CaCTFI: Introduction

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Outline

- *What is CaCTFI?*
- *Aim*
- *Motivation*
- *Cardiac thin myofilament*
- *Muscle contraction on microscopic scale*
- *Simplified model of myofilament contraction*

What is CaCTFI?

CaCTFI is a project acronym for :

- *Theoretical study of Ca^{2+} ion dependent cardiac thin filament activation using opened Ising chain with nearest-neighbor cooperative interaction.*

Aim

- *improve simple descriptive model of dependence of thin filaments contraction on concentration of Ca2+ ions*

- *detailed picture of heart muscle fibers on microscopic scale and role of the Ca^{2+} ions in the contraction mechanism*

Motivation

Looking for model describing cooperative behavior in thin filament

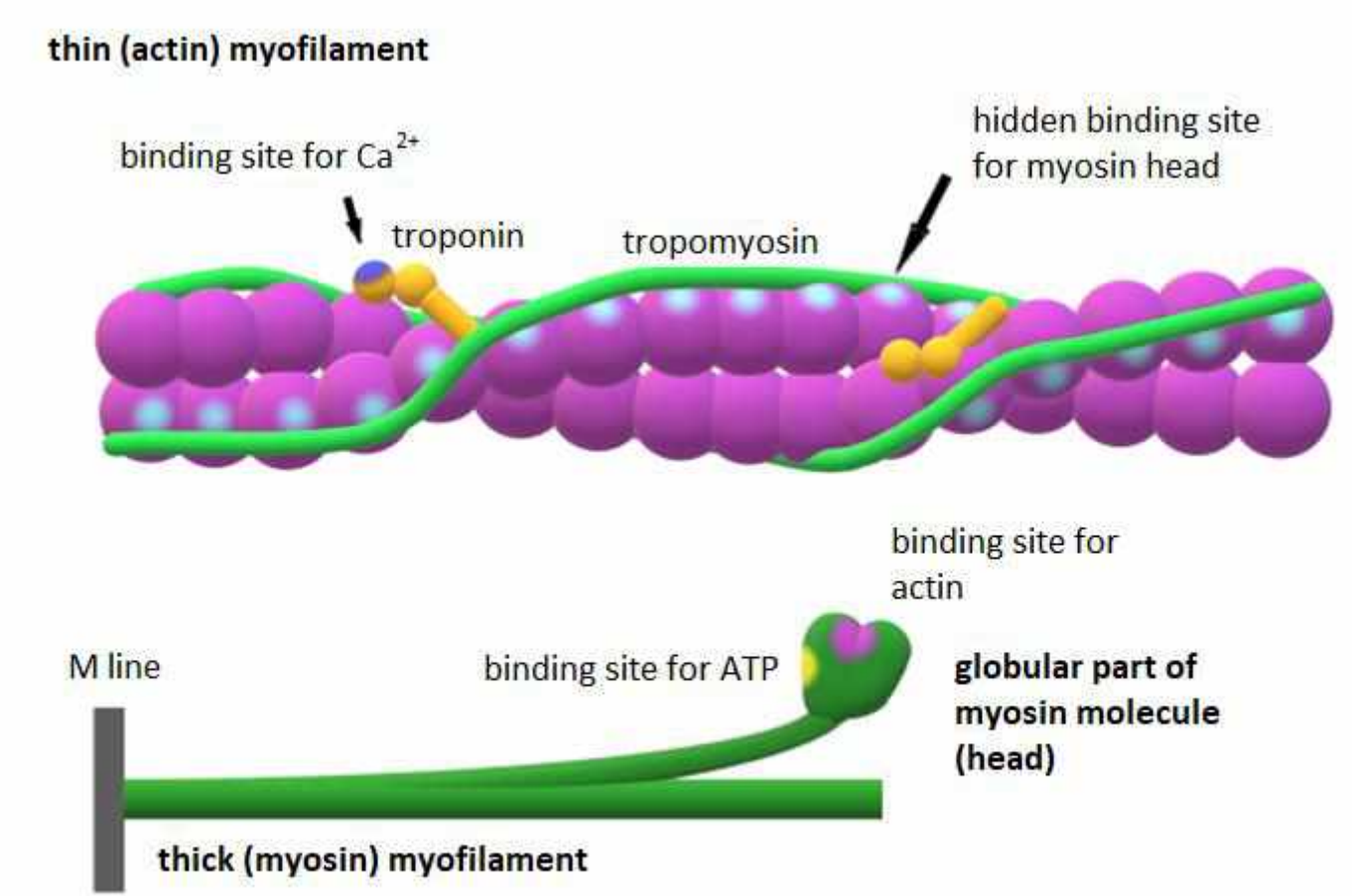
- *Hill a Langmuir 1910: describing binding of ligand to a macromolecule*

$$F = \frac{1}{1 + \left(\frac{[Ca_{50}]}{[Ca]}\right)^{N_H}}$$

Dobesh et al. 2002: measurement and description of cardiac myofilament contraction

- *Rice et al. 2003: 1D Ising model*
  - *periodic boundary approximation*
  - *describing experimental data with better precision*
- ***OUR TASK:*** *finding model in discrepancy with physiological description of cardiac thin myofilament*
  -> assuming open boundary condition

