Modeling cardiac mechanics on the sarcomere scale

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Go20 Conference, May 22-26 2023, Gozo, Malta

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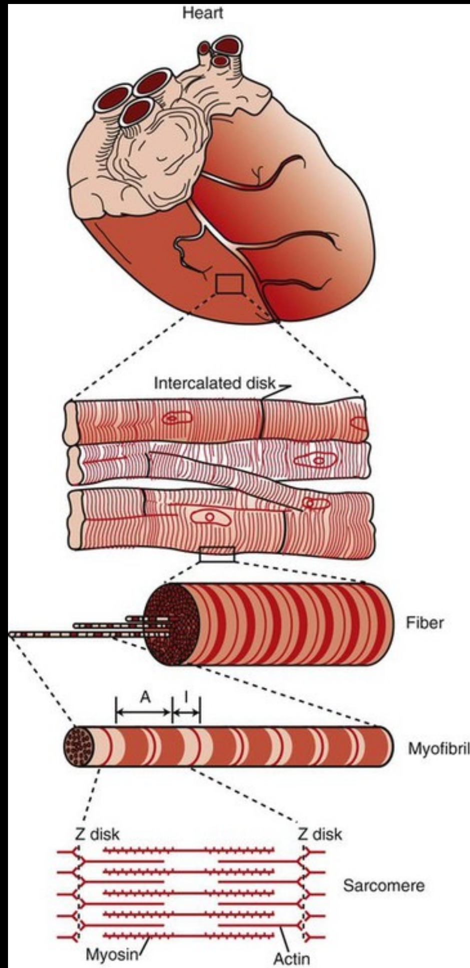
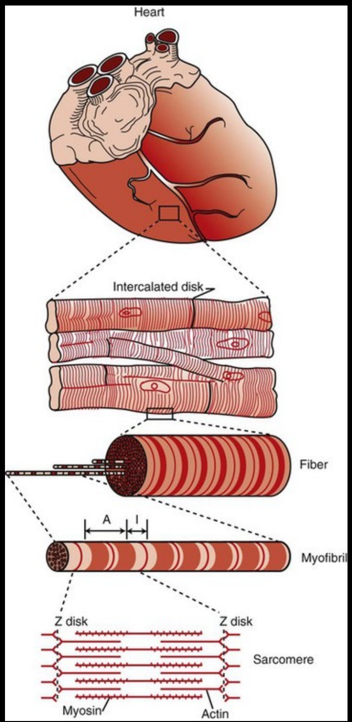
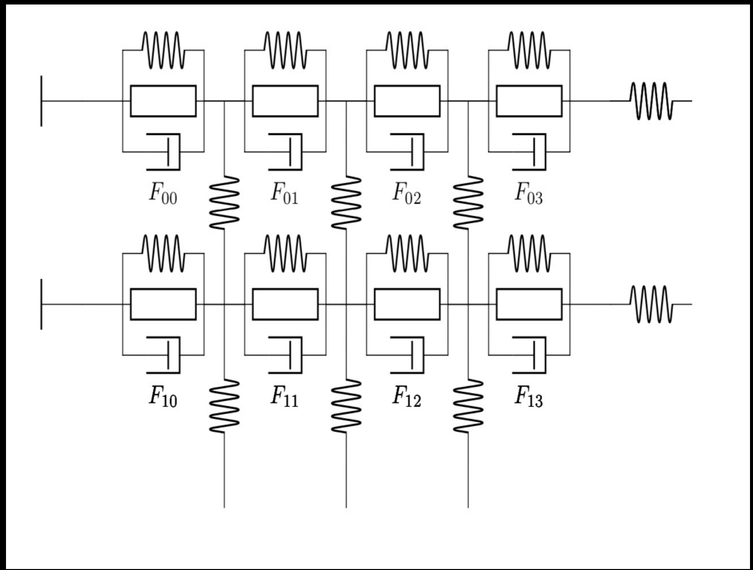


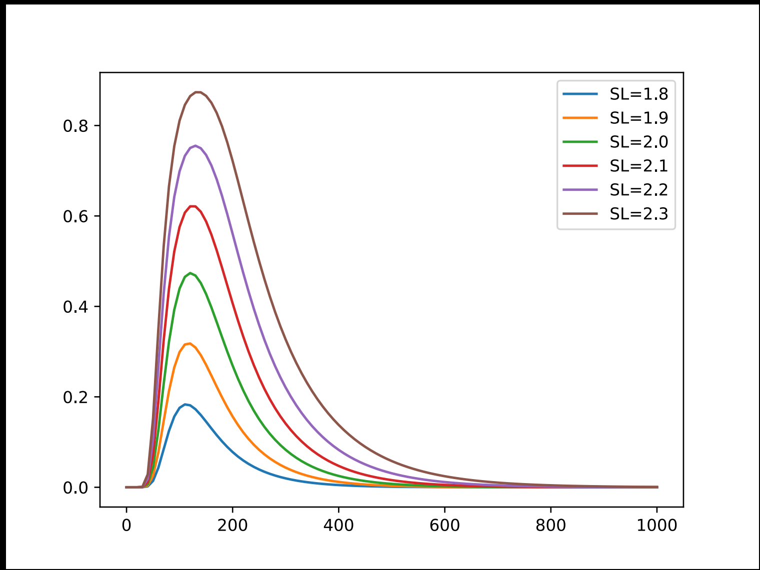
Outline



Motivation and background

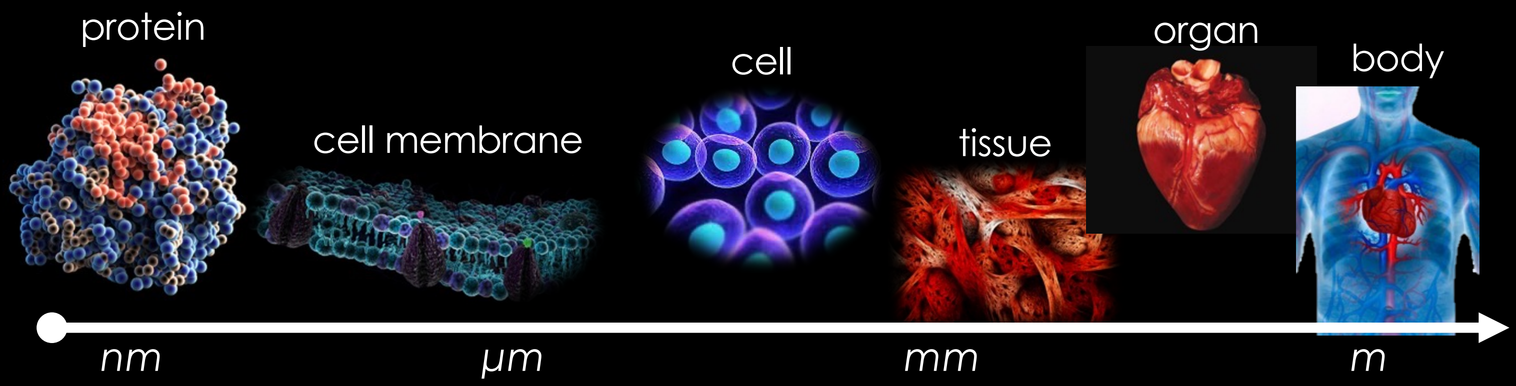


An ODE-based model for cardiac cell mechanics



Initial results

Computational models in physiology involves processes on a wide range of spatial scales



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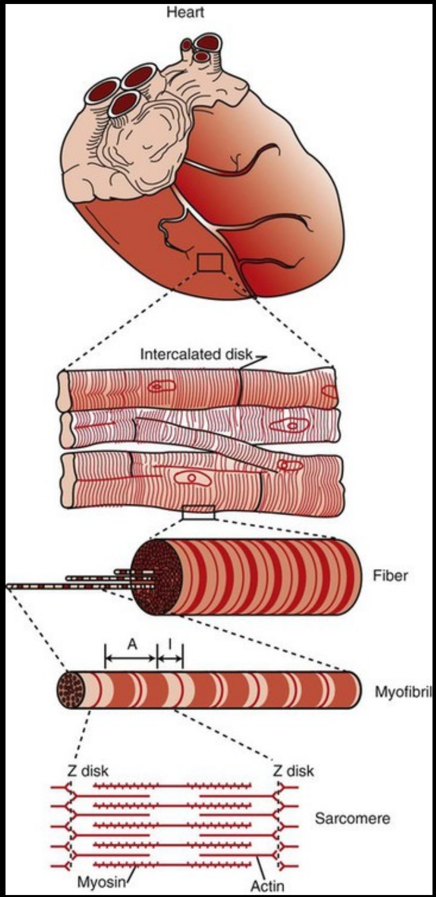
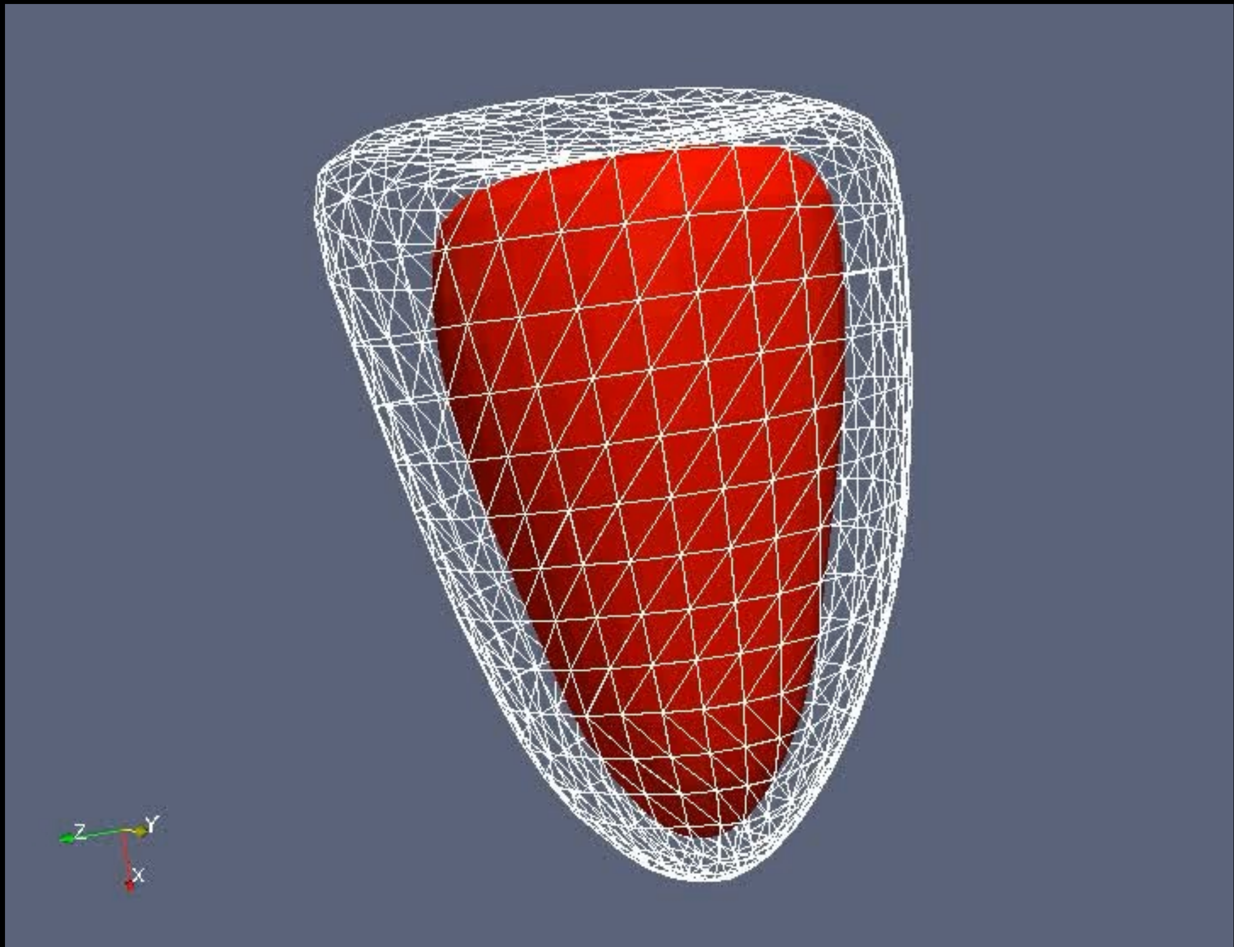
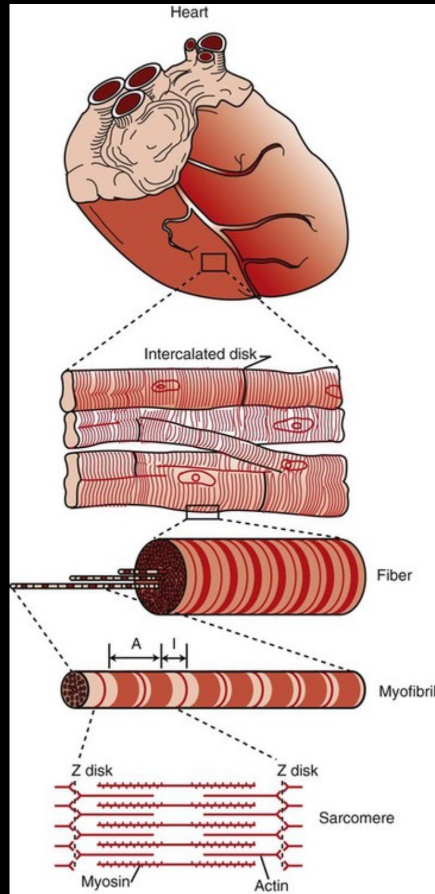
Basic multiscale cardiac physiology

