Multiscale Integration of Active and Passive Cardiomyocyte Mechanics to investigate effects of calcium and ATP levels on cardiac muscle

MEDICAL SCHOOL
MOLECULAR & INTEGRATIVE PHYSIOLOGY
UNIVERSITY OF MICHIGAN

Filip Jezek[1], Daniel A. Beard[1], and Anthony Baker[2]

[1]Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, I, USA,
[2]Department of Medicine, University of California, San Francisco, California

SUMMARY

- Passive force following a rapid stretch in cardiac muscle decays as a power-law time course
- The apparent viscous component of the passive force is sensitive to calcium concentration
- Our titin model fits passive viscoelastic decay for a range of calcium concentrations
- Our combined model fits the slack-restretch experiment, uncovering contribution of XB states

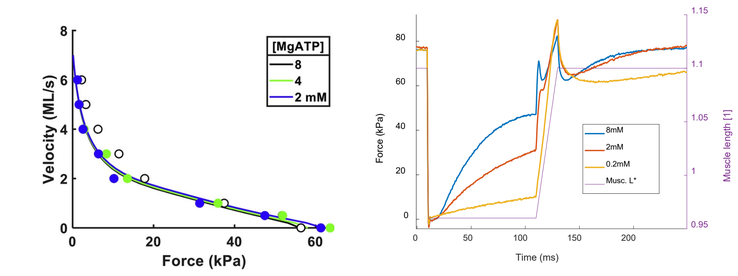
THE TEAM

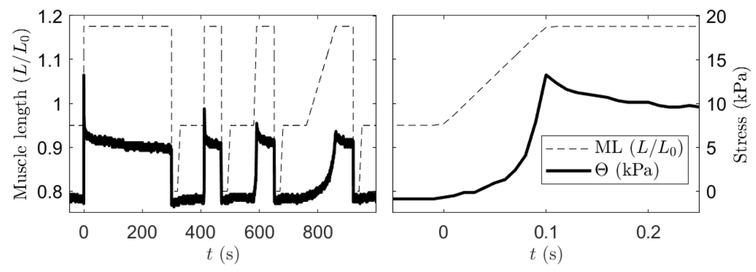
The modeler, the physiologist and the experimentalist

INTRODUCTION

Beard et al. [1] tested the effect of low ATP levels on myocardial contraction using demembranated murine cardiac muscle trabeculae preparations exposed to ATP levels typical of those found in non-failing and failing hearts. To quantify the effects of reduced ATP, we face the challenge of first simulating the entire protocol with saturated ATP levels.

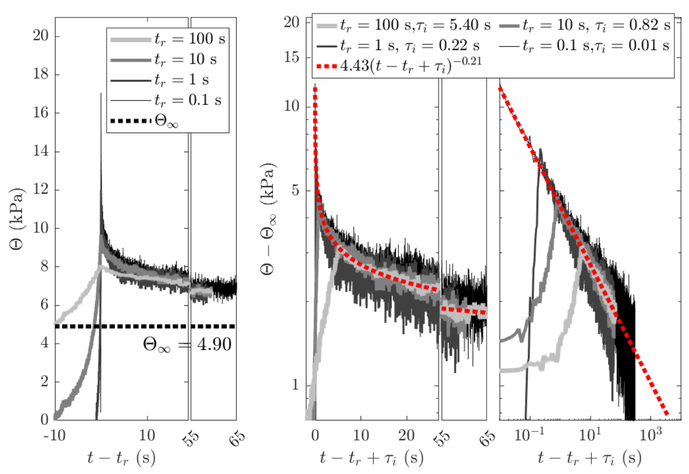
While investigating the restretch phenomenon, we identified a calcium-sensitive viscoelastic effect. We conducted a separate protocol to investigate this in detail, using preparations set to an initial muscle length (*L0*) at a sarcomere length (SL) of 2.0 µm. The set of four ramp-ups (100ms, 1s, 10s and 100s) from 0.95 to 1.175 *L0* were run in relaxing solution and then in activating solution (pCa 4.5) with force development suppressed using para-nitro-blebbistatin (PNB). The PNB alone did not affect the outcomes.





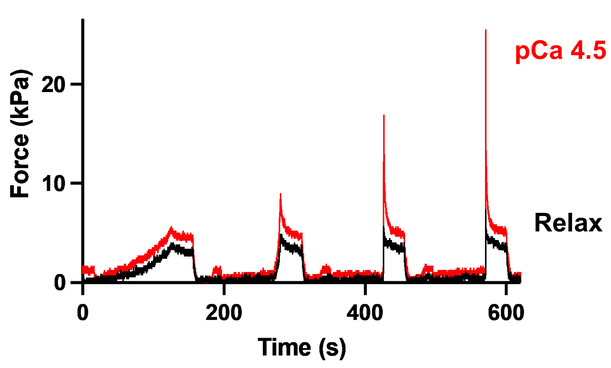
VISCOELASTIC DECAY

Passive force decay time courses following a ramp-up stretch obey the same power law, regardless of the ramp-up velocity. This consistency suggests a universal viscoelastic response in the myocardial tissue under the conditions tested.