Cardiac thin myofilament



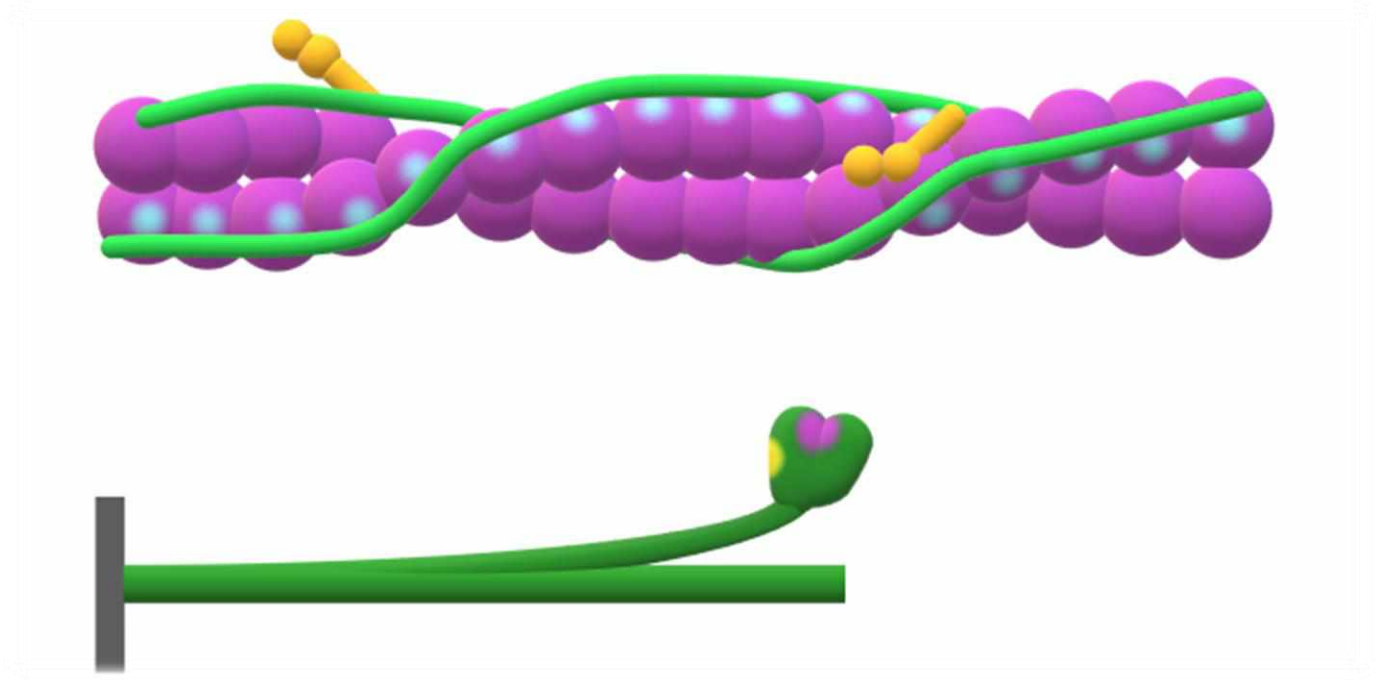
Troponin-tropomyosin unit T/T

- *7 actin units*
- *Troponin*
- *Tropomyosin*

Cardiac thin filament

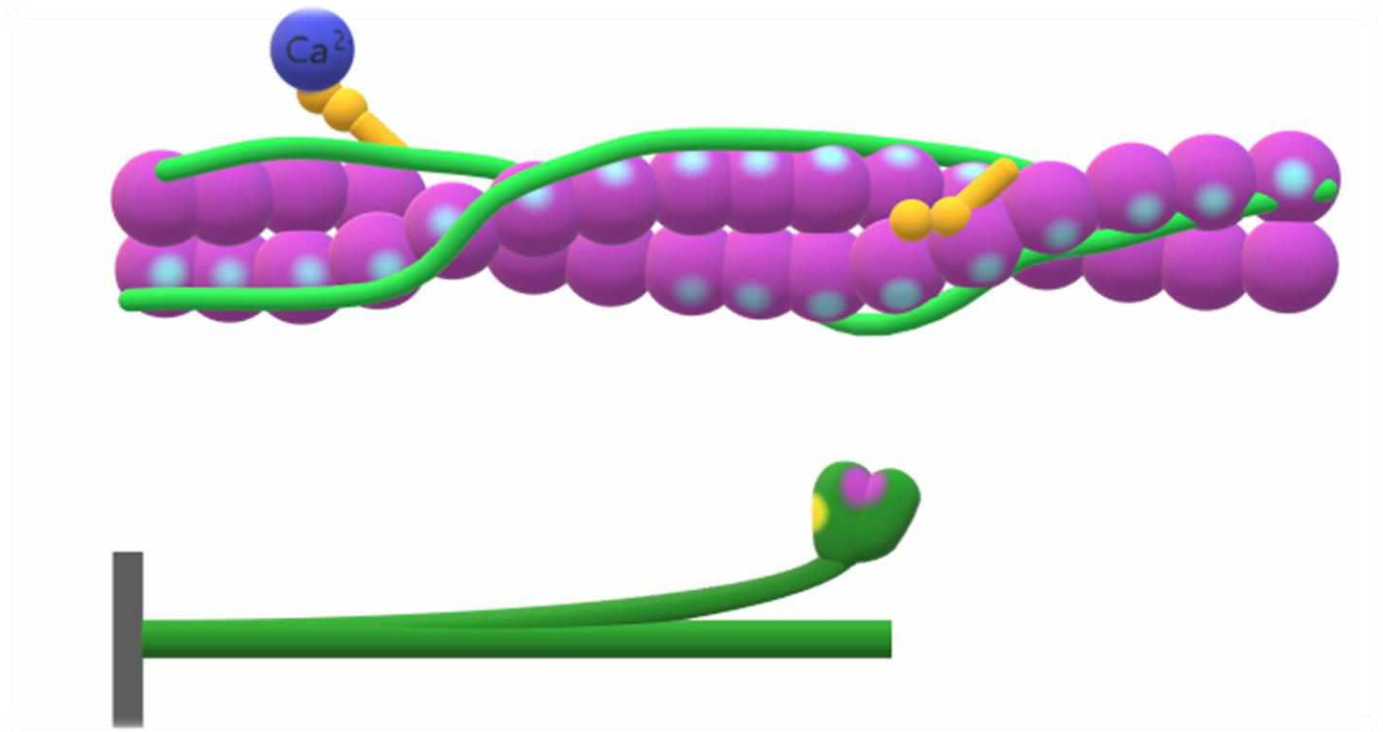
- *26 T/T units, which individually contributes to total contraction*
- *observable synergic effect*