1. What makes the heart contract?
   - Electrical activation
   - Intracellular calcium
   - Force development

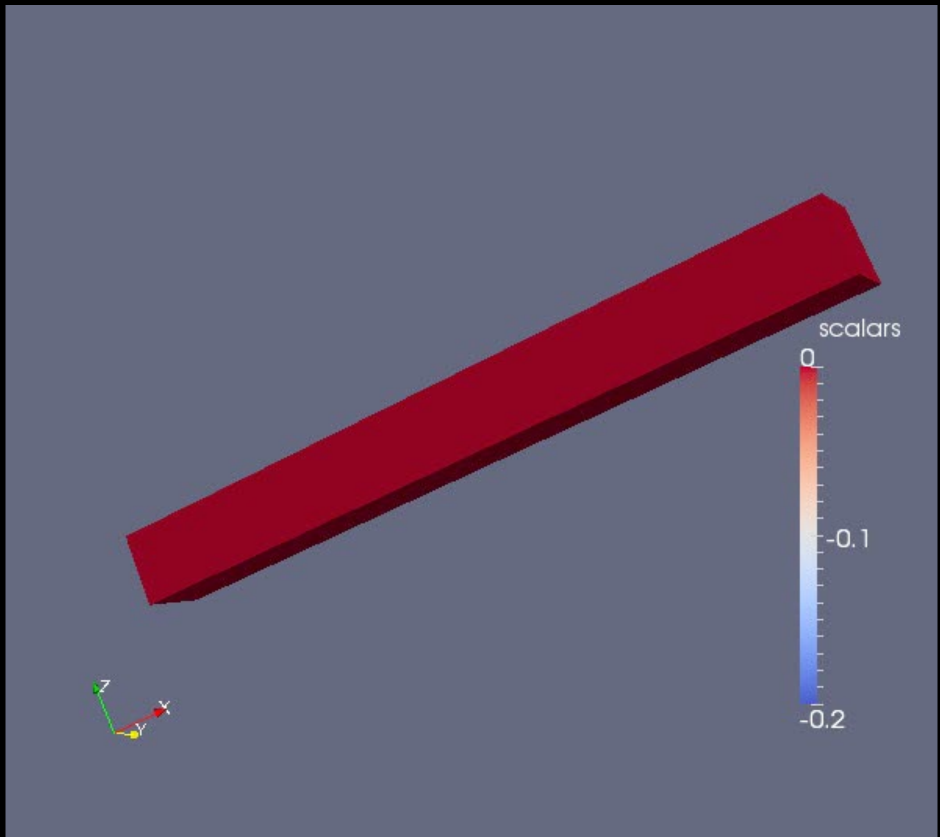
2. How is the force regulated?
   - The force-length relationship in muscle cells

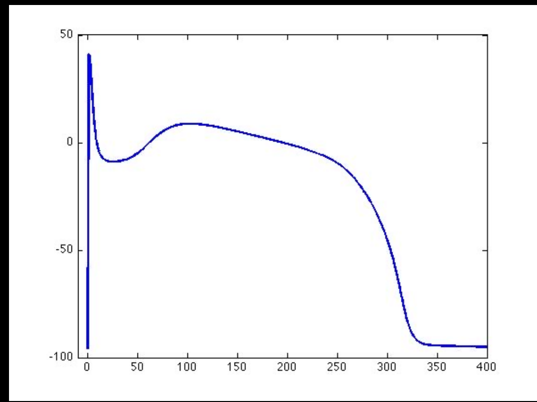


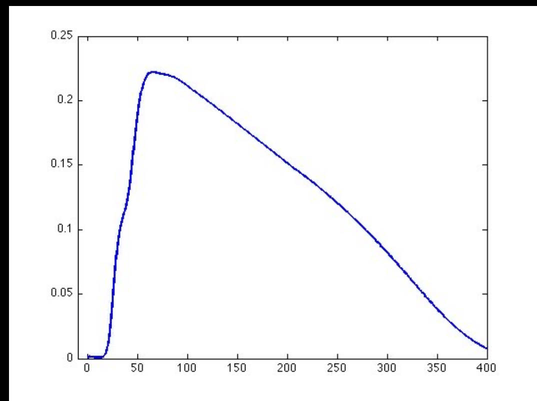

Z
Y
X

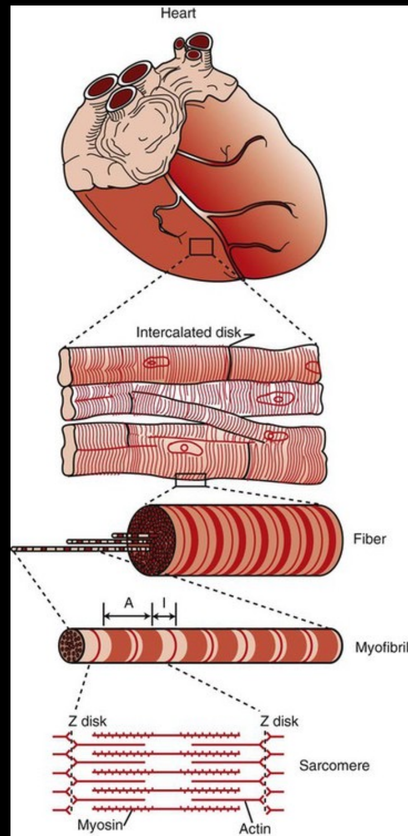

Heart
Intercalated disk
Fiber
A
I
Myofibril
Z disk
Z disk
Sarcomere
Myosin
Actin

Cell scale: Electrical activation => Increased intracellular calcium concentration => Contraction

