A simple kinetic model of cardiac muscle mechanics

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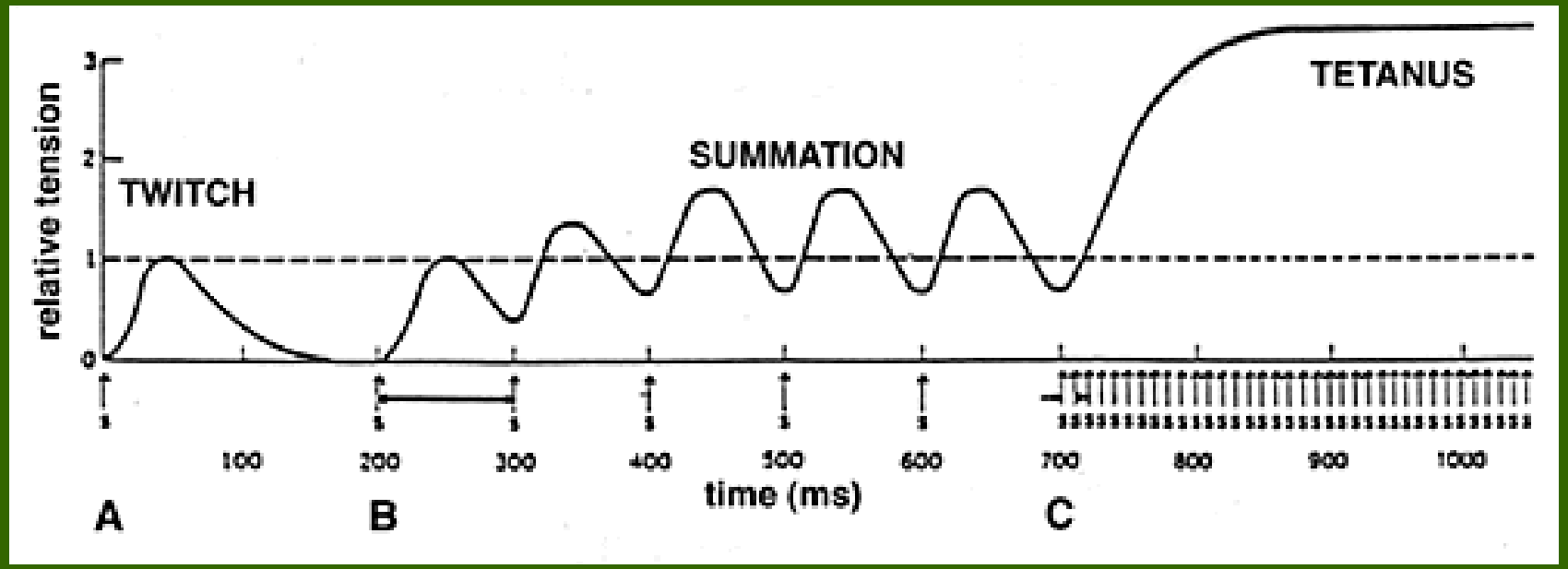
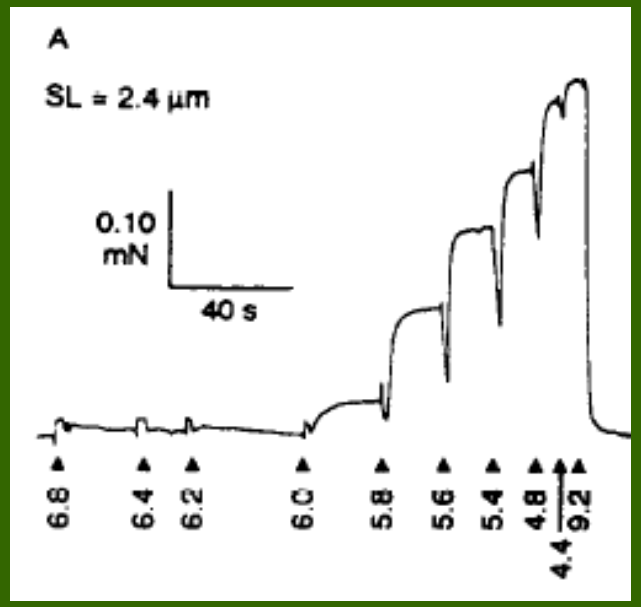
Moscow University