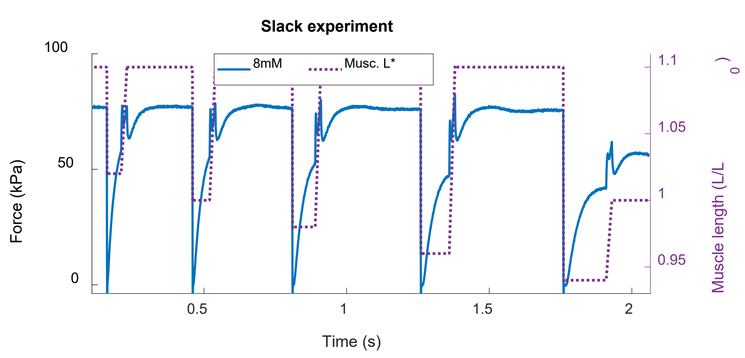
VISCOELASTIC DECAY CALCIUM SENSITIVITY

After suppressing more than 95% of the active contractility with PNB, the addition of Ca^{2+} substantially increased tension peaks. This effect persists even with complete force suppression and in myBP-C knockout mice (preliminary data, not shown), suggesting the effects may be attributed to titin.



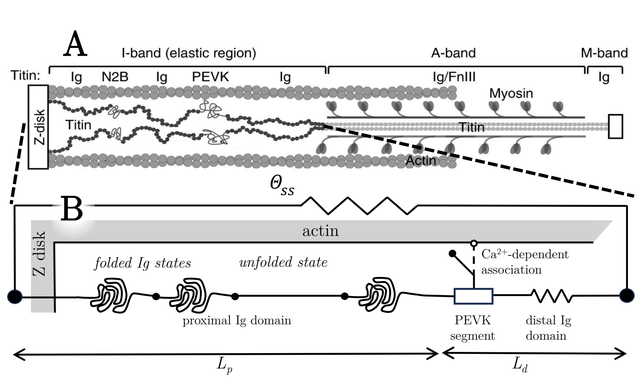
SLACK EXPERIMENT DATASET

The entire slack protocol represents an information-rich dataset, challenging to fit. It requires a range of mechanisms, including serial elasticity, force buildup, unloaded maximal velocity, and cross-bridge tearing.

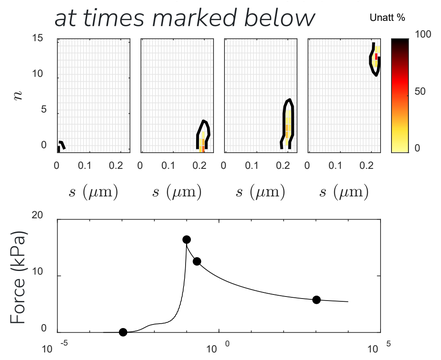


PASSIVE MUSCLE MECHANICS MODEL

We attribute the observed passive tension decay to titin, a large sarcomeric structural element, and we developed a probability-ensemble mechanistic model of titin incorporating immunoglobulin (Ig) domains that may unfold under stress. Each unfolded domain (represented as *n*-th state) introduces slack into the titin chain, shifting the passive stress-strain (Φ - *s*) curve. The force is then calculated from ensemble probability *p(n, s)*. Additionally, in presence of Ca, the PEVK segment can attach to the actin filament, as described in [2], so that $\sum_{n=0}^{N}\sum_{s=0}^{\infty}[p_{unattached}(n,s) + p_{unattached}(n,s)] = 1$

