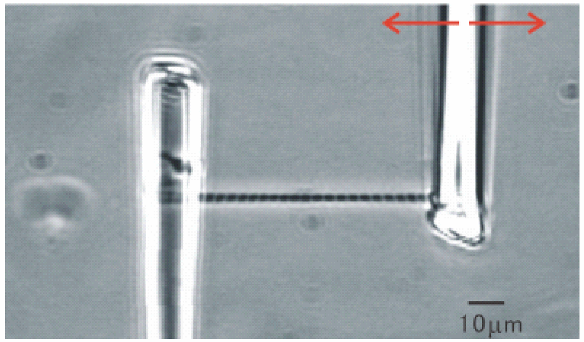
Structural basis for regulatory mechanism of muscle contraction: Role of filament lattice in auto-oscillation of sarcomeres

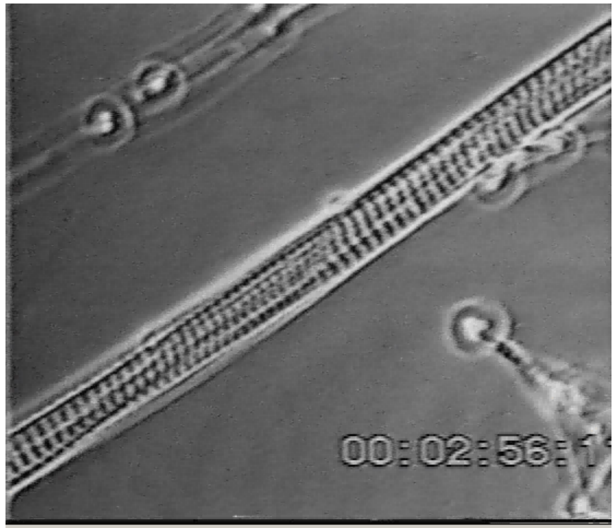
Katsuhiko Sato (Tohoku Univ.)
Yuta Shimamoto(Rockefeller Univ.)
Masako Ohtaki(Waseda Univ.)
Shin'ichi Ishiwata(Waseda Univ.)

Purpose of the present work

- Usually, muscle takes two states:
  - If calcium concentration in the cell is low, muscle goes into the relaxation state.
    - In which muscle generates no force and relaxes.
  - If the Ca concentration is high, muscle goes into contraction state.
    - In which muscle generates forces and shortens.
- The switching of these two states is controlled (regulated) by calcium concentration in the cell.
  - This is a well-established fact.
- At intermediate calcium concentrations muscle takes both states repeatedly, i.e., muscle oscillates, which phenomenon is named spontaneous oscillatory contraction of muscle (SPOC).
  - This is a surprising phenomenon because although the key factor of the switching of the state, the calcium concentration is kept constant throughout this phenomenon, muscle changes its state automatically.
- Although this phenomenon has been known since about 1980 (Fabiat et al. 1978, Okamura & Ishiwata 1988), the mechanism has not been clarified yet.
- So, I would like to challenge the strange problem and solveit.
  - This is the purpose of this work.



Experimental situation



Auto-oscillation of muscle

Outline of today's talk

- First, I review structure and functions of muscle briefly.
  - because we are not familiar with the mechanism of muscle very well.
- Next, I explain the experimental results of auto-oscillation of muscle.
- Finally, we provide a simple two-state model to describe it.
    - Our model is based on "three experimental facts," which are well-established empirical laws, so we can say that the model is not an artificial one, rather grabs the essential of the phenomenon.

Review of muscle
(types of muscle)

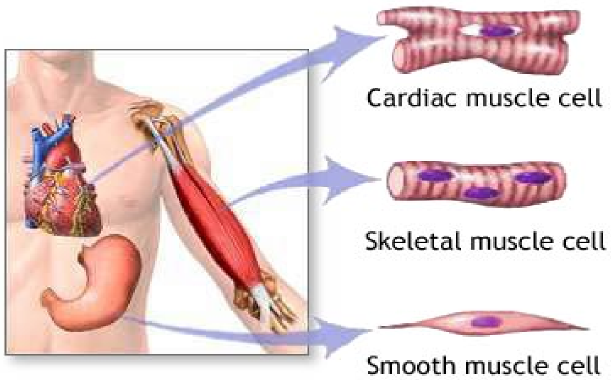
- There are three types of muscle:
  - Skeletal muscle
    - used for the movement of legs or arms.
    - Voluntary muscle.
  - Cardiac muscle
    - Muscle of the heart.
    - Pumps blood from the heart to the body.
    - Involuntary muscle.
  - Smooth muscle
    - Surrounding inner organs such as stomach or blood vessels.
    - Involuntary muscle.