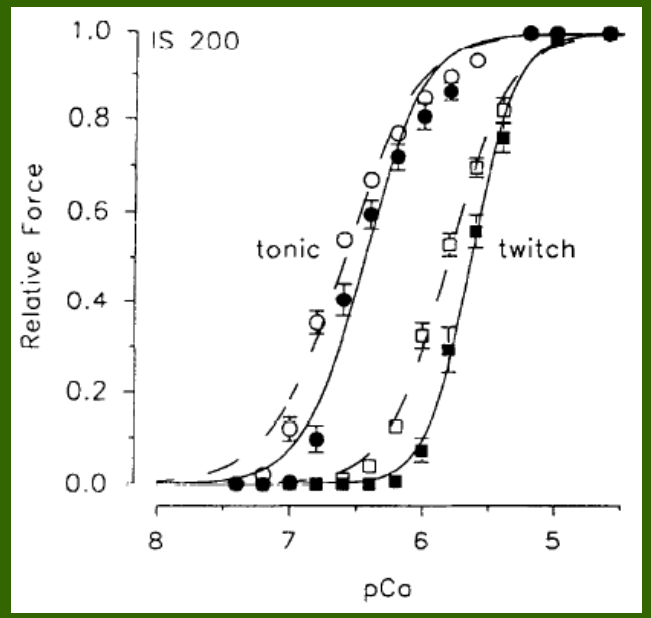
Activated muscle produces active mechanical tension and produces work