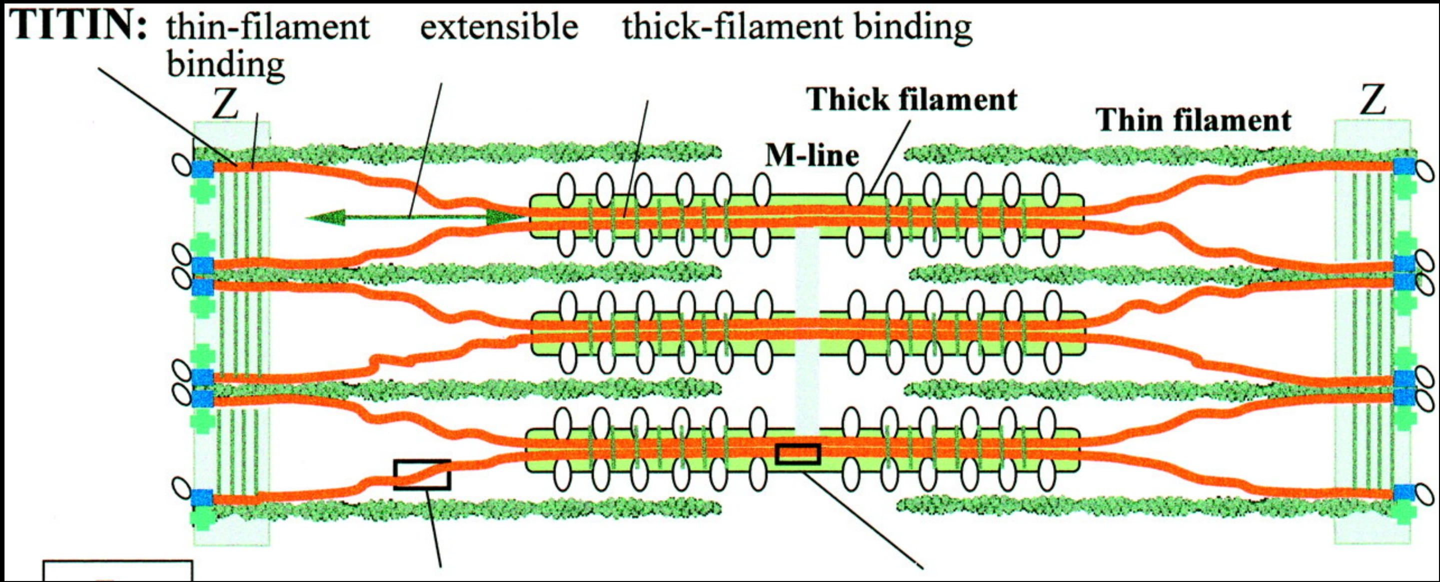


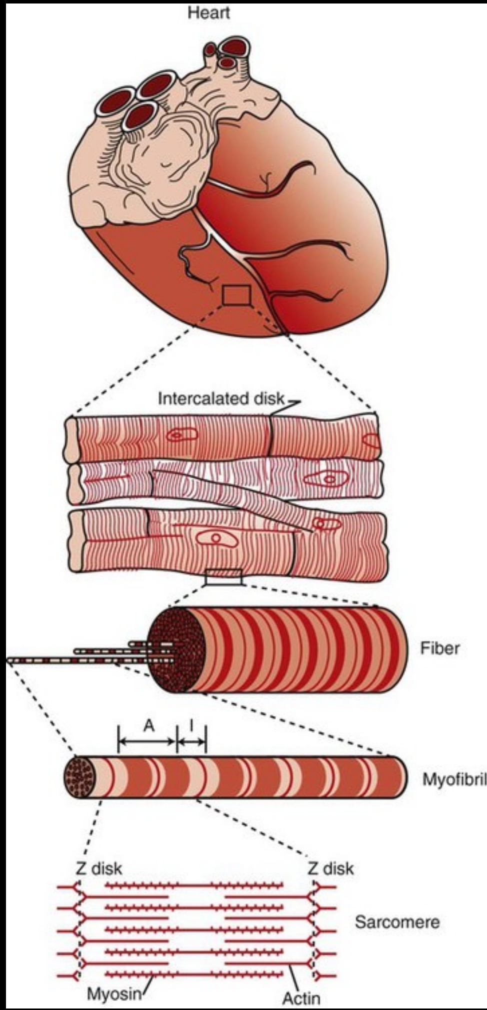




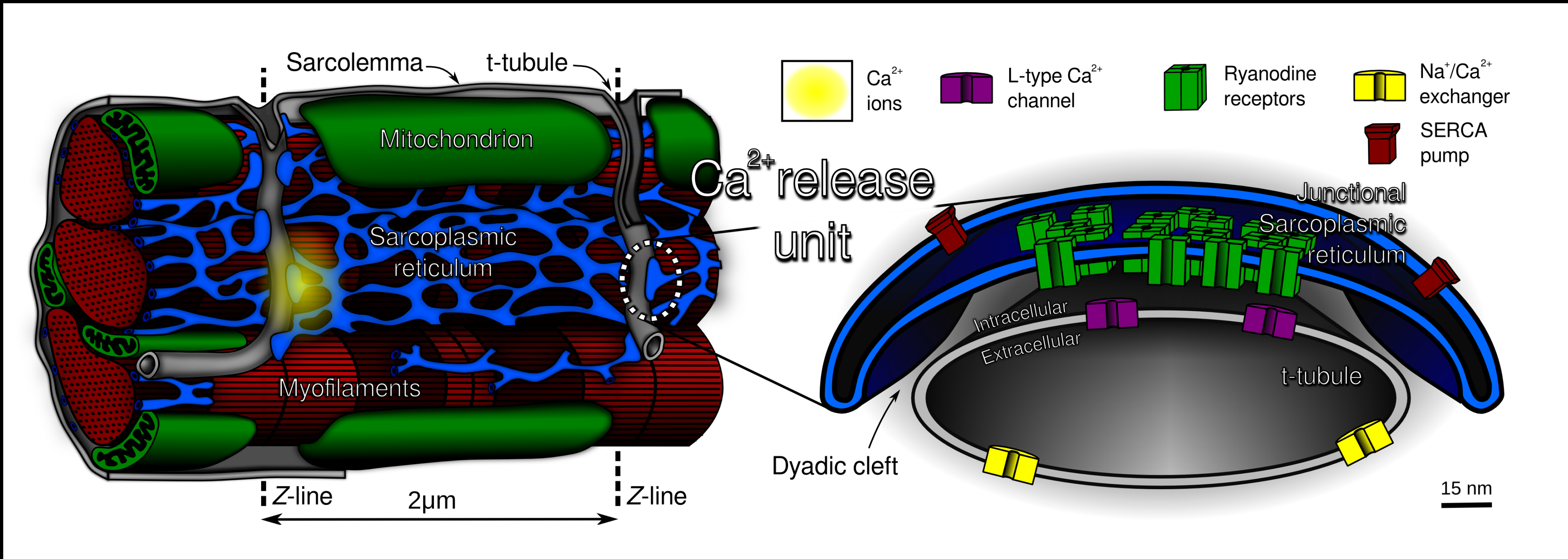


Sub-cellular scale: Thousands of *sarcomeres* contract in (relative) synchrony

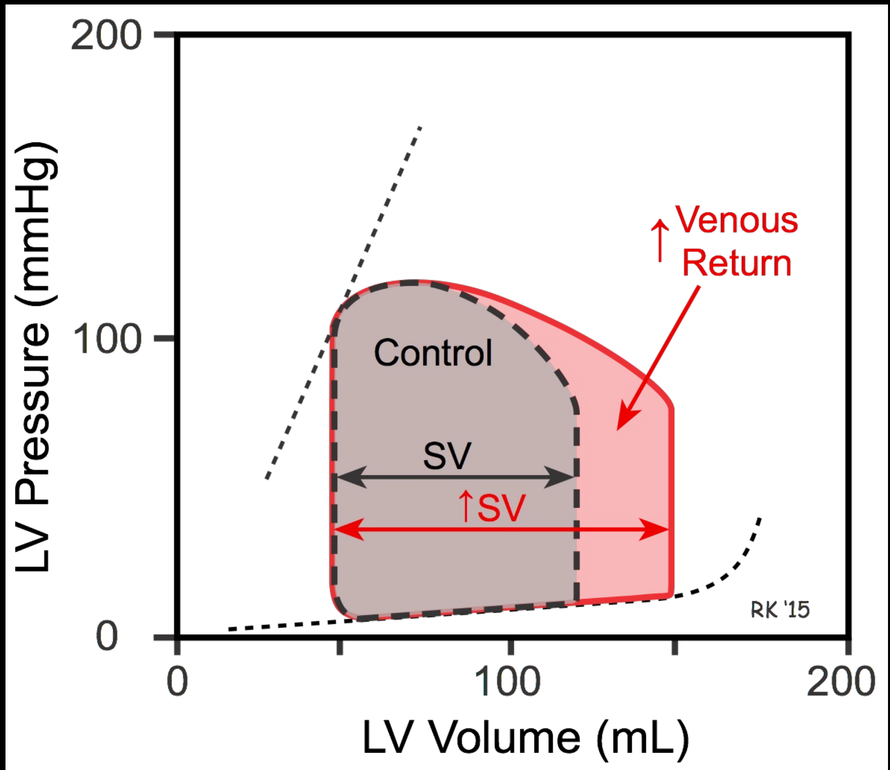


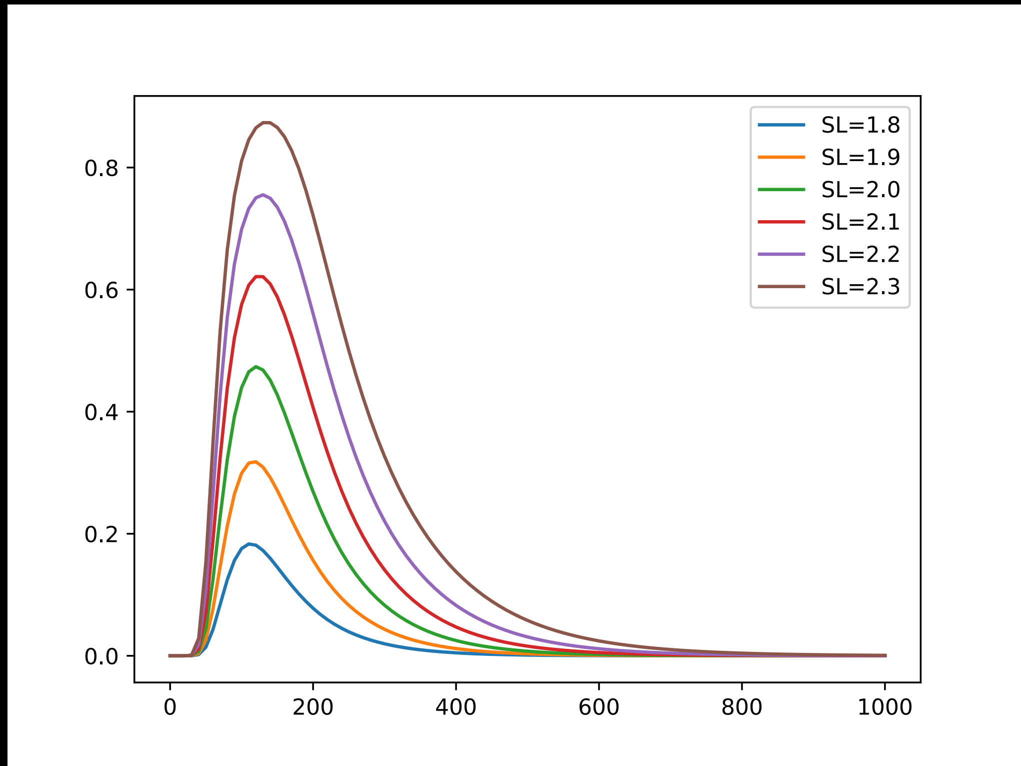


A complex network of T-tubules and calcium storage units ensures simultaneous calcium transients

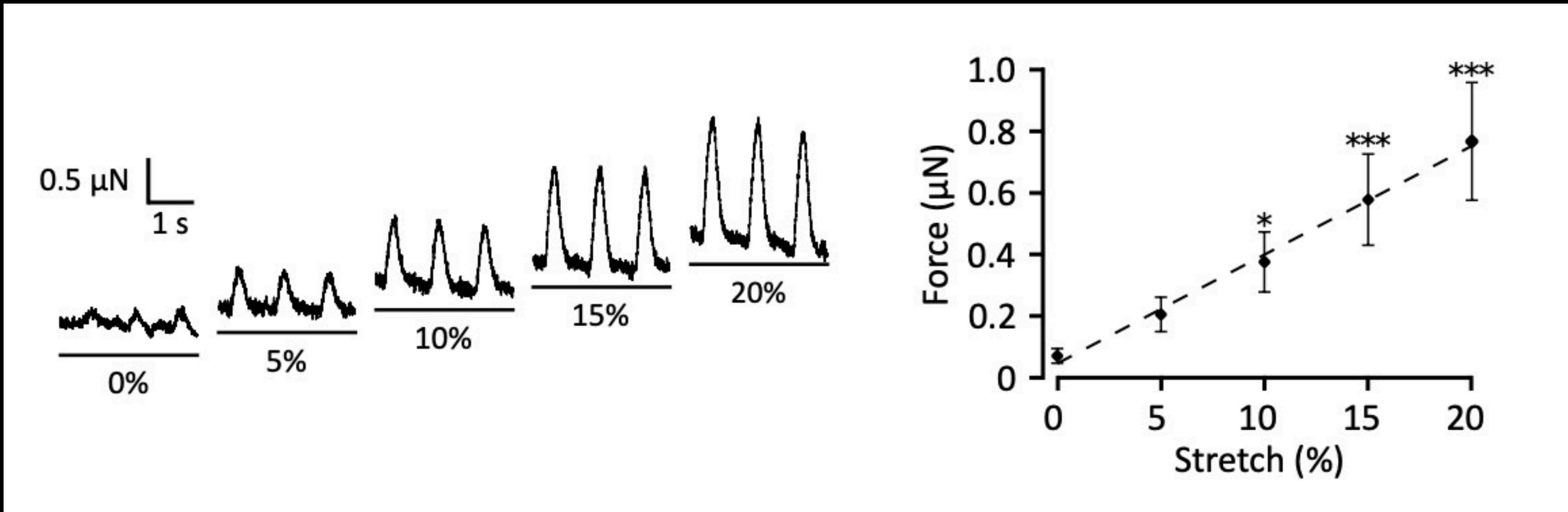


The Frank-Starling mechanism, AKA the force-length relationship or length-dependent activation (LDA)