Muscle contraction on microscopic scale



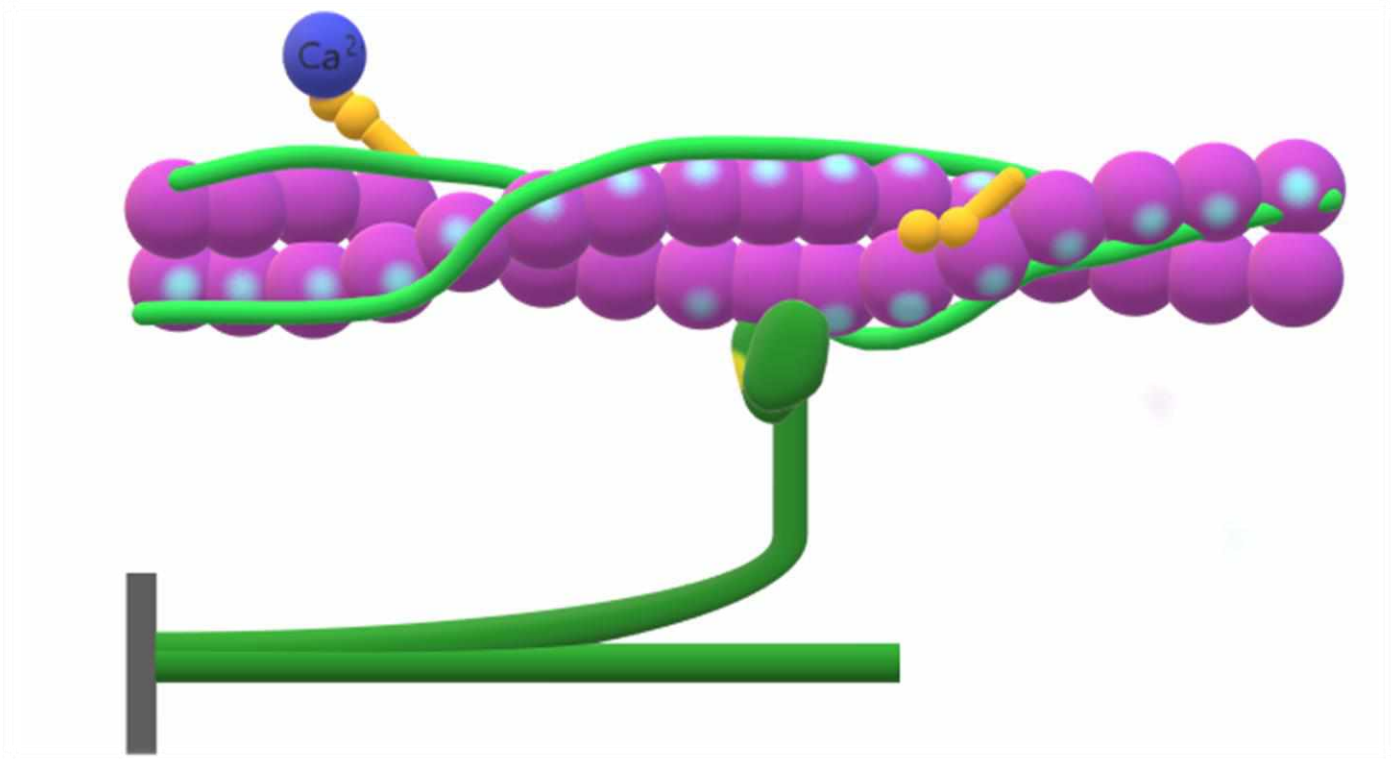
- *initial state*

Muscle contraction



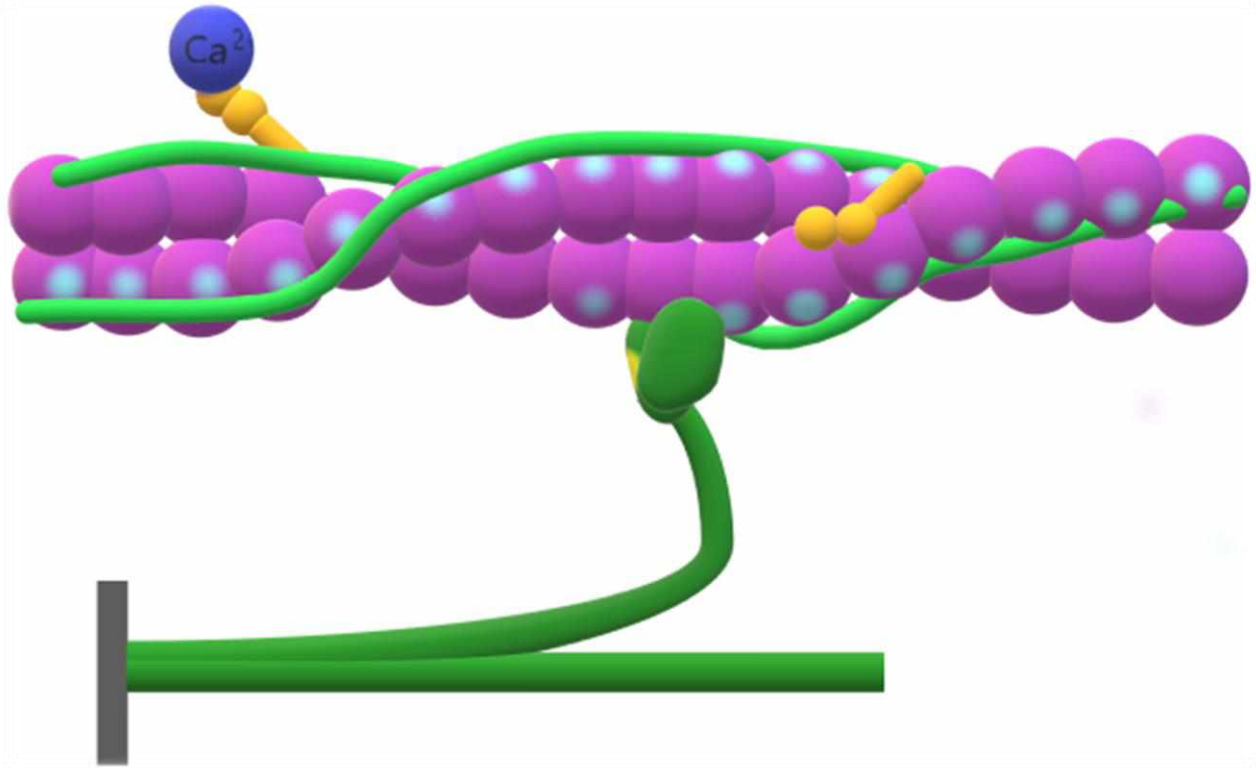
- *binding of Ca^{2+} to a TnC*
- *tropomyosin rearrangement*
- *revealing binding sites for myosin heads on actin units*