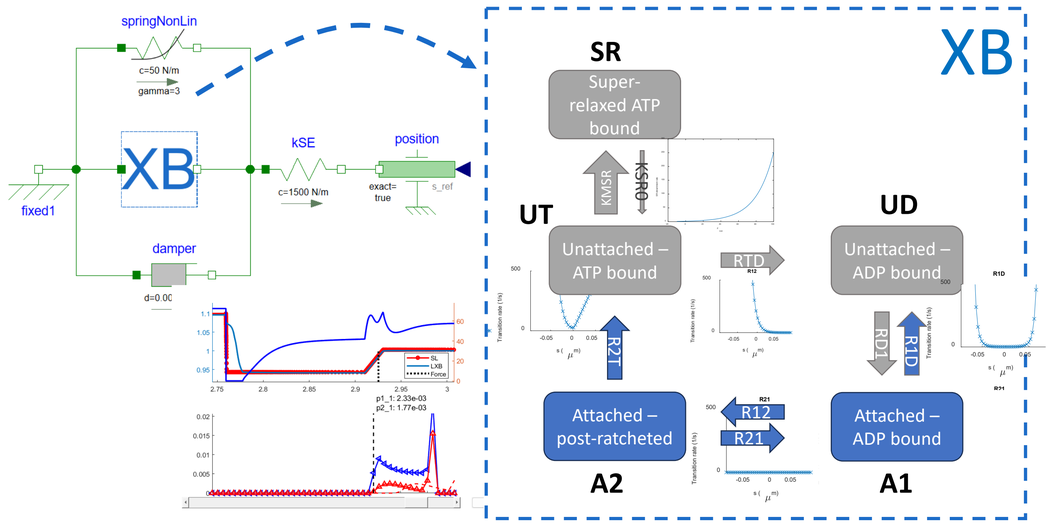


Ensemble probability *p(n,s)* *at times marked below*



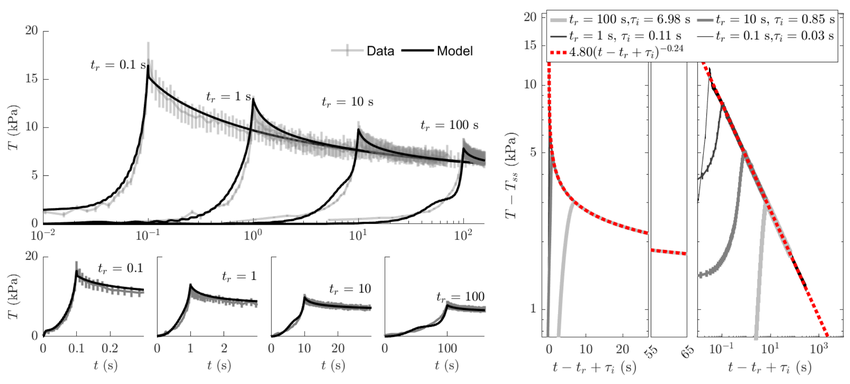
ACTIVE MUSCLE MECHANICS MODEL

The model builds upon previous models from our group [1], which we have tuned and refined. The developed model includes strain- and metabolite-dependent transitions between attachment, detachment, and super-relaxed states. The attached states (A1 and A2) are spatially explicit, with their transition rates depending on strain. The super-relaxed (SR) state transitions depend on actual force.



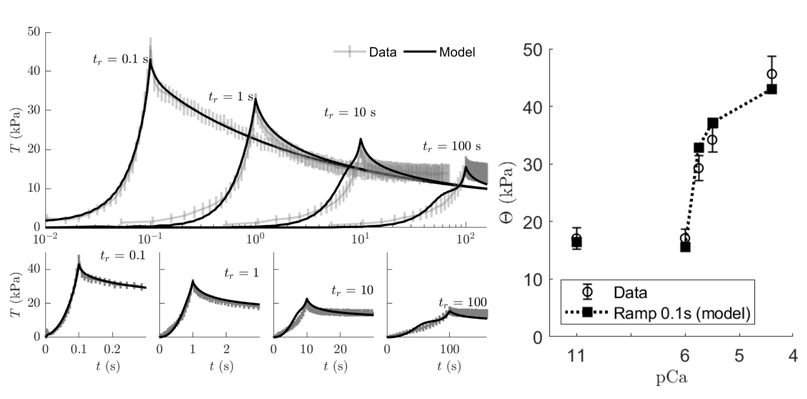
PASSIVE MODEL FIT: NO CALCIUM

Under calcium-free conditions, the model accurately fits peaks and decay time courses over the observed range of ramp speeds, exhibiting a power law with parameters closely matching the data.



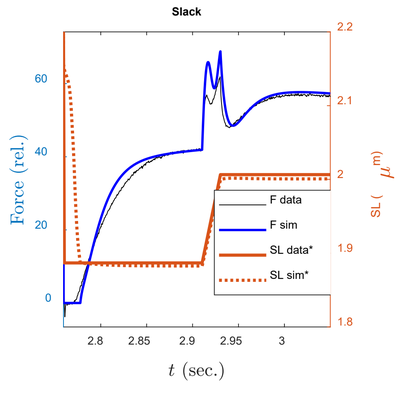
PASSIVE MODEL FIT: WITH CALCIUM

By increasing titin's stiffness and incorporating partial PEVK attachment, the model can represent observed decay dynamics over a range of calcium concentrations, from fully saturated to calcium-free.



COMBINED MODEL FIT WITH ACTIVE CONTRACTION

When integrating the active contraction model, it captures all features of the slack experiment. The breakup of cross-bridge states allows us to interpret underlying mechanisms.



REFERENCES

[1] Lopez R, Marzban B, Jezek F, Randall EB, Beard DA. Role of ATP supply in limiting reserve cardiac power output. Biophys J. 2022 Feb;121(3):124a.

[2] Squarci C, Bianco P, Reconditi M, Pertici I, Caremani M, Narayanan T, et al. Titin activates myosin filaments in skeletal muscle by switching from an extensible spring to a mechanical rectifier. Proc Natl Acad Sci U S A. 2023 Feb 28;120(9):

CONCLUSION

Although the influence of passive viscoelasticity is apparent in fast ramps, it becomes more prominent in activated muscles with calcium. Preliminary data confirmed the effect is not solely caused by remaining cross-bridges and it can't be attributed to myBP-C either, making the titin a plausible actor. Integration of the viscoelastic model with the cross-bridge model of active contraction allows to run fast experiments like slack-restretch. Further fine-tuning might be required to accommodate slight differences between individual slacks and to derive the ATP effect mechanism.