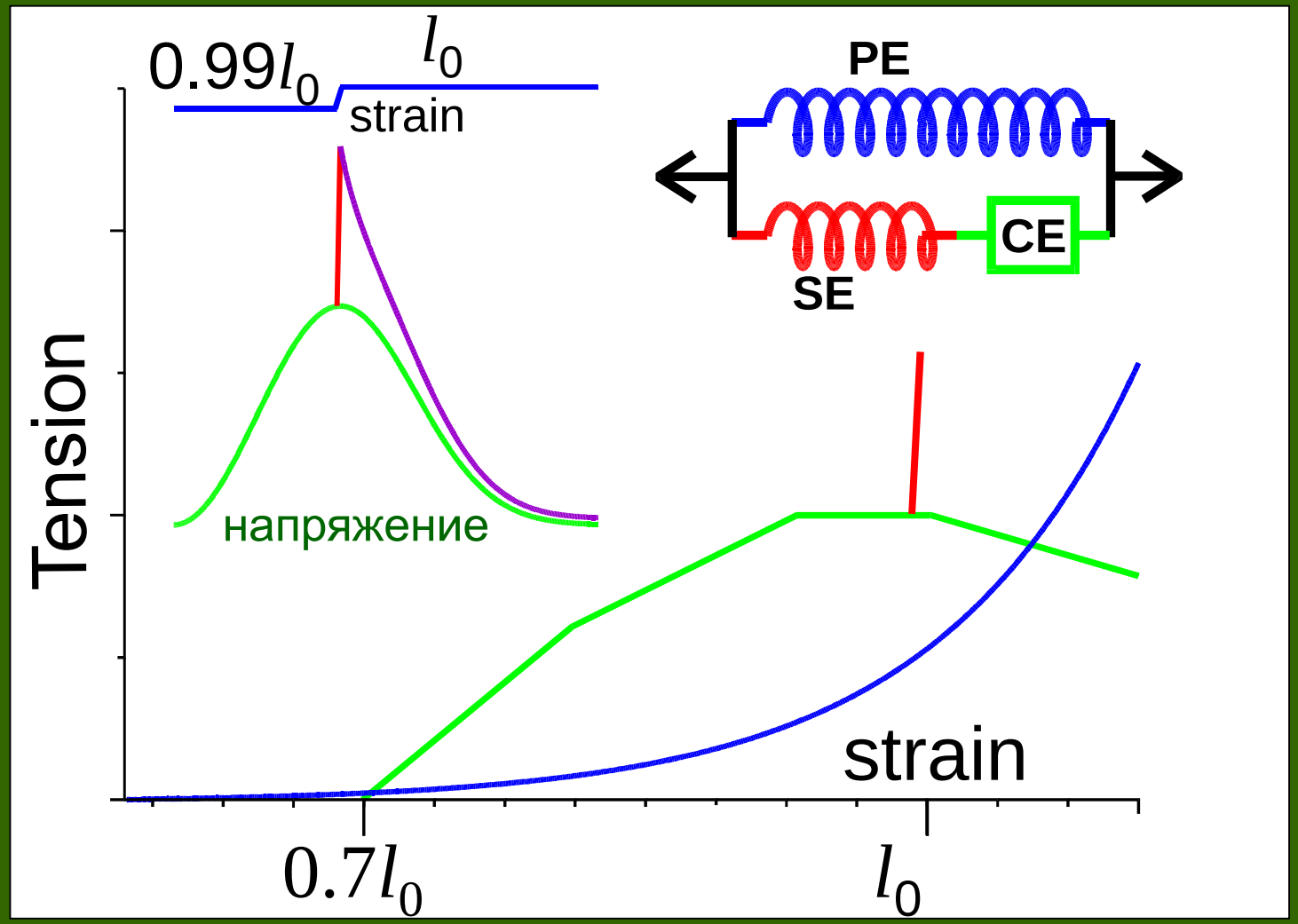
Main activator: Ca^{2+}

$pCa = -\lg[Ca^{2+}]$



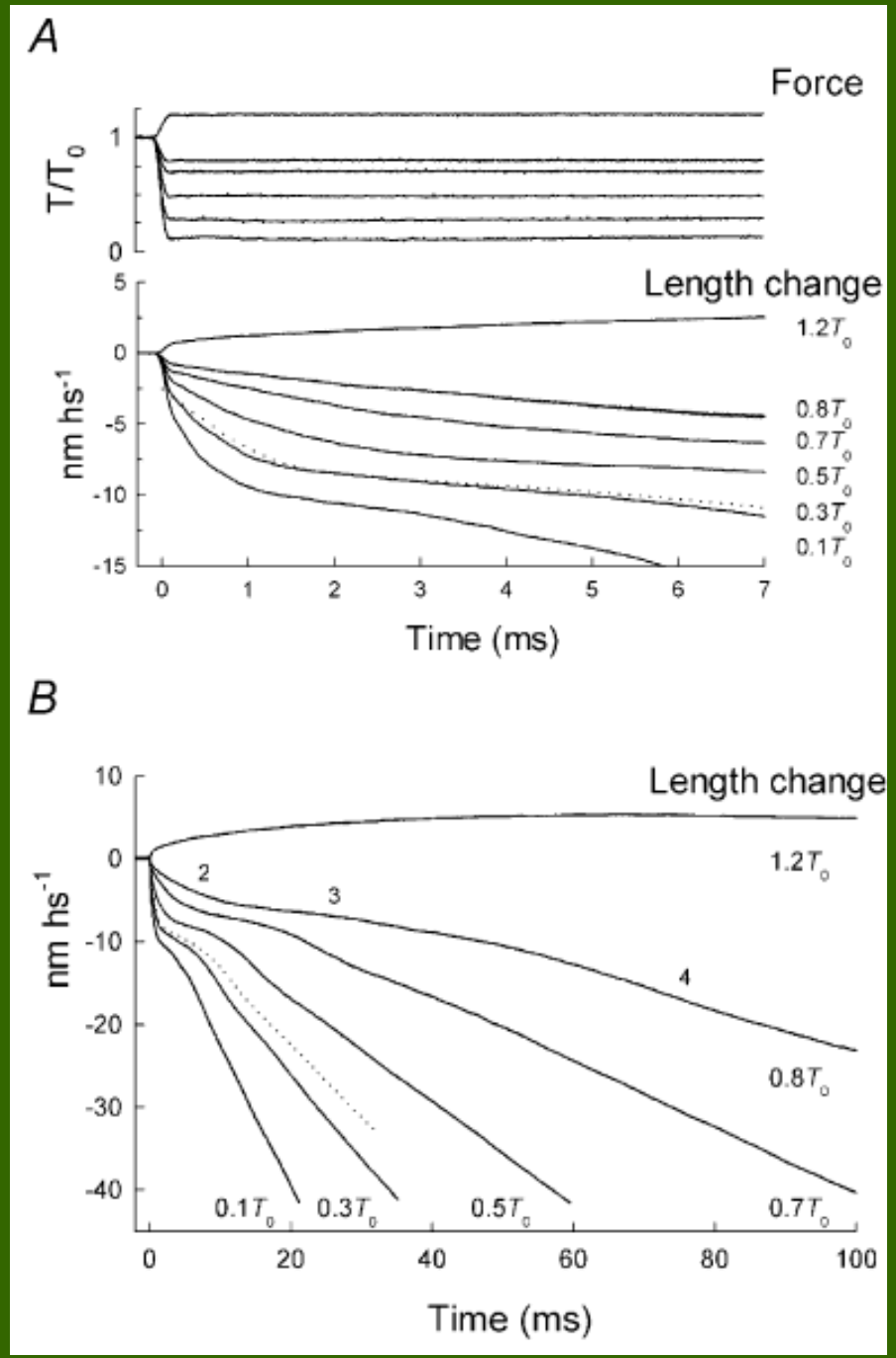
Muscle mechanics: parallel and serial elasticity