Muscle contraction



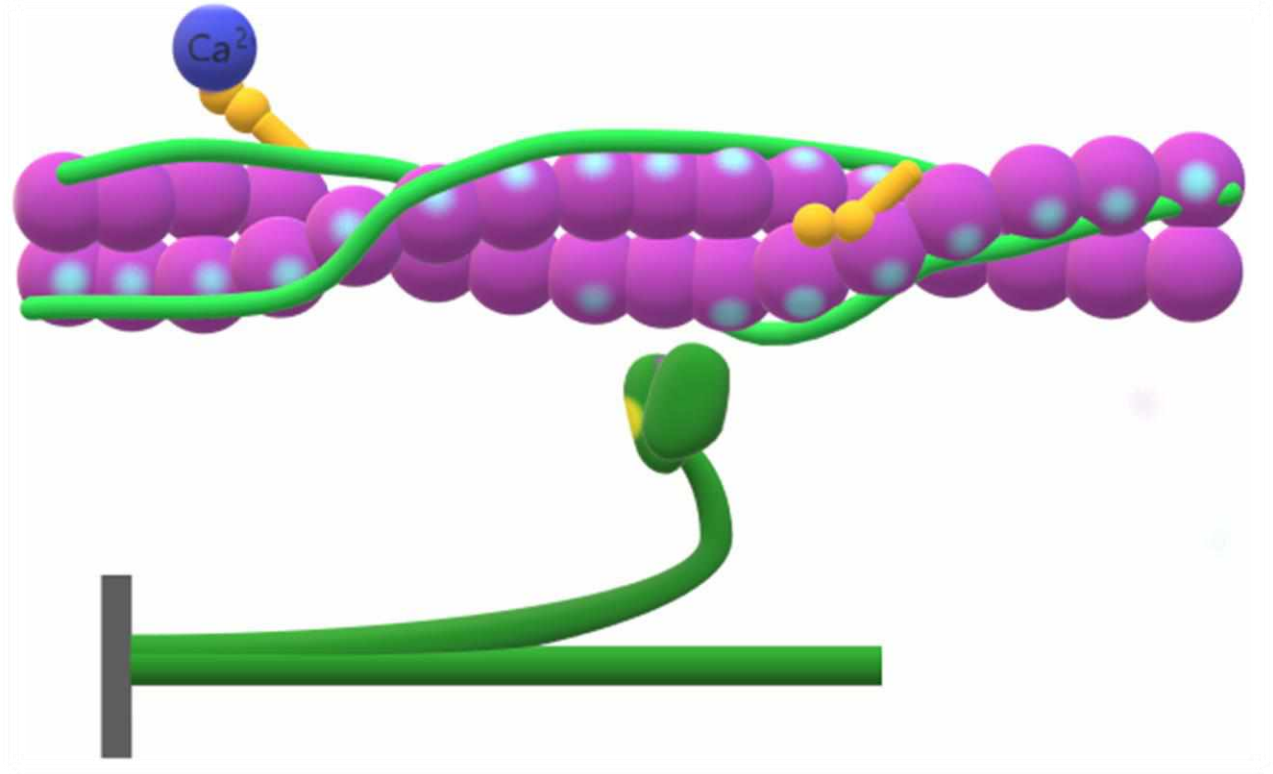
- *Joining myosin head to the actin unit*

Muscle contraction



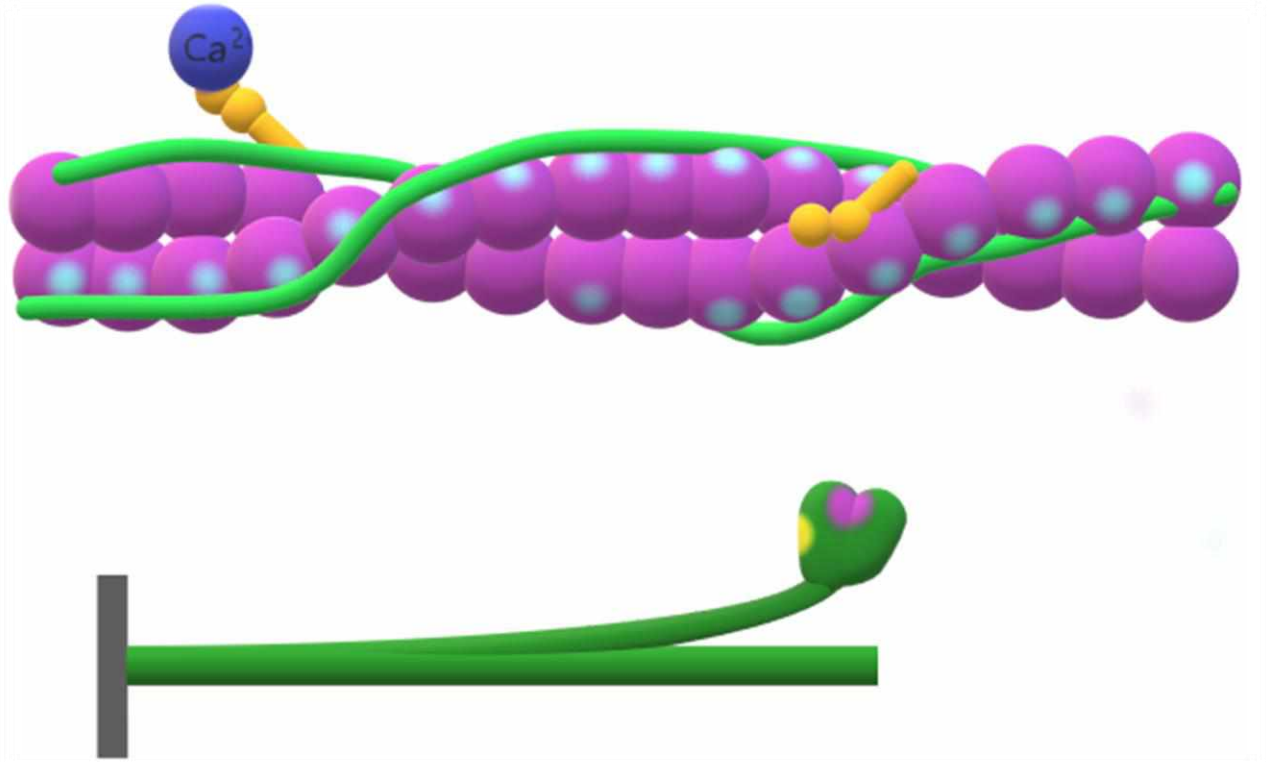
- *consumption of ADP myosin head movement*
  -> shifting of actin filament