  - Skeletal and cardiac muscles are called "striated muscle" because when we view them under a light microscope, their striations appears..

- Since the auto-oscillation of muscle occurs for both skeletal and cardiac muscles, we are concerned with the striated muscle hereafter.

	striation	smooth
voluntary	skeletal muscle	
involuntary	cardiac muscle	smooth muscle

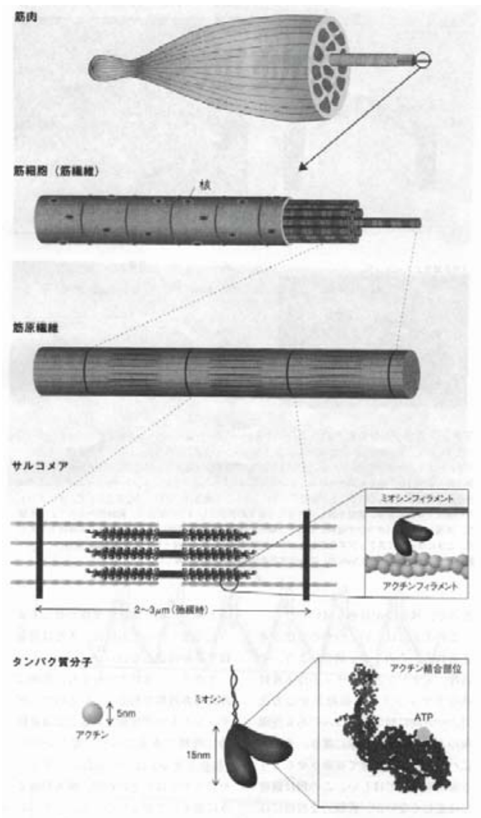
Classification of muscle



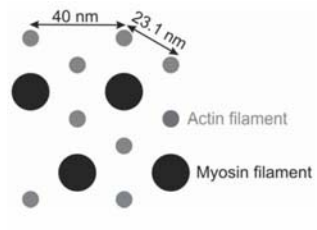
Schematic picture of muscle

Review of muscle
(structure of striated muscle)

- Striated muscle has hierarchical structure:
  - Muscle
    - Muscle fiber
      - Myofibril
        - » Sarcomere
- Sarcomere is the basic unit of striated muscles.
  - Sarcomere is made up of a set of two types of filaments, myosin filament and actin filament.
  - Due to these sliding filaments, muscle contracts.
    - the detailed mechanism is described in the next page.
  - The thick and thin filaments form a lattice, to be specific, hexagonal array.
    - The distance between thick and thin filaments is called "lattice spacing."



Hierarchical structure of muscle



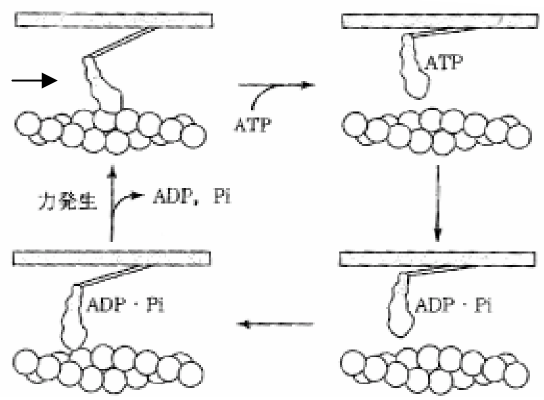
Cross-sectional view of filament lattice

Review of muscle

(mechanism of sliding filaments)