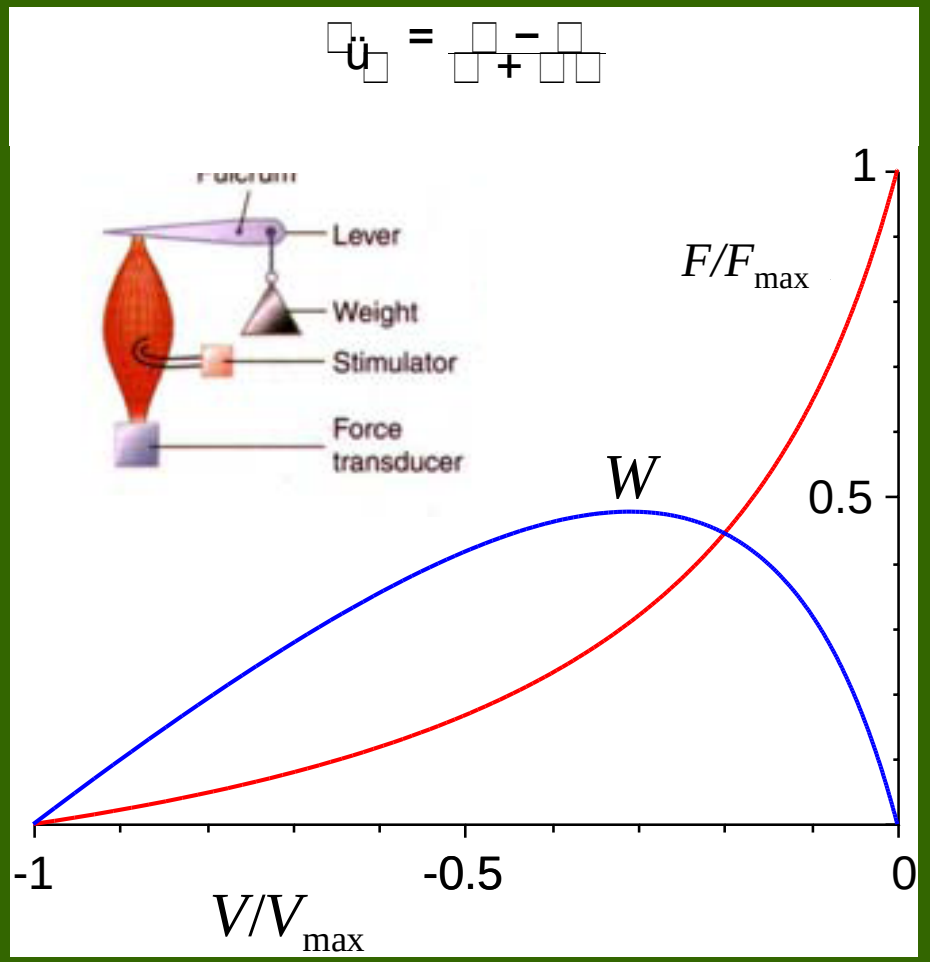
A.V. Hill (1886-1977), FRS (1918)
Nobel price in Physiology and Medicine (1922)



