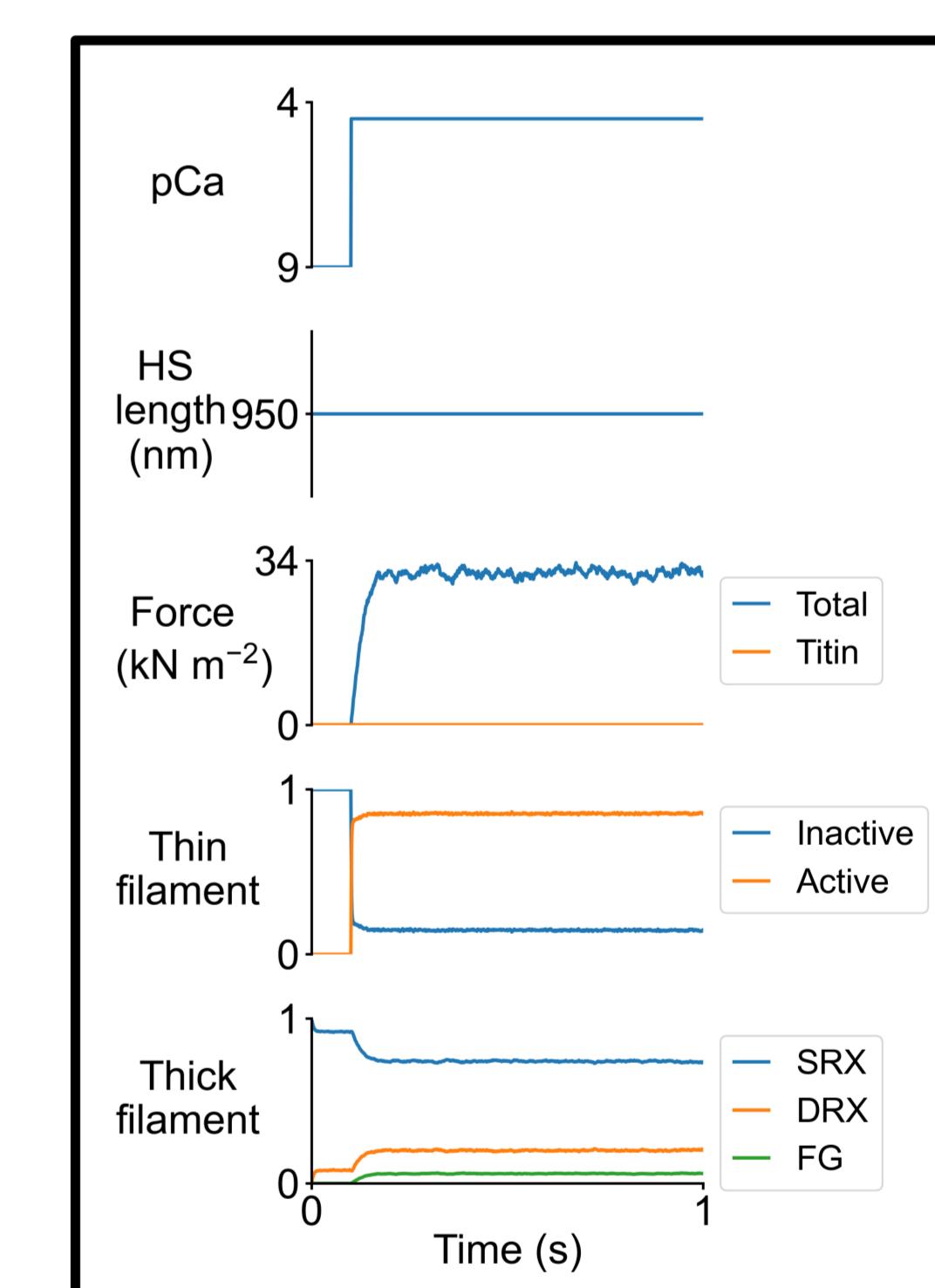
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Isometric activations = simulations run at pCa 4.5 for a fixed half-sarcomere length