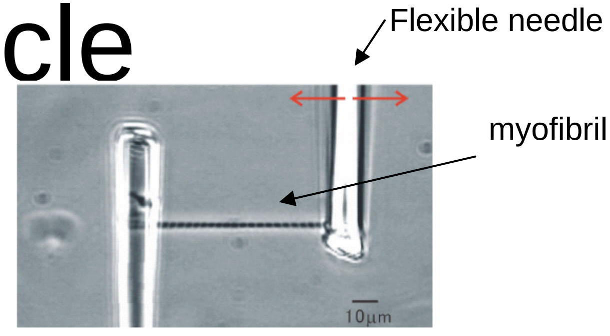
- How do the filaments slide past one another?
  - Myosin-head strokes itself using chemical energy from hydrolysis of ATP.

- How myosin heads generate forces is as follows.
  - (1) Myosin head attaches to the thin filament.
  - (2) Using the chemical energy of hydrolysis of ATP, myosin head changes its conformation.
    - In which forces are generated.
  - (3) Myosin-head is detached from the thin filament and returns to the original conformation.



Cycle of myosin head

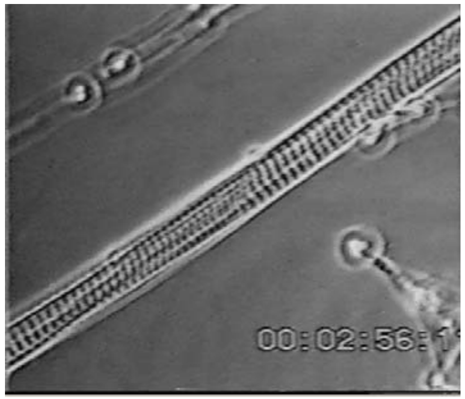
Experimental results of auto-oscillation of muscle



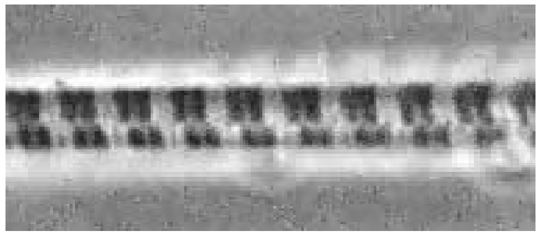
Preparation of experiments

- Experimental procedure
  - (1)Prepare a single myofibril.
  - (2)Attach each end of the myofibril to two needles
  - (3)Dunk them into the bathing solution in which Ca and ATP are kept constant.

- If we choose the Ca concentration to be some intermediate value, an auto-oscillation begins.

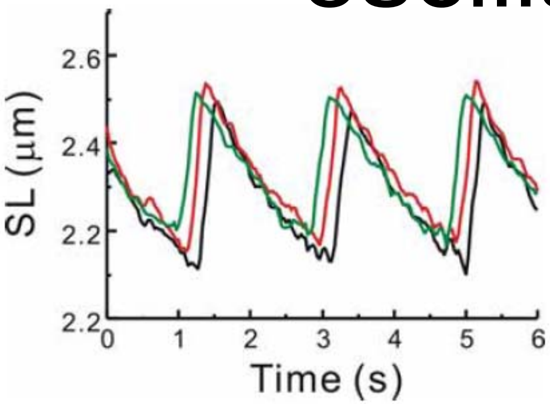


Wave of auto-oscillation of muscle

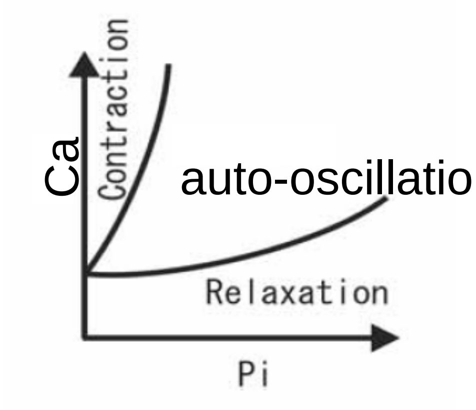


Enlarged picture

Experimental results of auto-oscillation of muscle



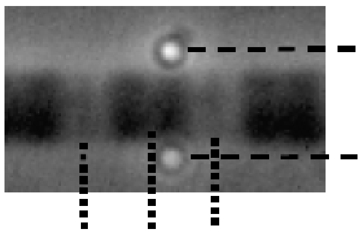
Time-series of SL during auto-oscillation
(a saw-tooth wave form)