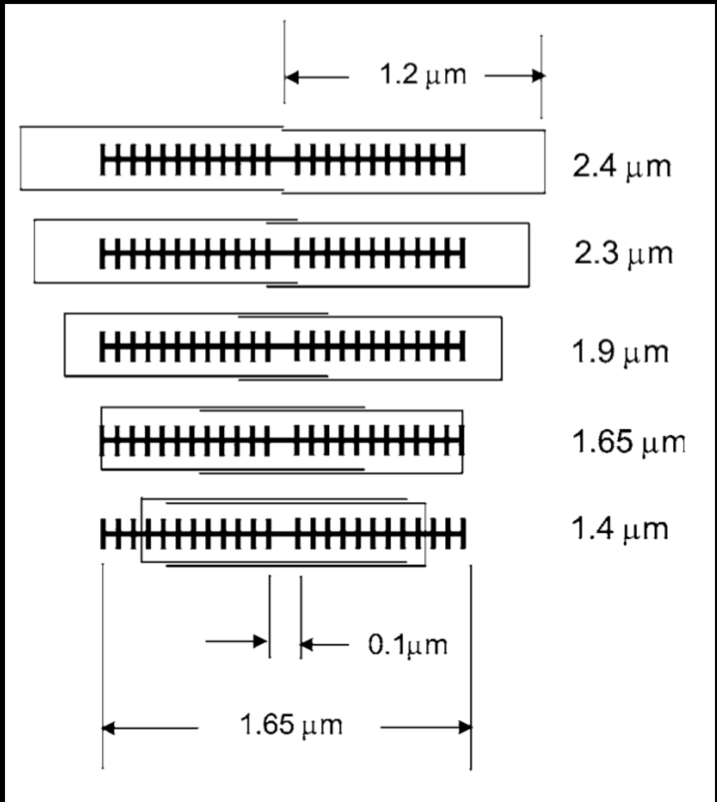




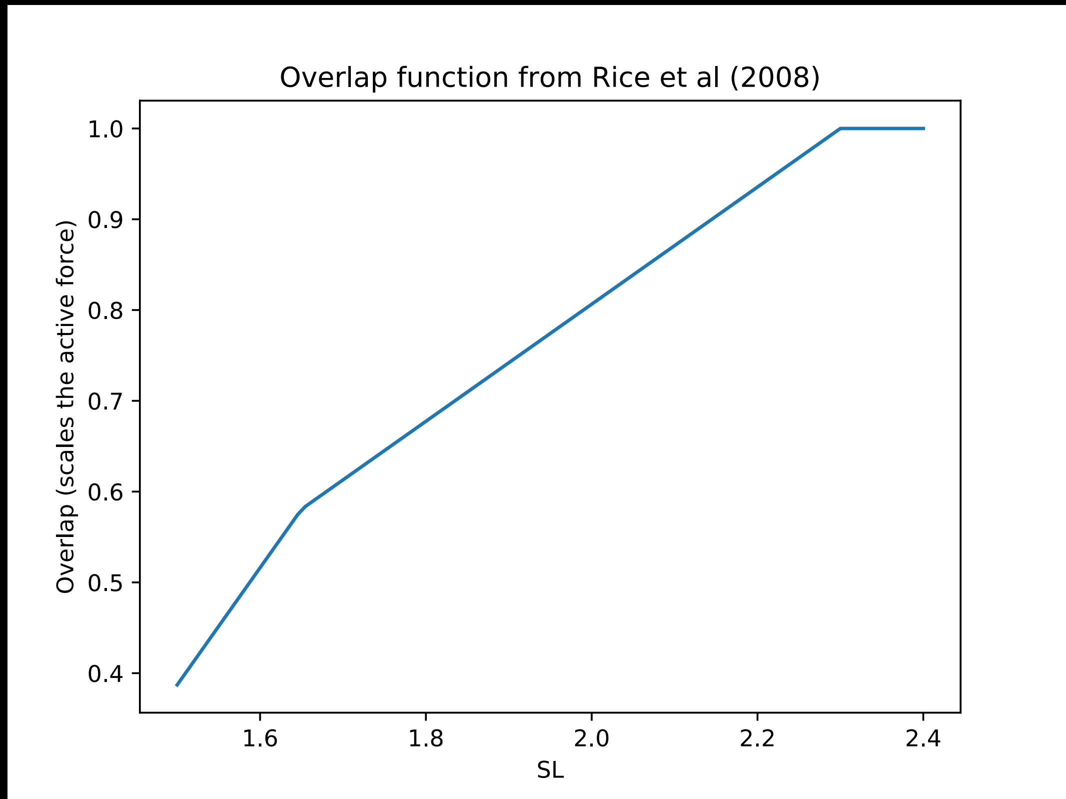
Force-length curve from experimental data



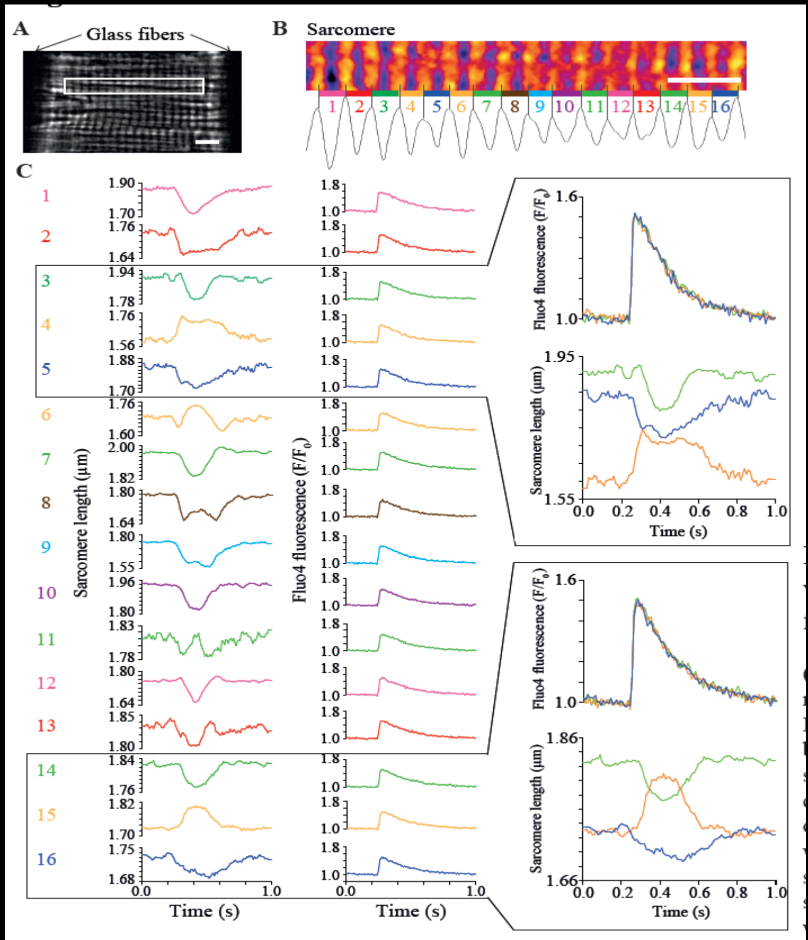
The force-length relationship can be partly explained by the overlap of sarcomere filaments

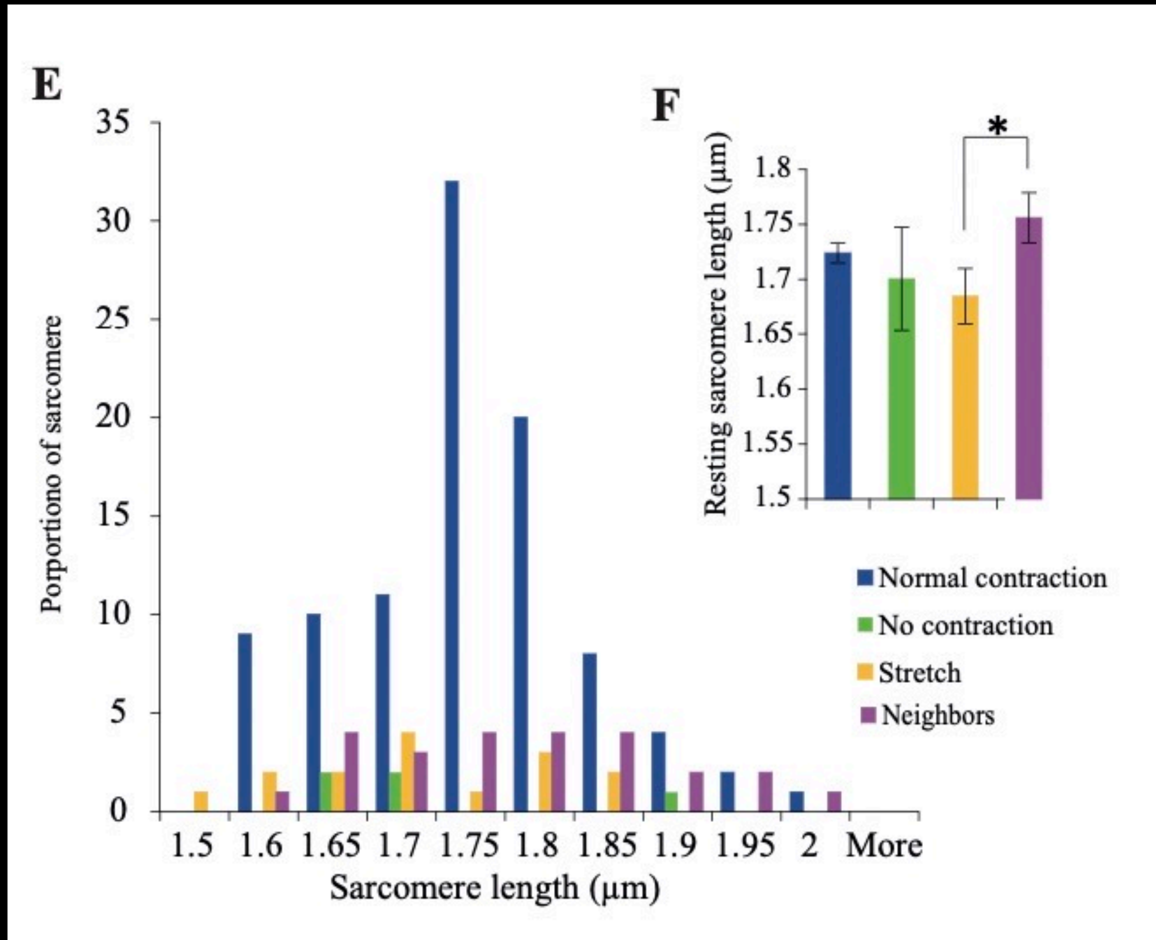


From Rice et al (2008)