Instantaneous stiffness of fully activated muscle in >100 times higher than that of relaxed muscle

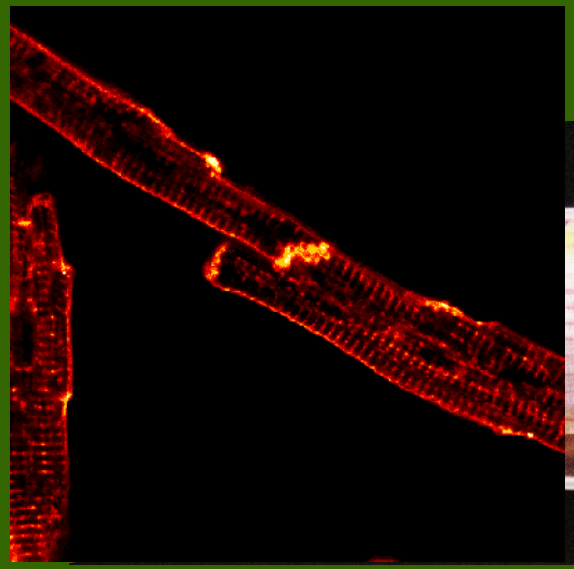
Force-velocity relation (Hill, 1938)

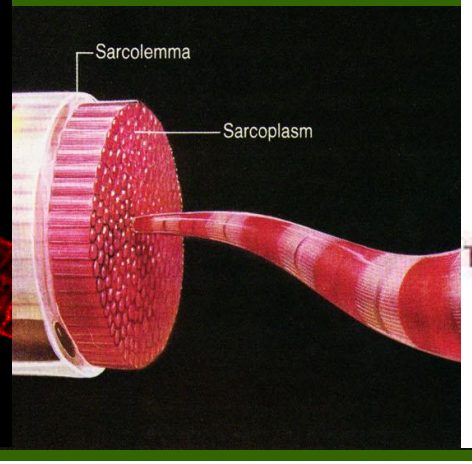


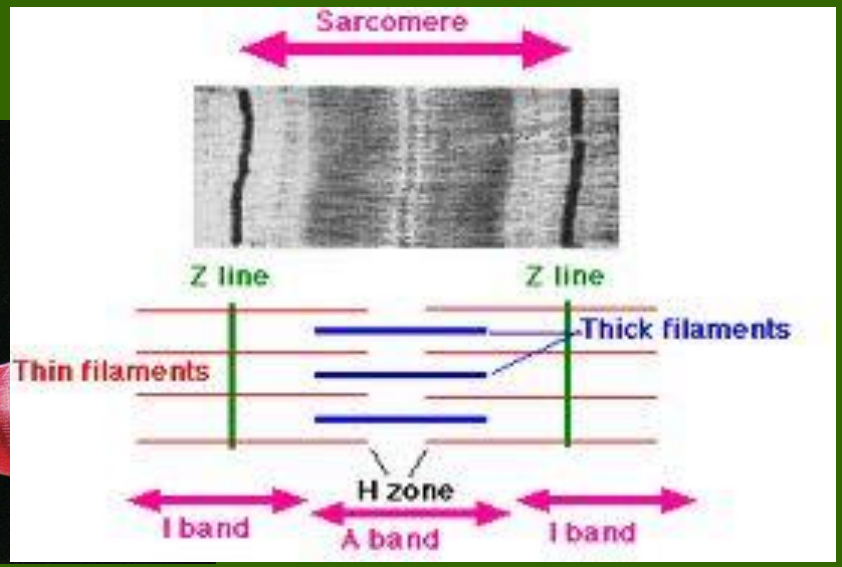


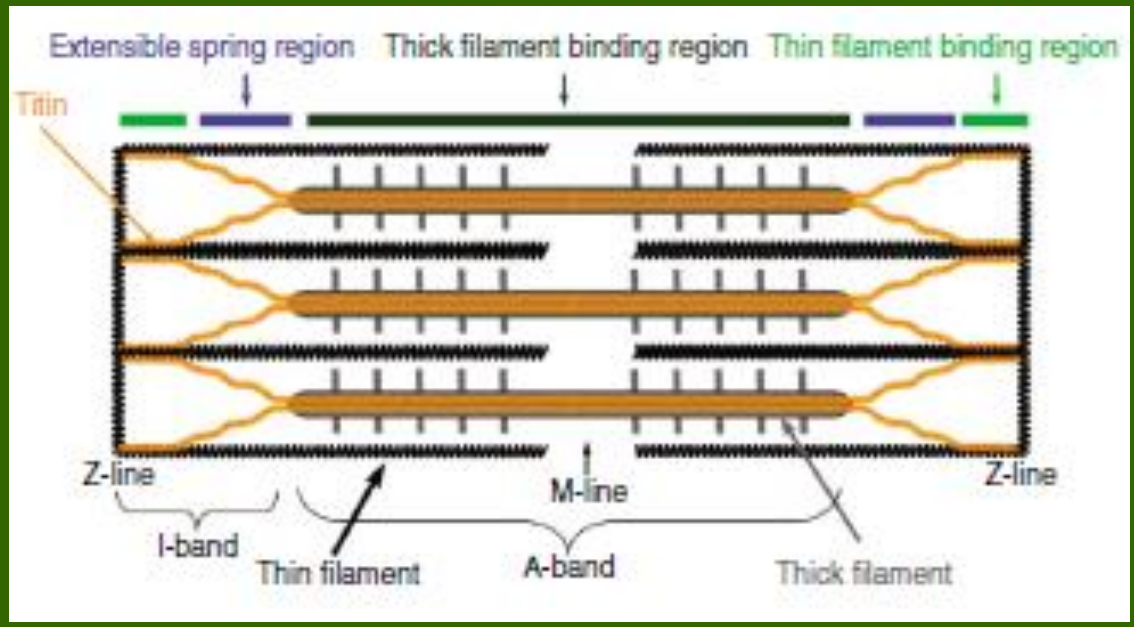
Changes in muscle length induced by step changes in load (Plazzesi, *et al*., *J.Physiol*., 2002)