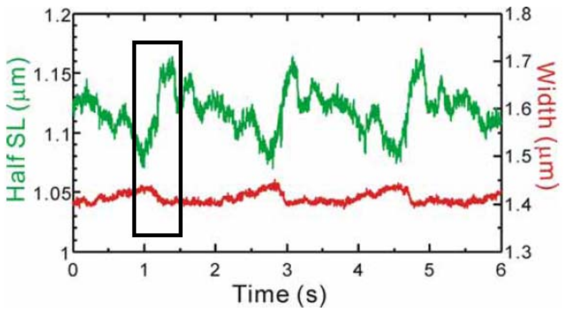


Phase diagram
At Intermediate activation level, oscillation occurs.

Then, what is the mechanism of the auto-oscillation of muscle?

From some experimental result,
we expect that the key is “lattice spacing.”

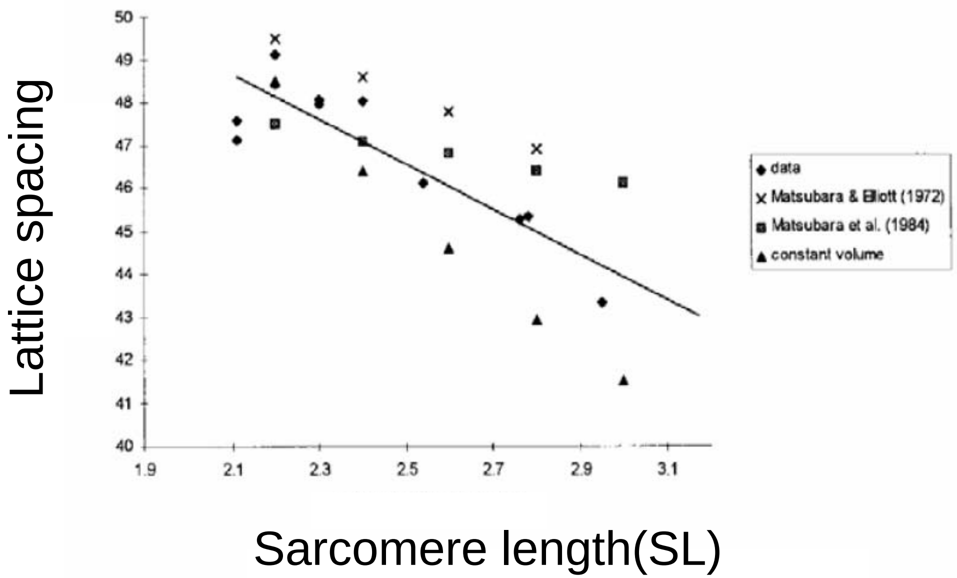




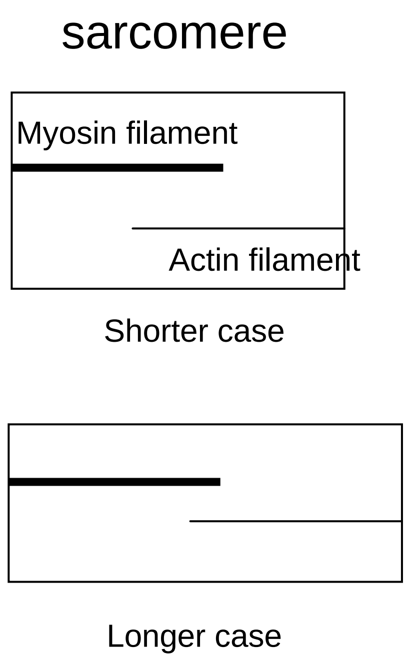
Three Experimental Facts

concerning “lattice spacing”

- Experimental fact I:
  - In the relaxed state, the lattice spacing decreases with the increase in SL.
  - We call this experimental fact “lattice volume constant law.”