Muscle contraction



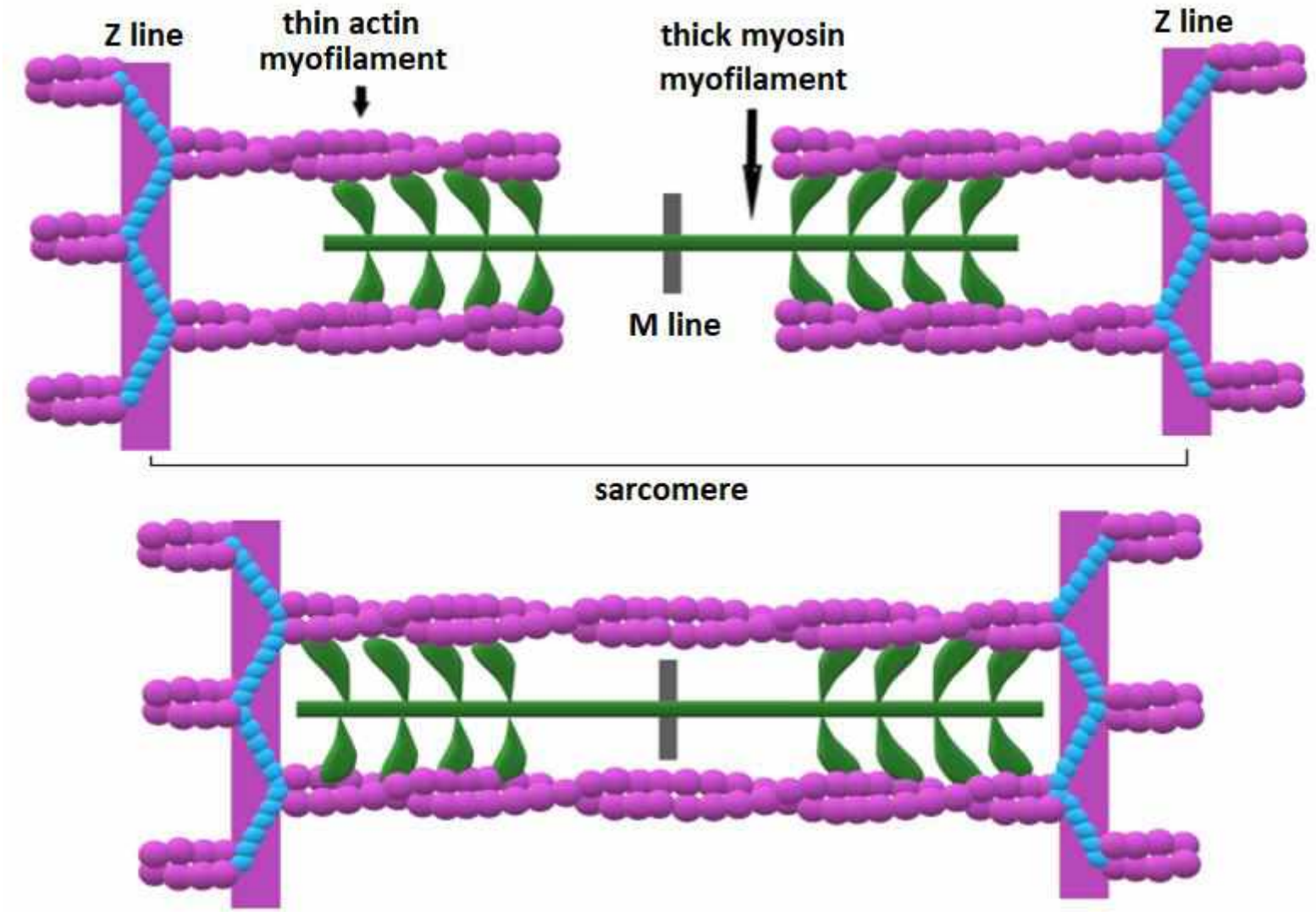
- *binding of ATP and releasing of myosin head*