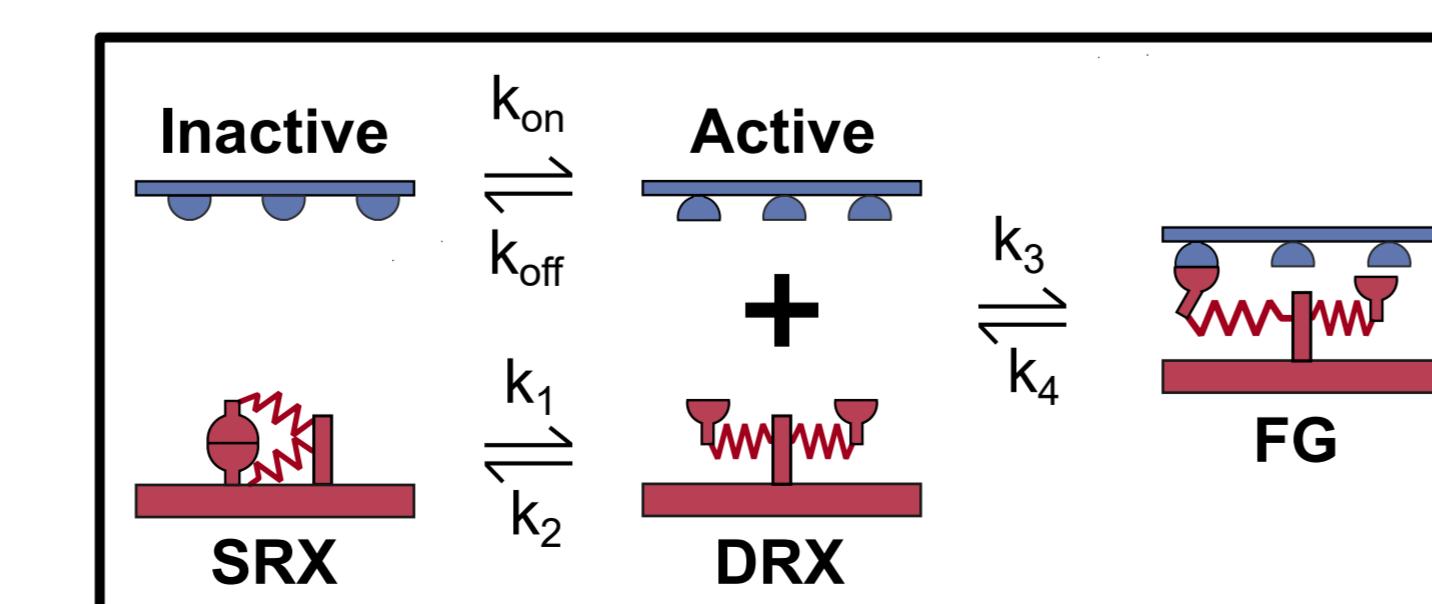
0% Mava-bound myosins



50% Mava-bound myosins

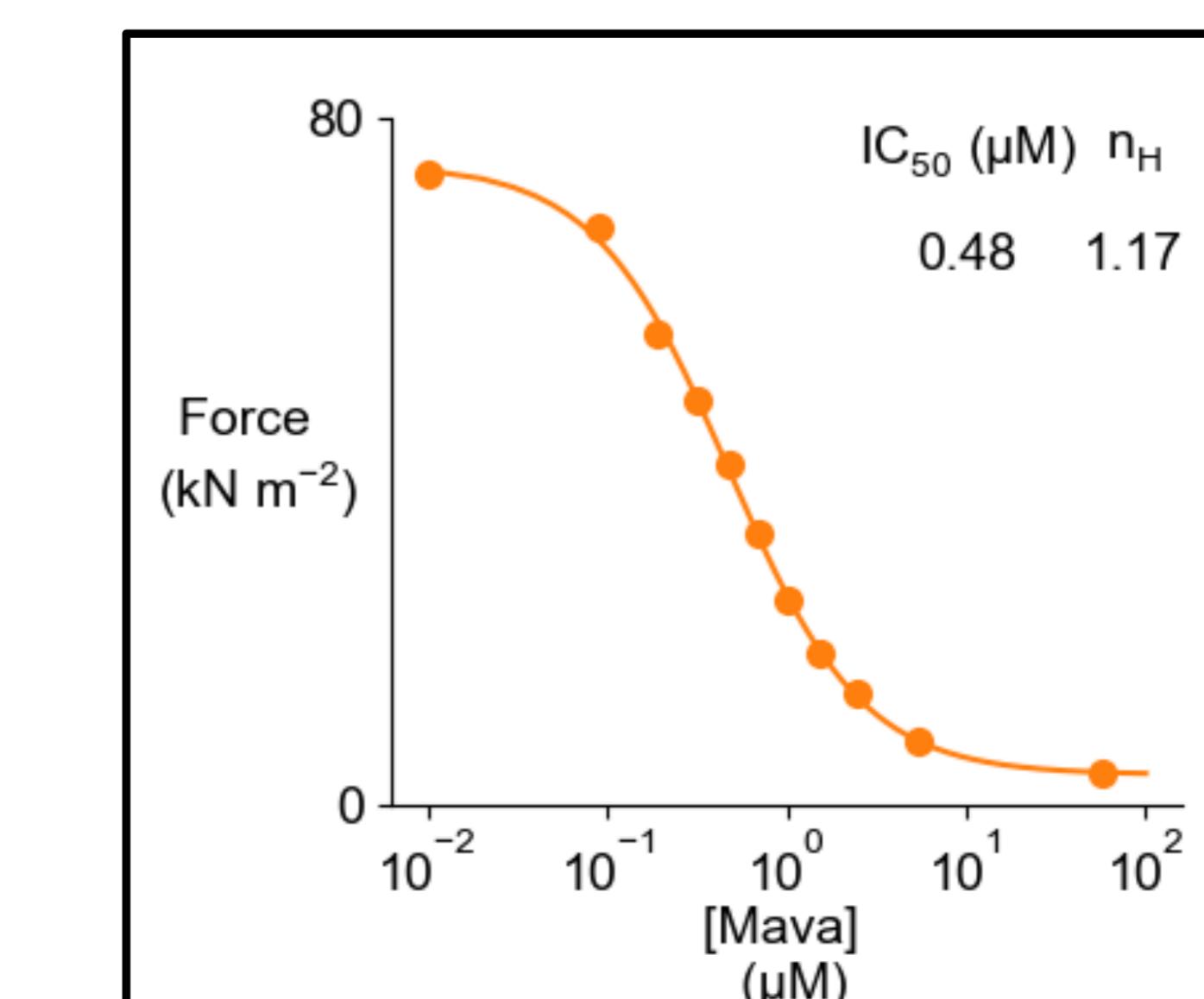


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Kinetics model = actin and myosin kinetics are user-definedActin binding sites: *inactive* or *active*Myosin heads: *super-relaxed* (SRX), *disordered-relaxed* (DRX) or *force-generating* (FG) state

k_{on} : calcium-dependent
 k_{off} : constant
 k_1 : force-dependent
 k_2 : constant
 k_3 and k_4 : stretch-dependent

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Dose-dependent response curve = isometric force is plotted as a function of Mava concentration

Mava dose for 50% isometric force (IC_{50}) is 40% lower than K_D for human cardiac myosin S-1 (~0.7 μM)

→ Contractile force is more sensitive to Mava than ATPase of myosin molecules