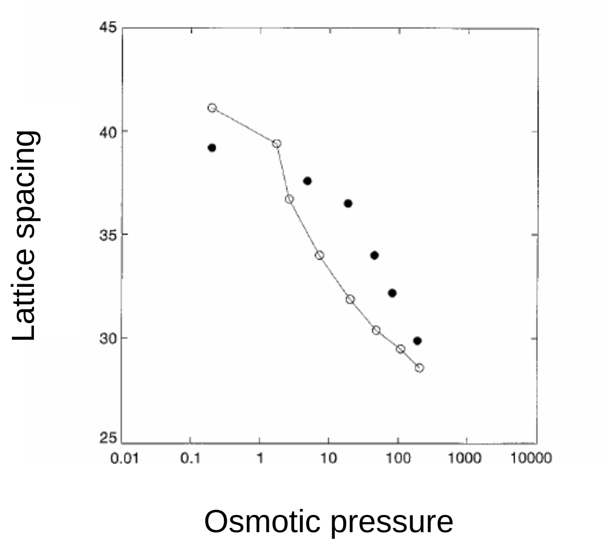
Relation between lattice spacing and SL



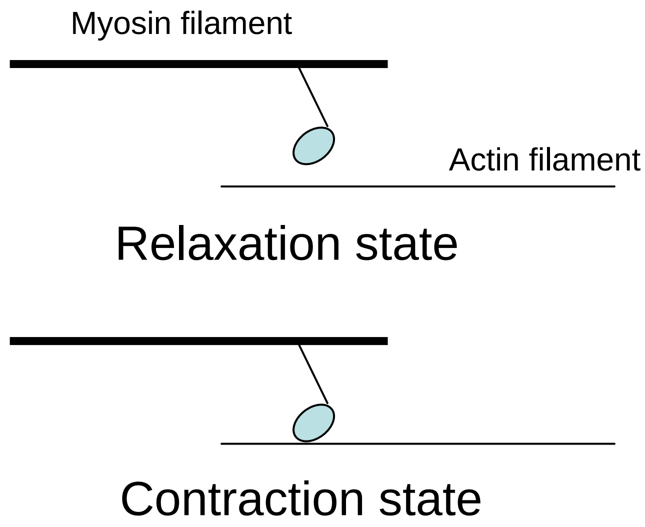
Schematic picture of the change in lattice spacing with SL

Three Experimental Facts
concerning “lattice spacing”

- Experimental fact II:
  - Lattice spacing depends not only on the SL but also on the state of muscle.
    - If we fix the SL at some value and change the state of muscle from relaxation to the contraction state, in general the lattice spacing is shortened.



White circle: for relaxation
Black circle: for activation (contraction)

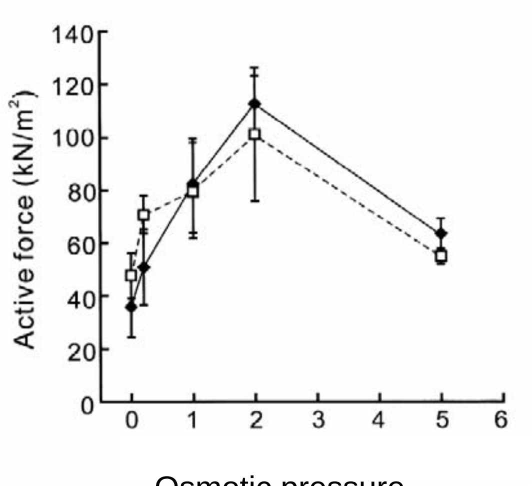


Schematic picture
the change in lattice spacing due to the attachment of myosin head

Three Experimental Facts

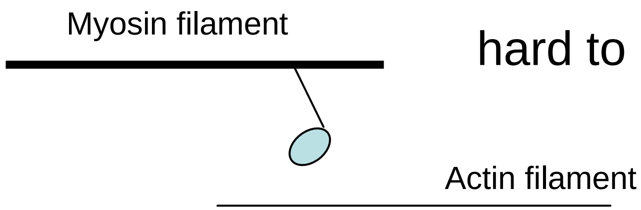
concerning “lattice spacing”

- Experimental fact III:
  - The rate of attachment of myosin head to the thin filament depends on the lattice spacing.
    - It’s easilly accepted.