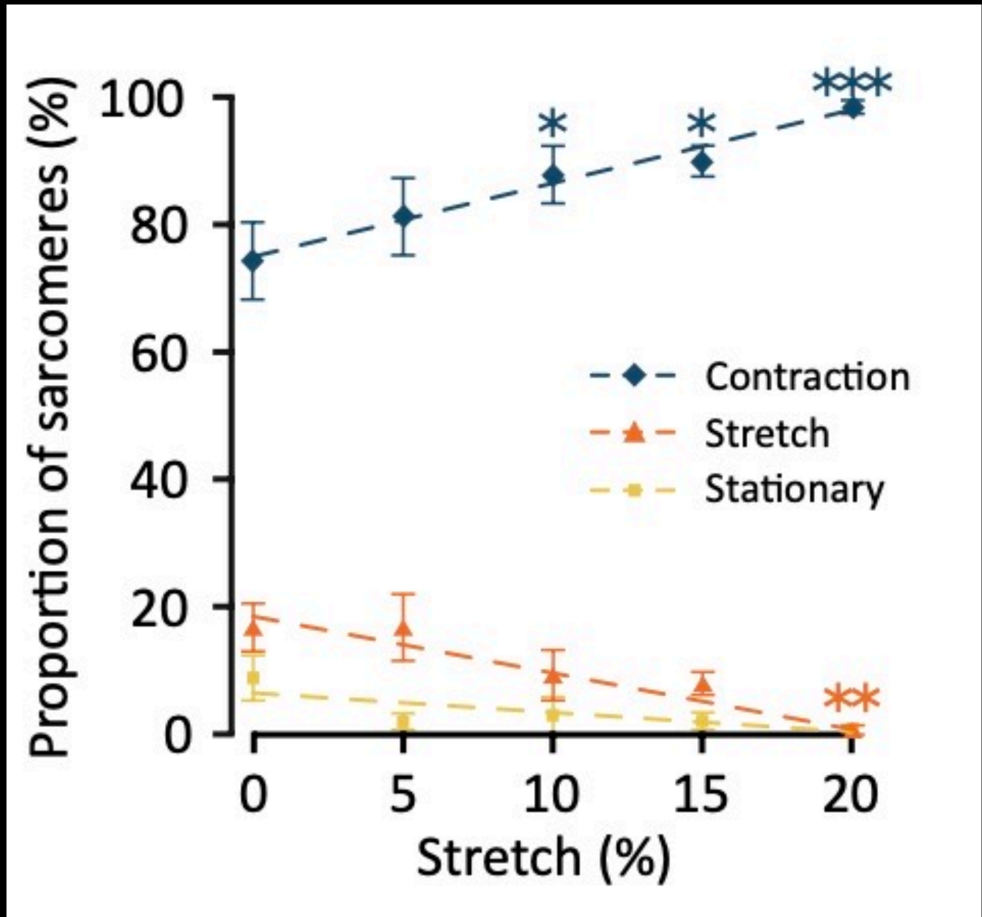


Experimental results: Sarcomere contraction is dyssynhronous even if calcium concentration is completely homogeneous





Stretching the cell tends to synchronize the sarcomeres



Key observations:

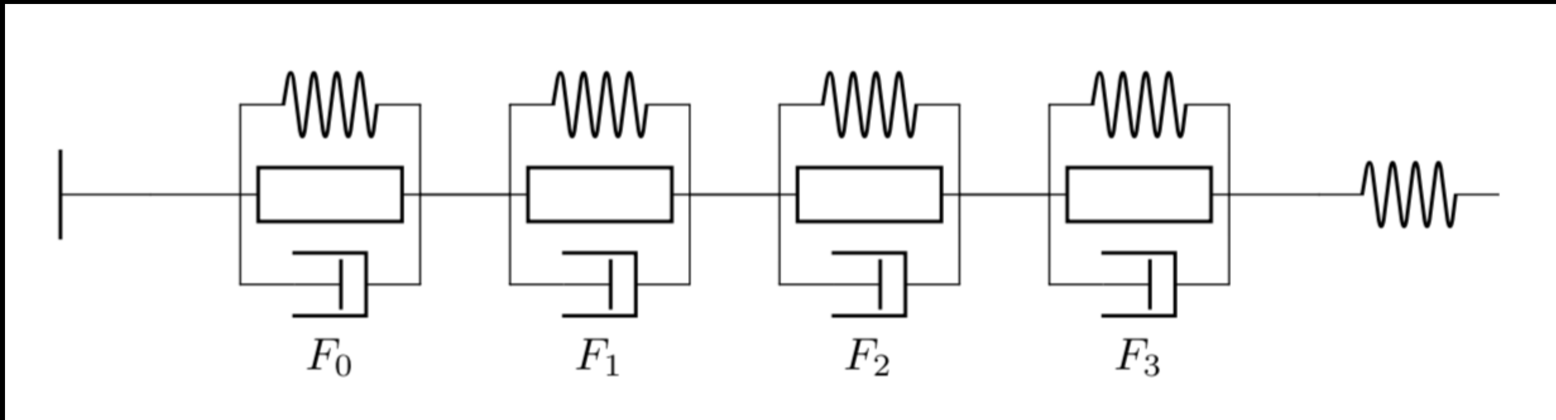
1. Contracting sarcomeres are long at rest
2. Stretched or non-contracting sarcomeres are short
3. Neighbors of stretched are long
4. Stretching the cell appears to homogenize contraction

These observations raised two natural research questions:

1. Can the dyssynchronous sarcomere contraction, and the synchronization with stretch, be explained by the force-length relationship of individual sarcomeres?

2. Does the synchronization of sarcomeres with stretch play a role in the overall force-length relatationship?

Model 1: a string of connected sarcomeres (i.e., a single myofibril)



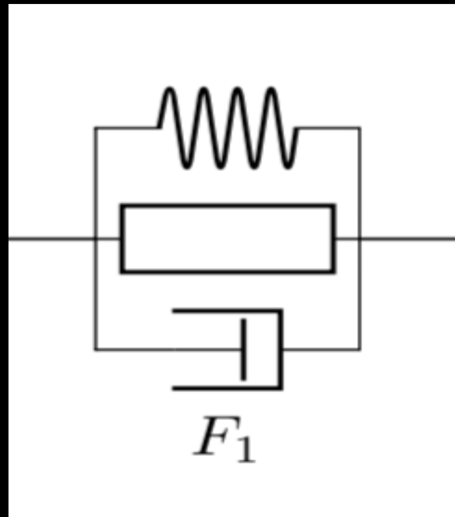
- N sarcomeres connected in series
- Serial elastic element, set stiff for nearly isometric conditions
- Sarcomeres are connected end-to-end, fully rigid

Homogeneous calcium, equal contraction models, different initial sarcomere length

Force balance in a single sarcomere:

$$F_e + F_a + F_v = F_{app},$$

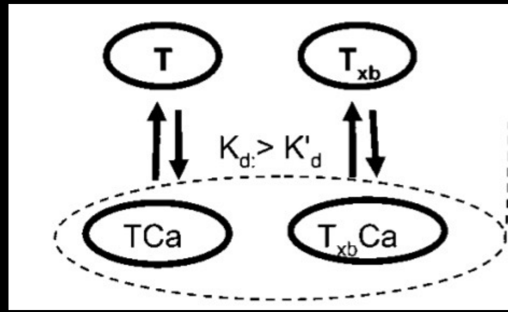
Elastic force: $F_e = F_e(SL)$
Active force: $F_a = F_a(s,SL)$
Applied force: F_{app} *(serial spring)*
Viscous force: $F_v = F_v(dSL/dt)$

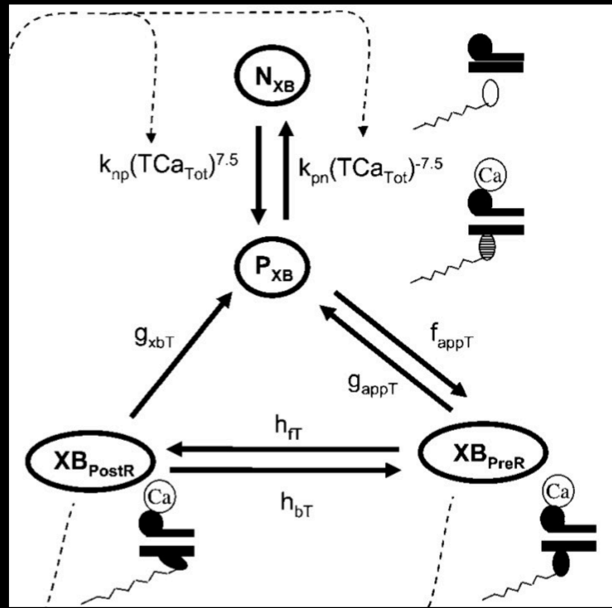


$$\nu \frac{dSL_i}{dt} = F_{app} - F_a(s_i, SL_i) - F_e(SL_i),$$

Active force model from Rice et al (2008)

- Ca binding to thin filaments
- Cross-bridge attachement and cycling
- Force computed by viewing crossbridges as linear springs
- 7 state variables:
  - 2 for bound Ca
  - 3 for XB states
  - 2 mean XB distortions