Muscle contraction

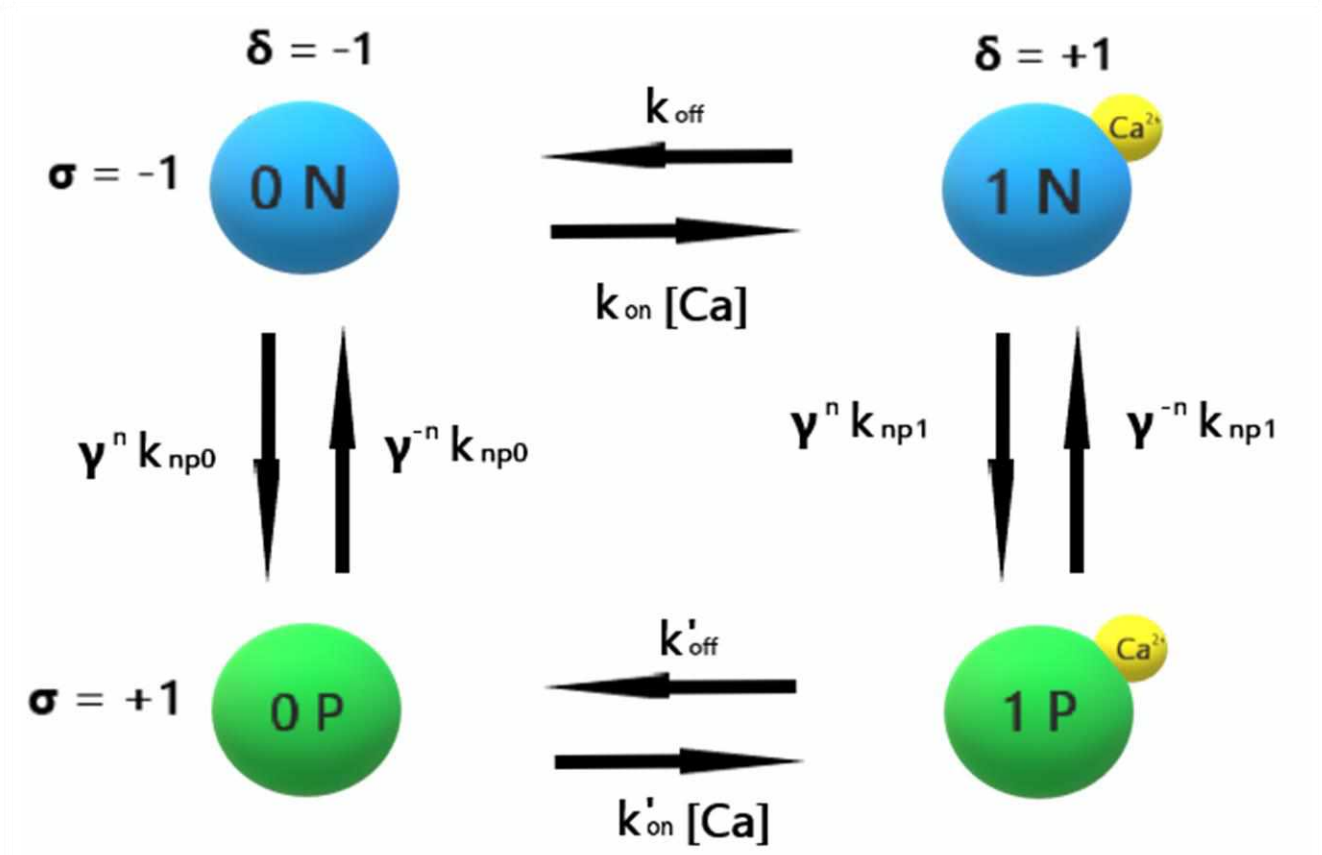


- *energy gained from ATP consumption is used for preparation of myosin head for next iteration*

Muscle contraction



Simplified model of myofilament contraction



- Introduction of spin variables σ_i a δ_i
- Parameters γ, μ, K_d a Q defined by relations:

$$K_d = \frac{k_{off}}{k_{on}}$$

$$K'_d = \frac{k'_{off}}{k'_{on}} = \frac{k_{off}/\mu}{k_{on}} = \frac{K_d}{\mu},$$