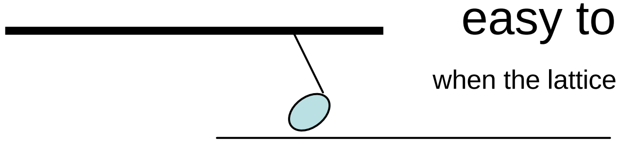
Osmotic pressure
which corresponcs to 1/(lattice spacing)

Relation between active force and lattice spacing



hard to attach

If the lattice spacing is greater than the natural length of myosin head, the myosin-head is hard to attach to the thin filament.

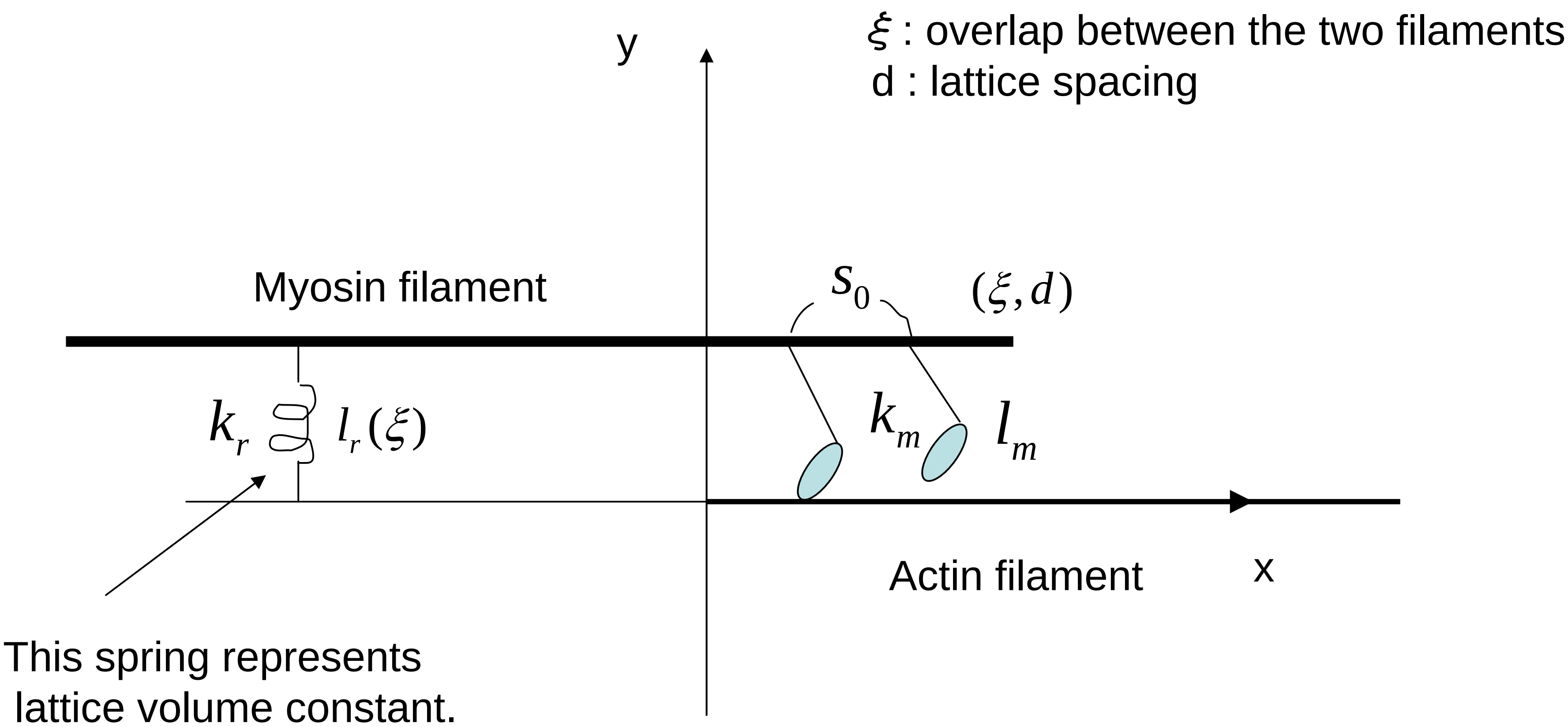


easy to attach

when the lattice spacing is close to the natural length.