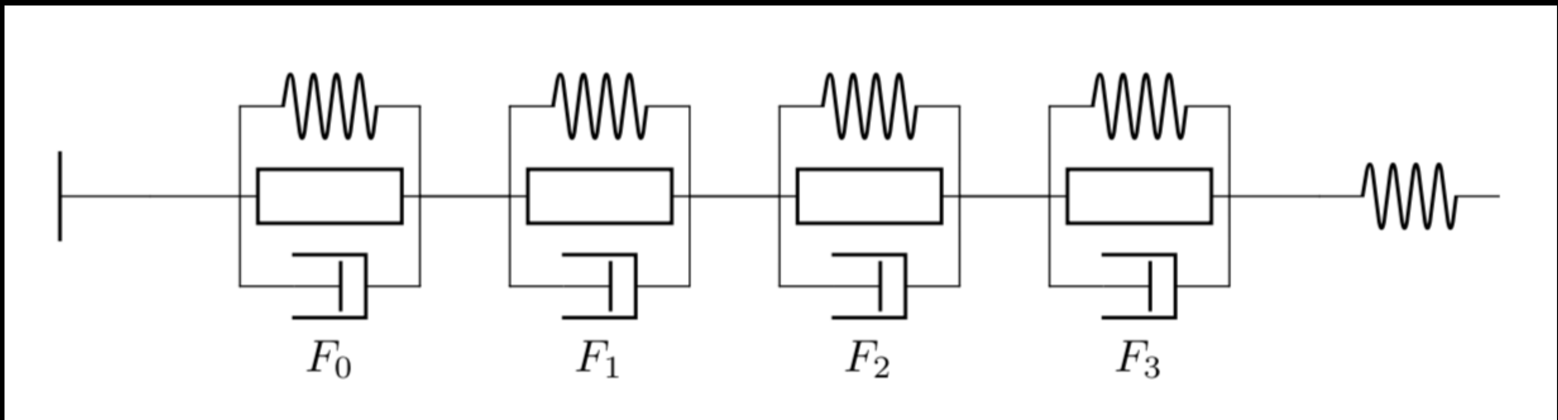


System of 8 ODEs for each sarcomere

$$F_a = k_{XB}\left(XB_{preR}dXP_{preR} + XB_{postR}\, dXP_{postR}\right)$$

$$\frac{ds_i}{dt} = f(t, s_i, SL_i)$$

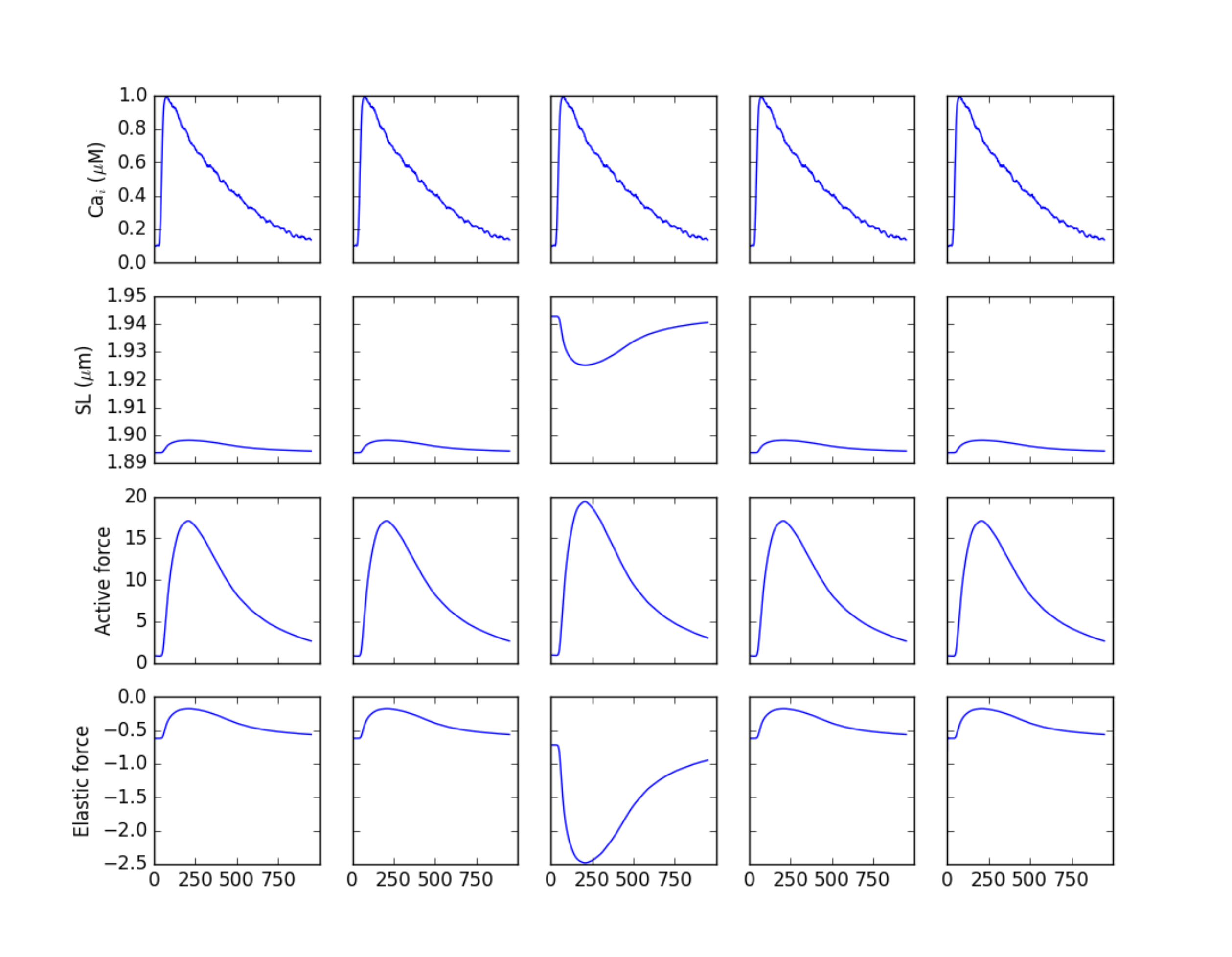
$$\nu\frac{dSL_i}{dt} = F_{app} - F_a(s_i, SL_i) - F_e(SL_i)$$



Prototype model implemented in Python

- Standard SciPy ODE solvers (solve_ivp, RK45)
- 8 x N_{sarc} ODEs
- Very slow, only works for small N_{sarc}
- Not currently possible to reproduce statistical results from experiments (~1500 sarcomeres)

Sarcomere string results



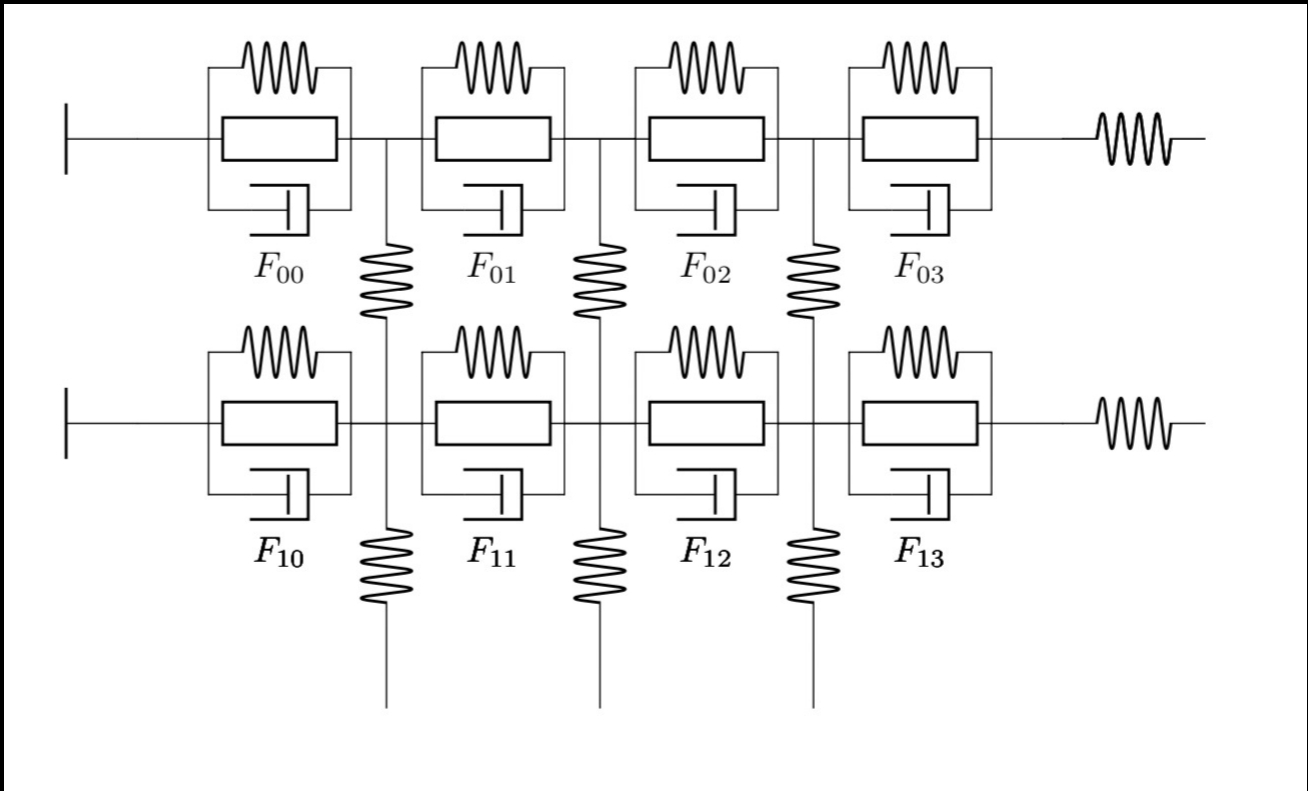
String of 5 sarcomeres

- All identical except length
- All short except middle one

Main observations:

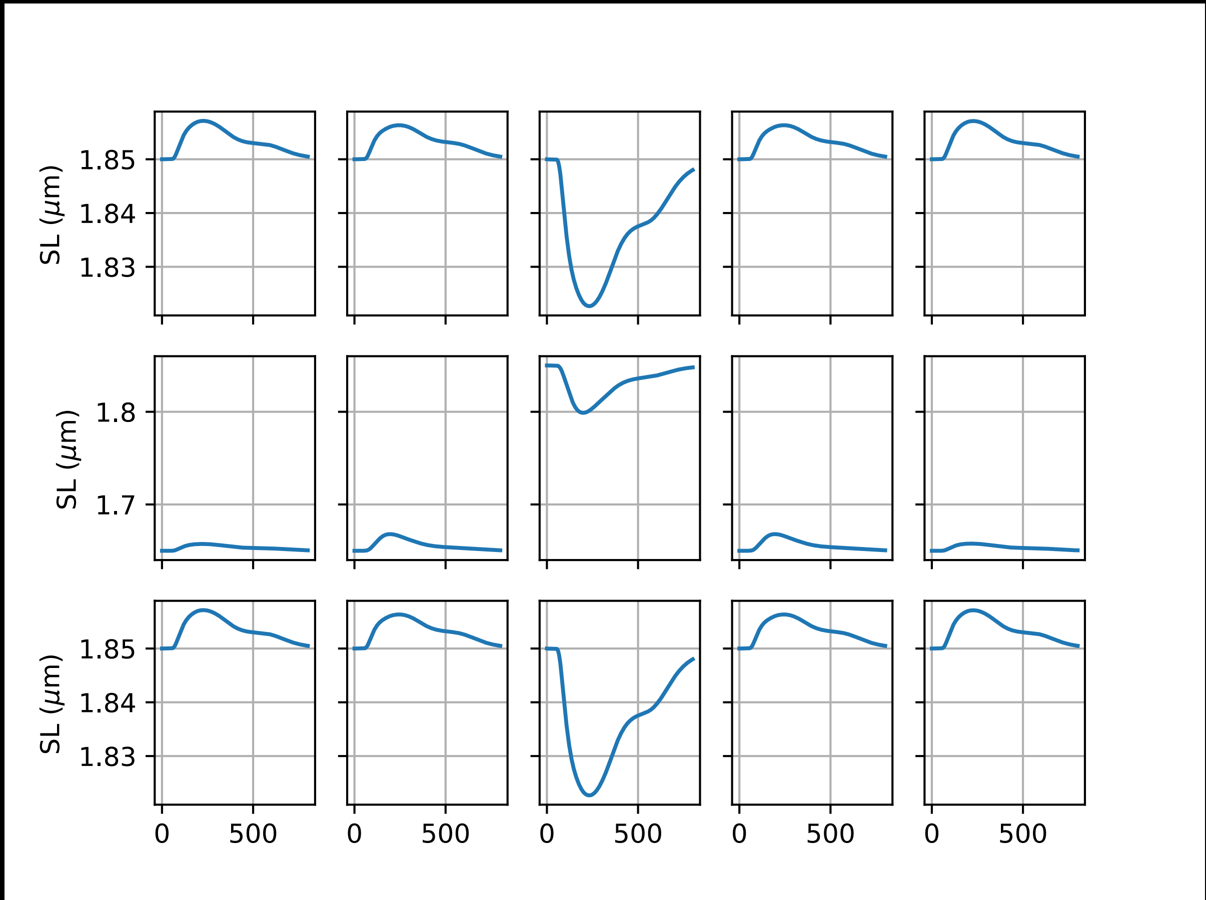
- Short sarcomeres are stretched
- Long sarcomeres contract
- *Neighbors of long/strong sarcomeres are not stretched more than others*