$$k_{np1} = Q k_{basic} \quad \gamma = e^{-\Delta E/2}$$

$$k_{np0} = k_{np1}/\mu = Q k_{basic}/\mu$$

To the Ising formalism

- *1D Ising model describing thin cardiac myofilament made of 26 T/T units*
- *Using chemical equilibrium condition we obtain relations*

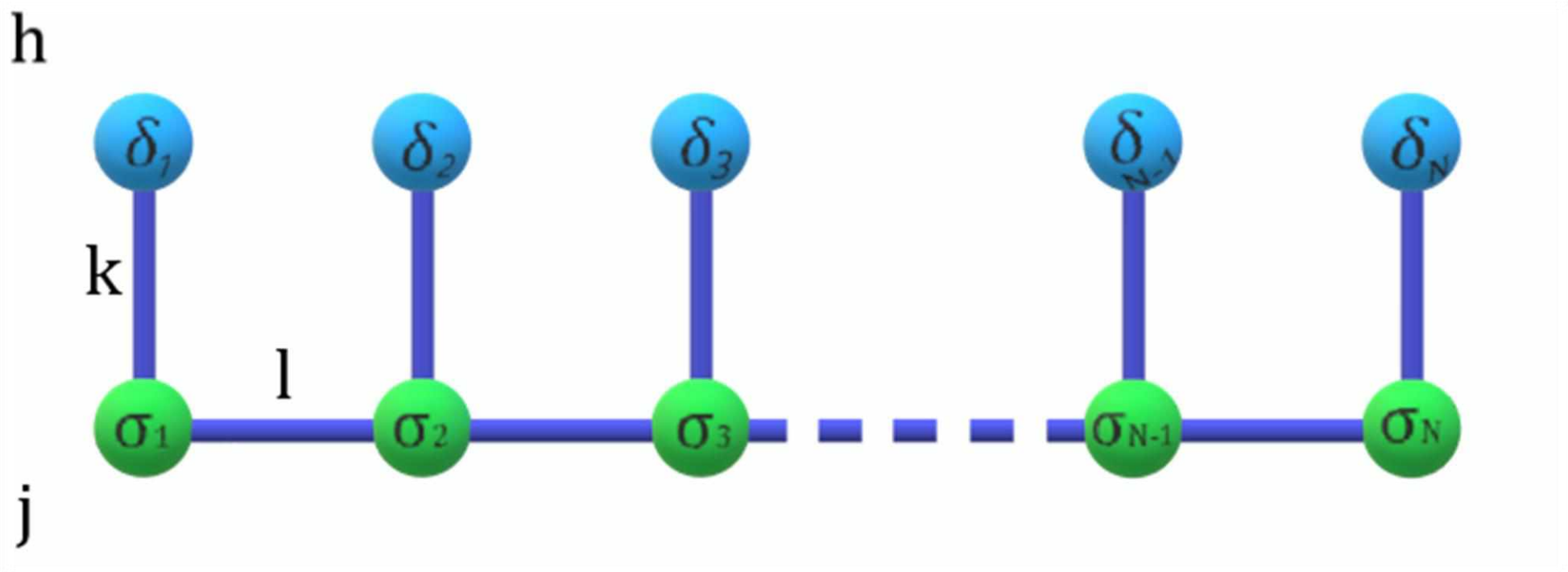
$$\mathcal{H} = -\sum_{i=1}^{N}(h\delta_i + j\sigma_i + k\delta_i\sigma_i + l\sigma_i\sigma_{i+1})$$