Only by combining these three experimental facts, we can reproduce the auto-oscillation of muscle.

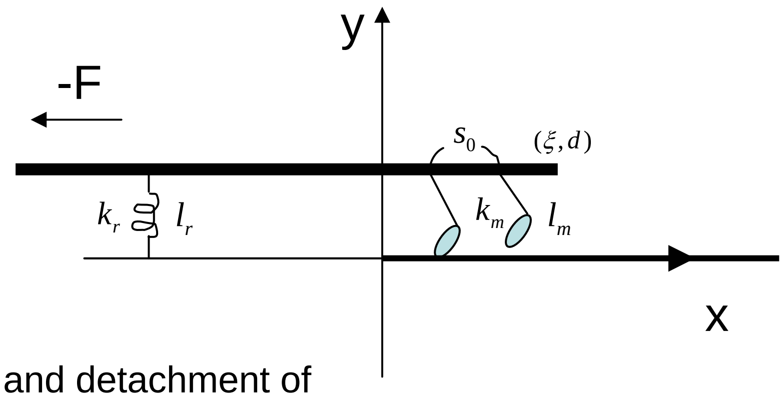
Model



Schematic picture of model

This model is supposed to represent one sarcomere.

Equations of the model



Time evolution equation for P

$$\frac{dP}{dt} = \alpha(d)(1-P) - \beta(d)P \qquad \text{--(1)}$$

- where α and β are transition rates of attachment and detachment of myosin-heads.

Force balance equation in the x-direction

$$-F + a\xi P - \zeta\xi P \frac{d\xi}{dt} = 0 \qquad \text{--(2)}$$

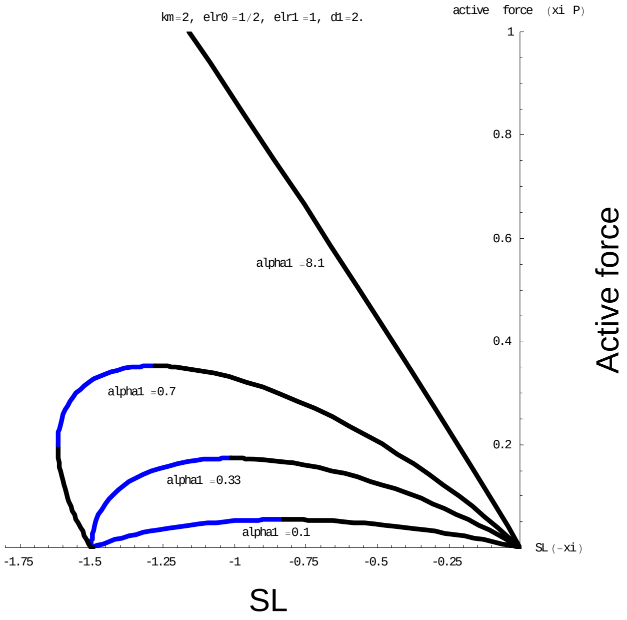
- where F is the external force, and a and ζ are some positive constants.

Force balance equation in the y-direction

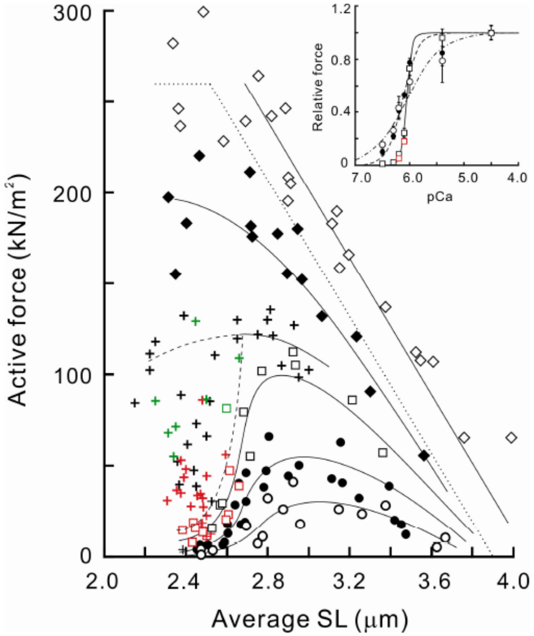
$$k_r(d - l_r(\xi)) + \frac{\xi}{s_0} P k_m (d - l_m) = 0 \qquad \text{--(3)}$$

- where kr, km and lm are positive constants, and lr is a function of ξ .