Model 2: an array of sarcomeres



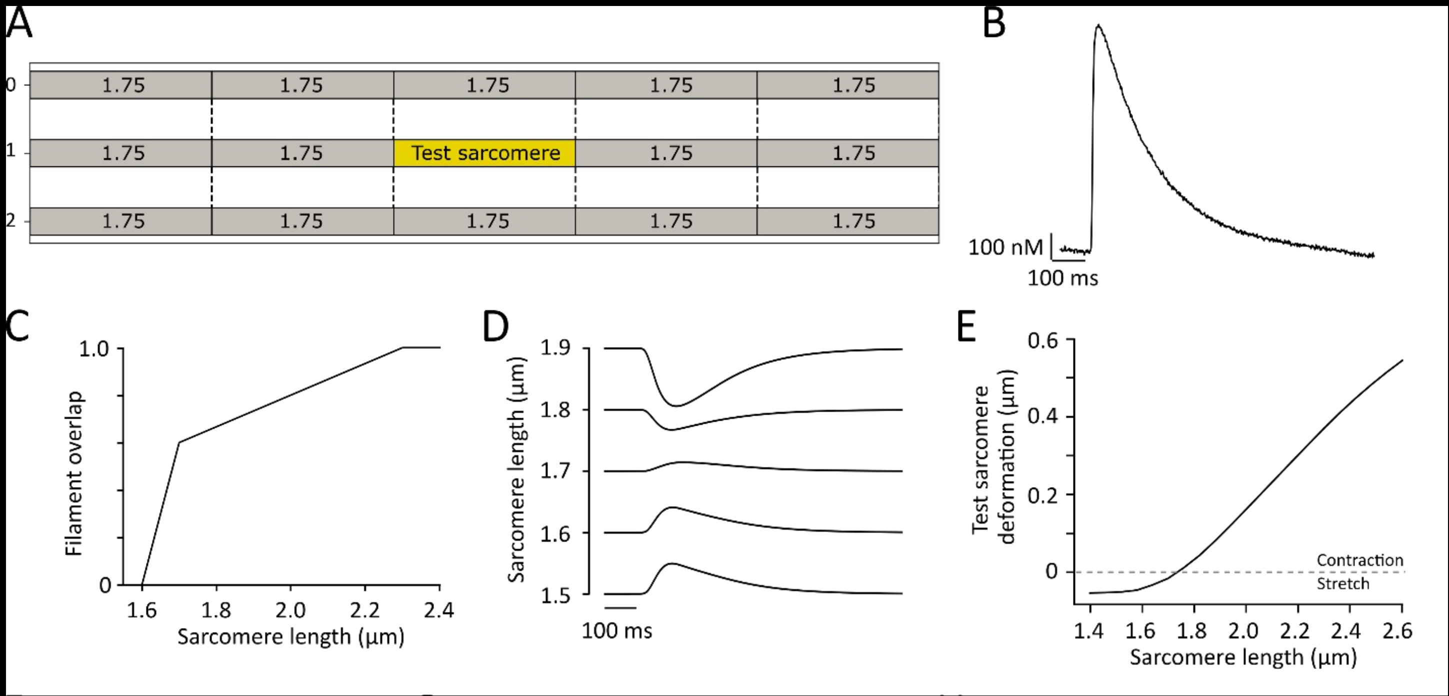
- N x M sarcomeres connected in 2D array
- Neighboring sarcomere strings connected by elastic springs at the z-lines

Initial sarcomere array results



- 5 x 3 sarcomere array
- All are short except the middle one
- *Neighbors of strong sarcomeres are stretched more than others*

Varying the resting length of the test sarcomere shows the expected behavior

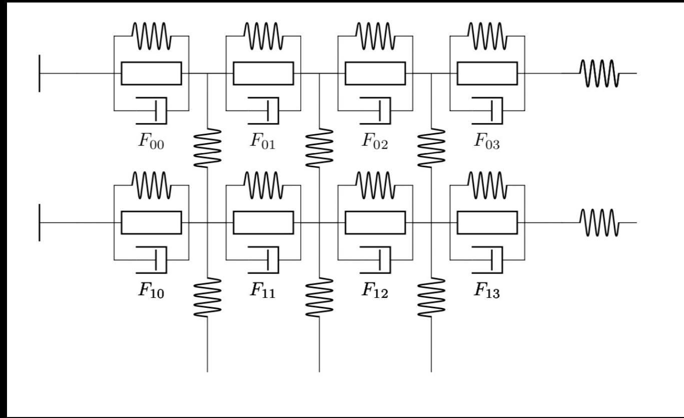


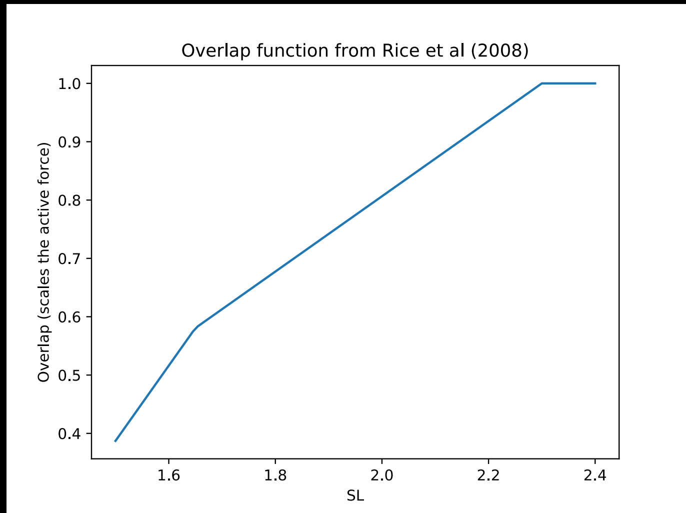
- 3 x 5 array of sarcomeres
- All equal except the middle one

Model 3: Array of sarcomeres in equilibrium

- N x M 2D array
- Same connections
- Assume full activation, no ODEs
- No viscosity
- Identical passive elastic force
- Identical force-length relation of active force