$$\frac{k_{xy}}{k_{yx}} = \exp\left[-\beta\left(\mathcal{H}(x) - \mathcal{H}(y)\right)\right]$$

$$\beta h = \beta k + \frac{1}{2}\ln Ca \qquad \beta k = \frac{1}{4}\ln \mu$$

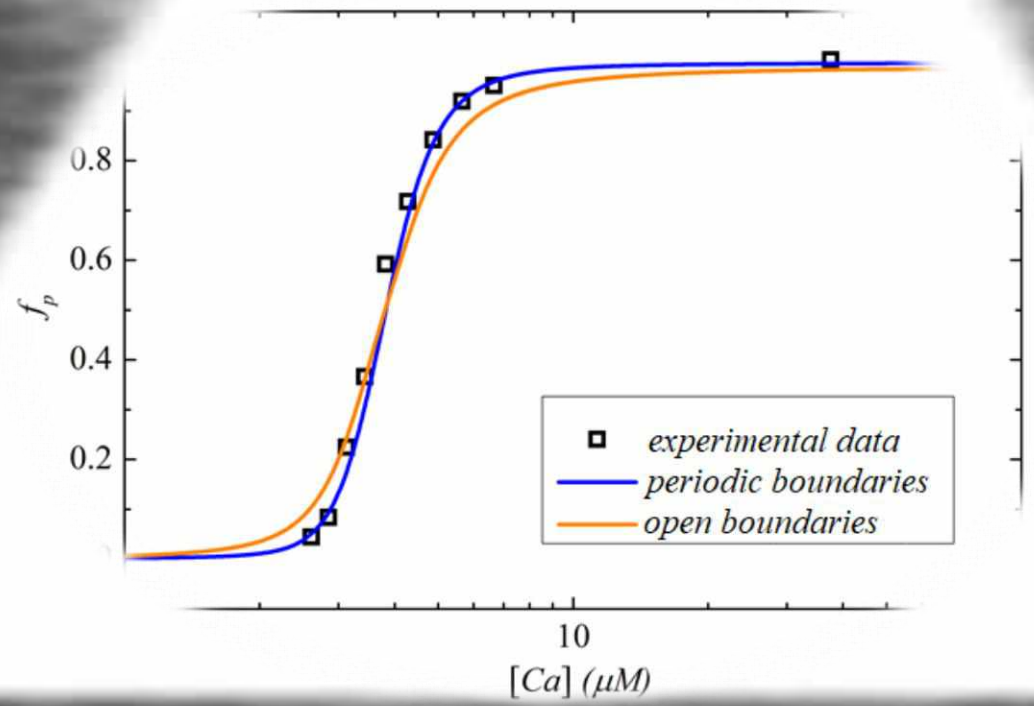
$$\beta j = -\beta k + \frac{1}{2}\ln Q \qquad \beta l = \frac{1}{2}\ln \gamma$$

To the Ising formalism



SNEAK PEEK

- *Experimental values from work by Dobesh et al. [1]*
- *Model with periodic boundaries from work by Rice et al. [2]*
- *Model with open boundaries with same set of parameters -> observable difference*



Will you help us?

Literature

[1] DOBESH, D. P. - KONHILAS, J. P. - DE TOMBE, P., P. , *Cooperative activation in cardiac muscle: impact of sarcomere length.* In *American Journal of Physiology-Heart and Circulatory Physiology*, 2002, vol. 282, no. 3, p. 1055–1062.

[2] RICE, J. J. - STOLOVITZKY, G. - TU, Y. - DE TOMBE, P. P. , *Ising model of Cardiac Thin Filament Activation with Nearest-Neighbor Cooperative Interactions.* In *Biophysical Journal*, 2003, vol. 84, no. 2, p. 897-909.