Results



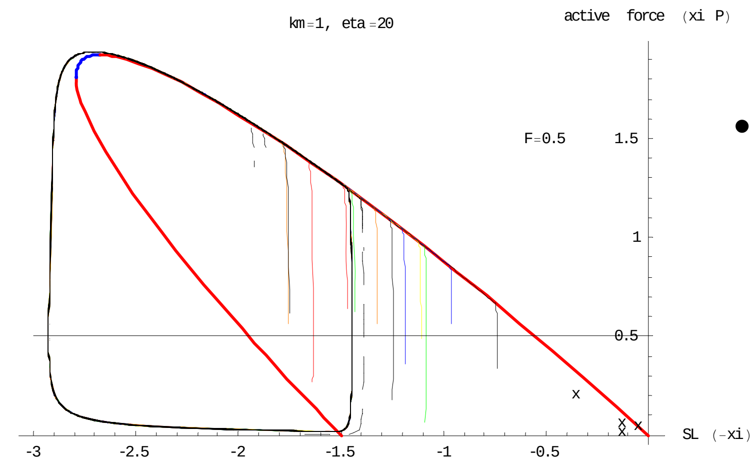
Results from the model



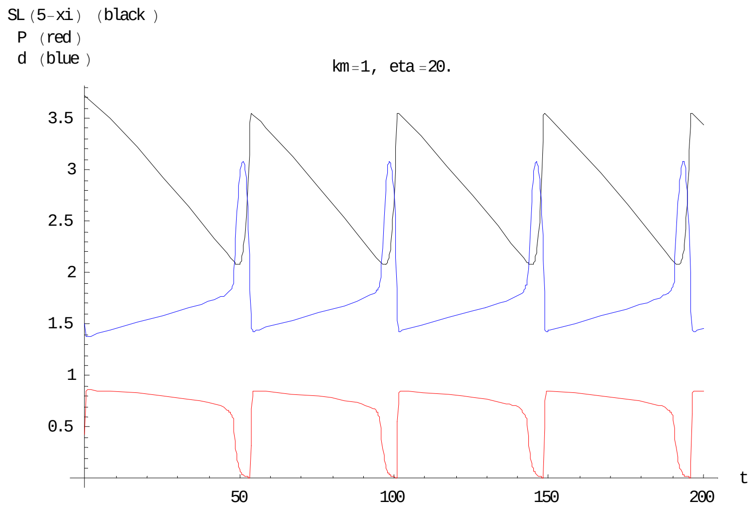
Experimental results

Relationship between active force and sarcomere length in various activation levels (various values of $\alpha 1$).

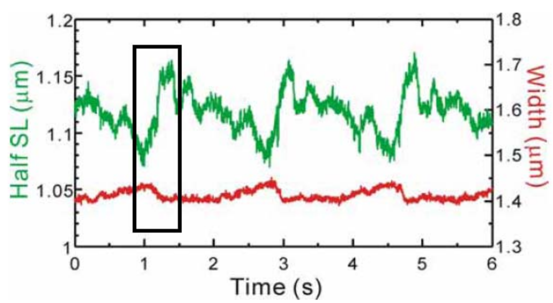
Results



- If we choose an intermediate activation level and appropriate strength of the external force, an auto-oscillation occurs.
  - This result is consistent with experimental results.



Data from the model



Experimental data

Summary

- Based on three experimental facts concerning lattice spacing, we constructed a simple two-state model.
- In terms of this model, we succeeded in reproducing all main features of auto-oscillation of muscle.

- Remaining future works:
  - We should study the connected model in series in more detail.
  - In real, the actin and myosin filaments form a hexagonal array, so we have to deal with the its lattice spacing more carefully.
    - A 2-dimensional lattice model is to be considered.