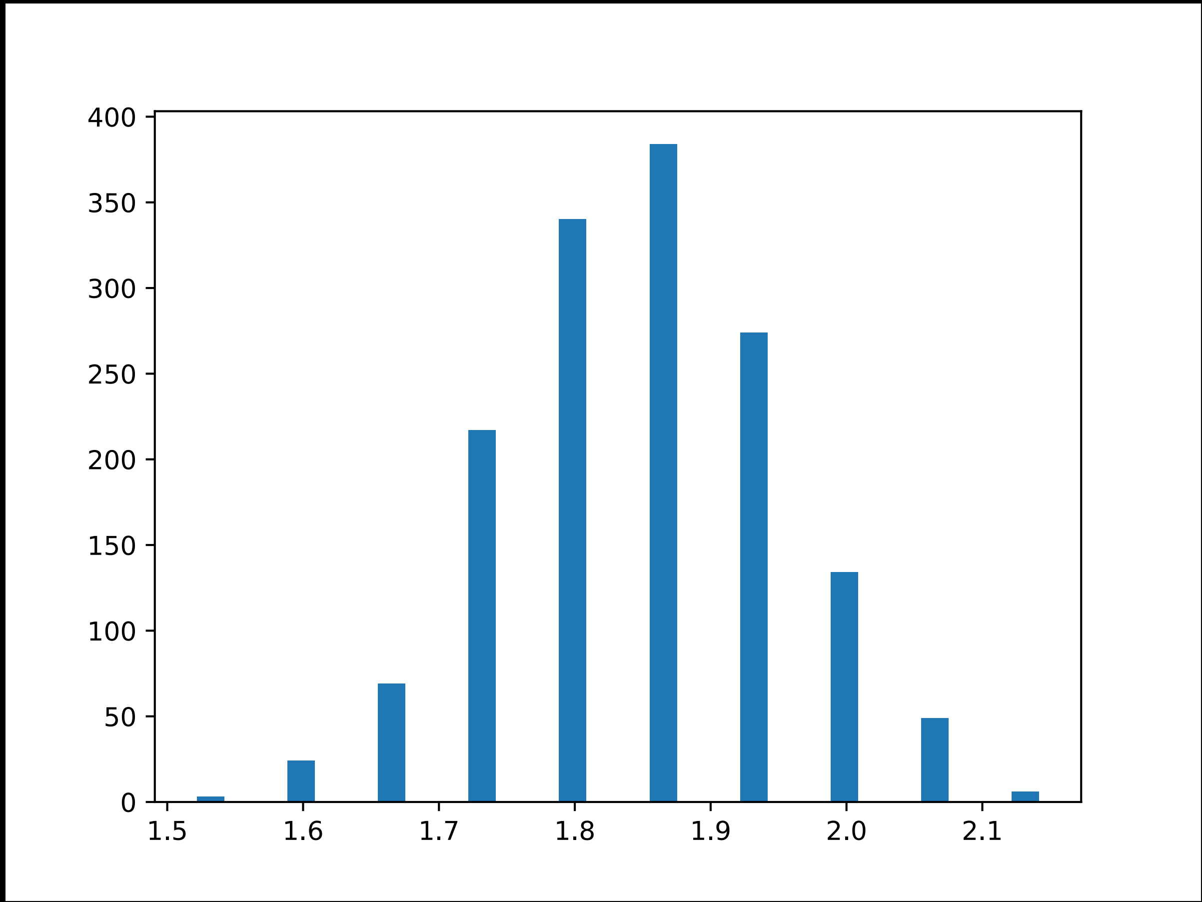
$$F_{app} - F_a(SL_i) - F_e(SL_i) = 0$$



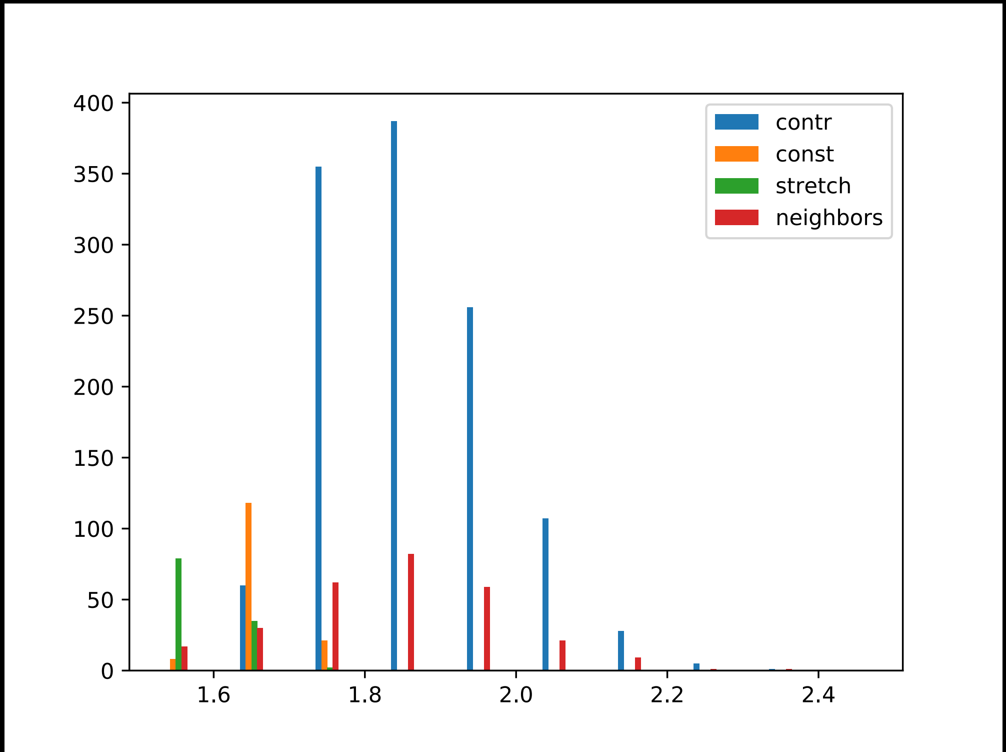


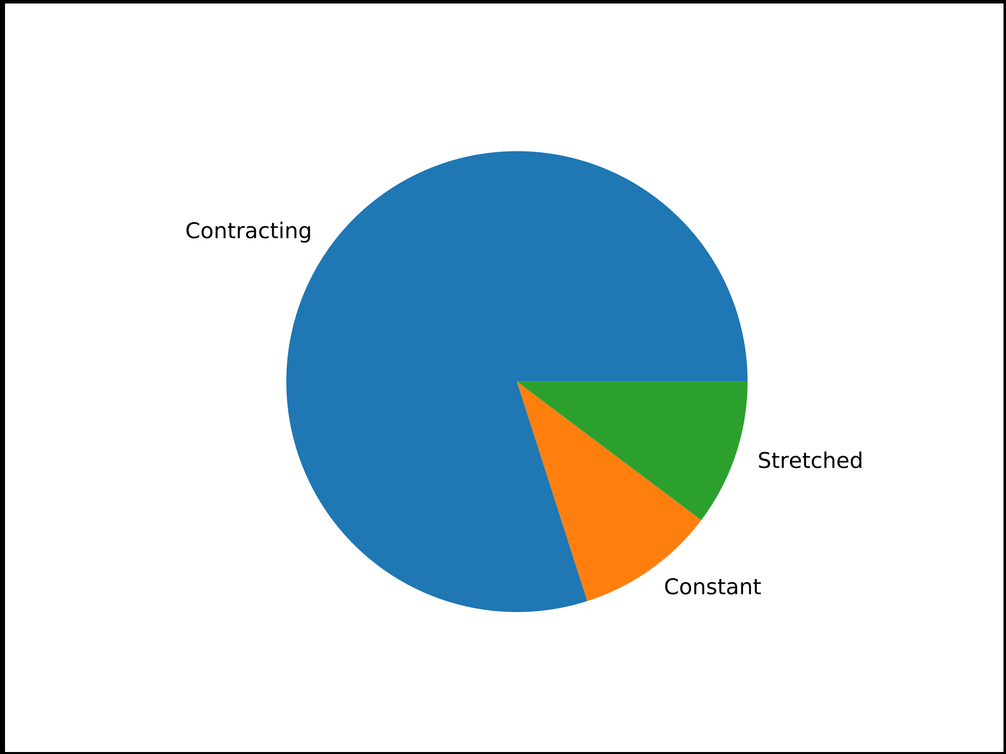
Equilibrium test case: 30 x 50 sarcomeres

- Resting SLs sampled from a normal distribution
- Solve for equilibrium SLs

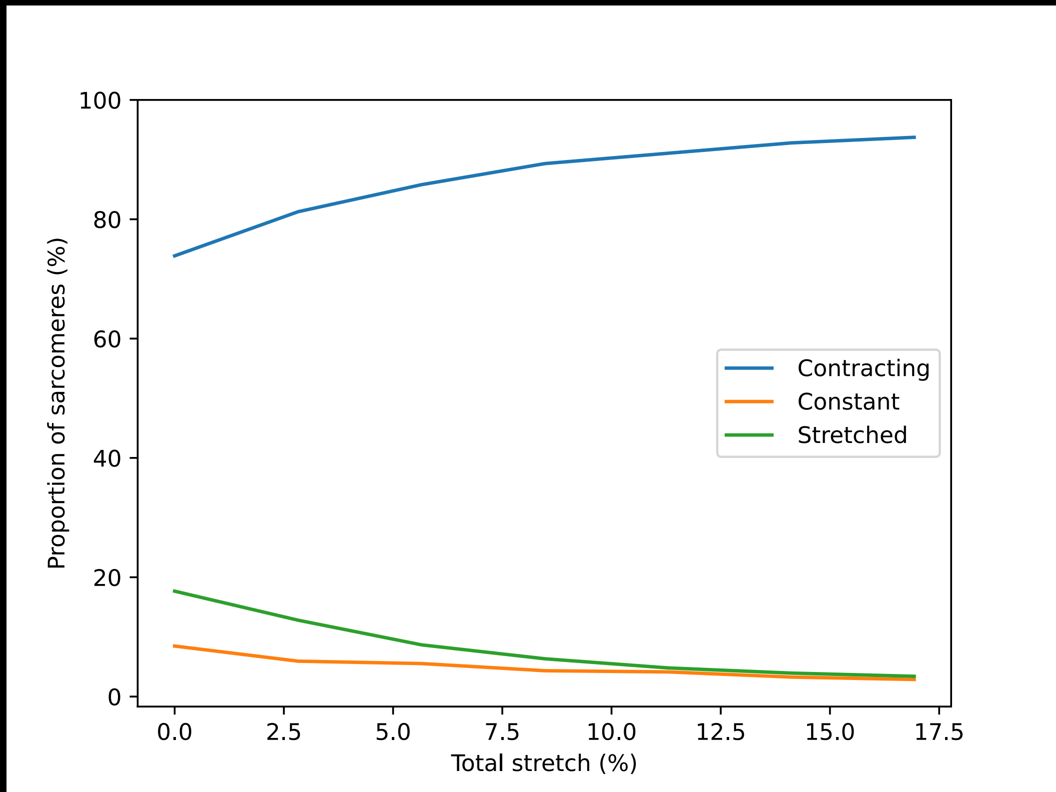


Parameters were tuned to match experimental results at 0% stretch





Stretching the array makes all sarcomeres contract, similar to experiments



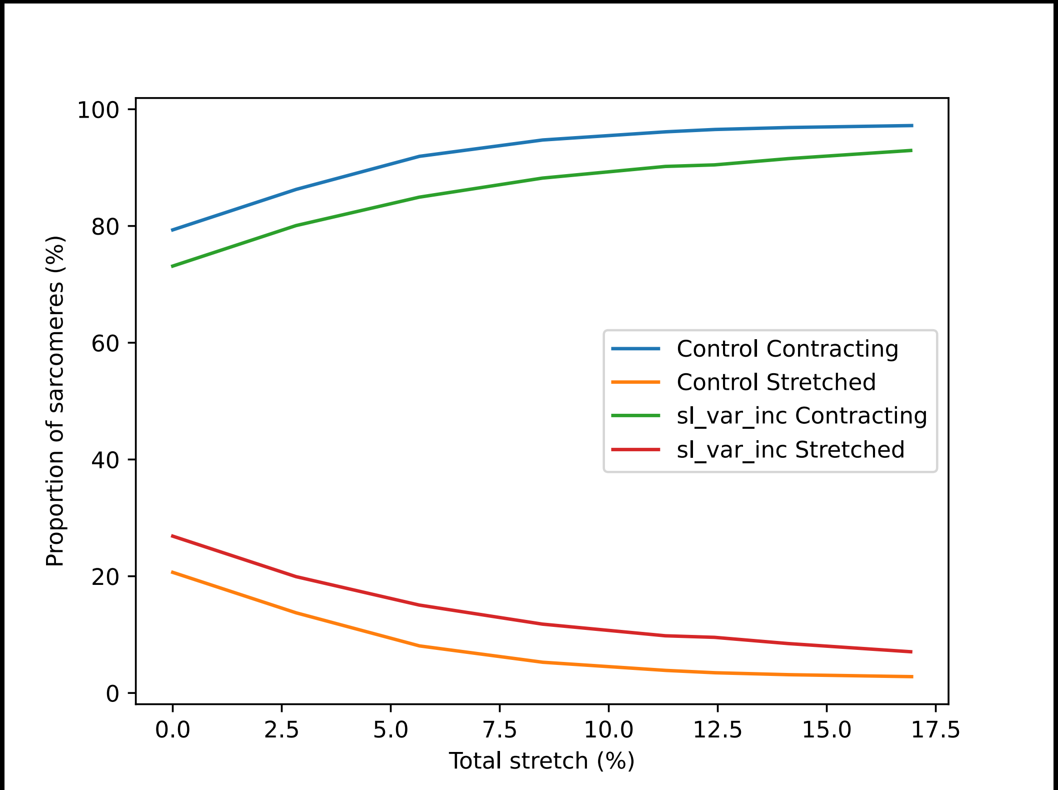
RQ2: Does the synchronization of sarcomeres contribute to the force-length relationship?

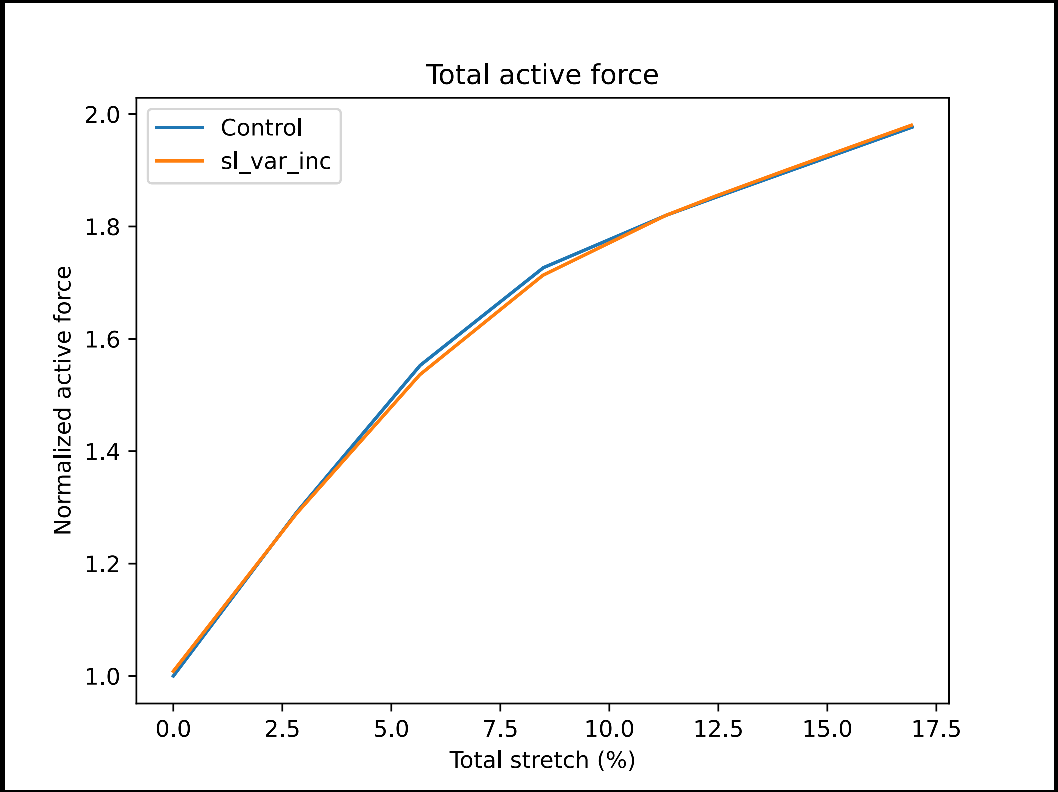
Initial test; increased variability of resting lengths:

- => Larger portion of stretched sarcomeres

- More synchronization (recruitment) of sarcomeres?
- Steeper force-length curve?

Very little impact on synchronization and the force-length curve





Summary and outlook

- Model results support that sarcomere dyssynchrony can be explained by the force-length relationship and the variable resting lengths
- No indication that sarcomere recruitment is important for the force-length relationship and the Frank-Starling metchanism
- Ongoing and future work:
    - Improve dynamic ODE model (run a complete 3D cell)
    - Updated contraction model
    - Experiments with genetic modifications, to explore the reasons for variable resting lengths and synchronization