Cardiac muscle cell, skeletal muscle fibre, myofibril, sarcomere, thick, thin and titin filaments









Sliding filaments and myosin cross-bridges

(A.F.Huxley, Niedergerke, 1954; H.E.Huxley, Hanson, 1954)

No. 4412 May 22, 1954 NAT

STRUCTURAL CHANGES IN MUSCLE DURING CONTRACTION

Interference Microscopy of Living Muscle Fibres

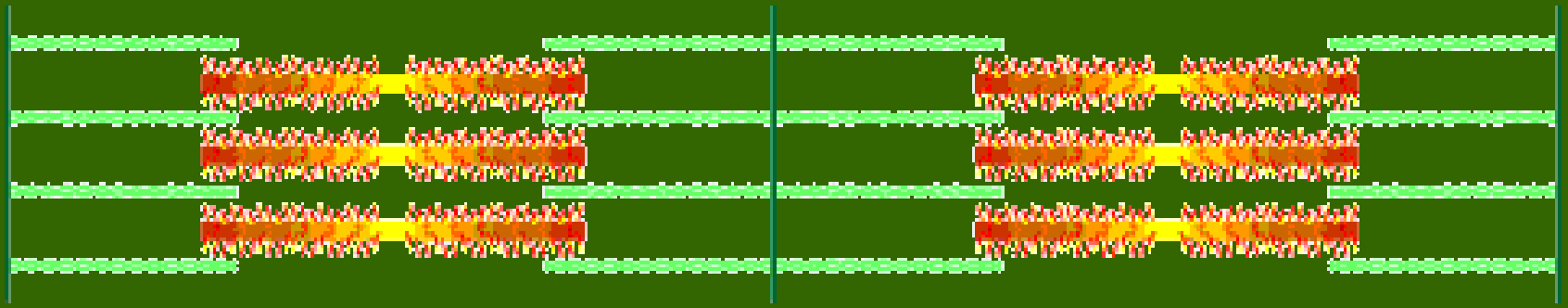
By A. F. HUXLEY and Dr. R. NIEDERGERKE*

Physiological Laboratory, University of Cambridge

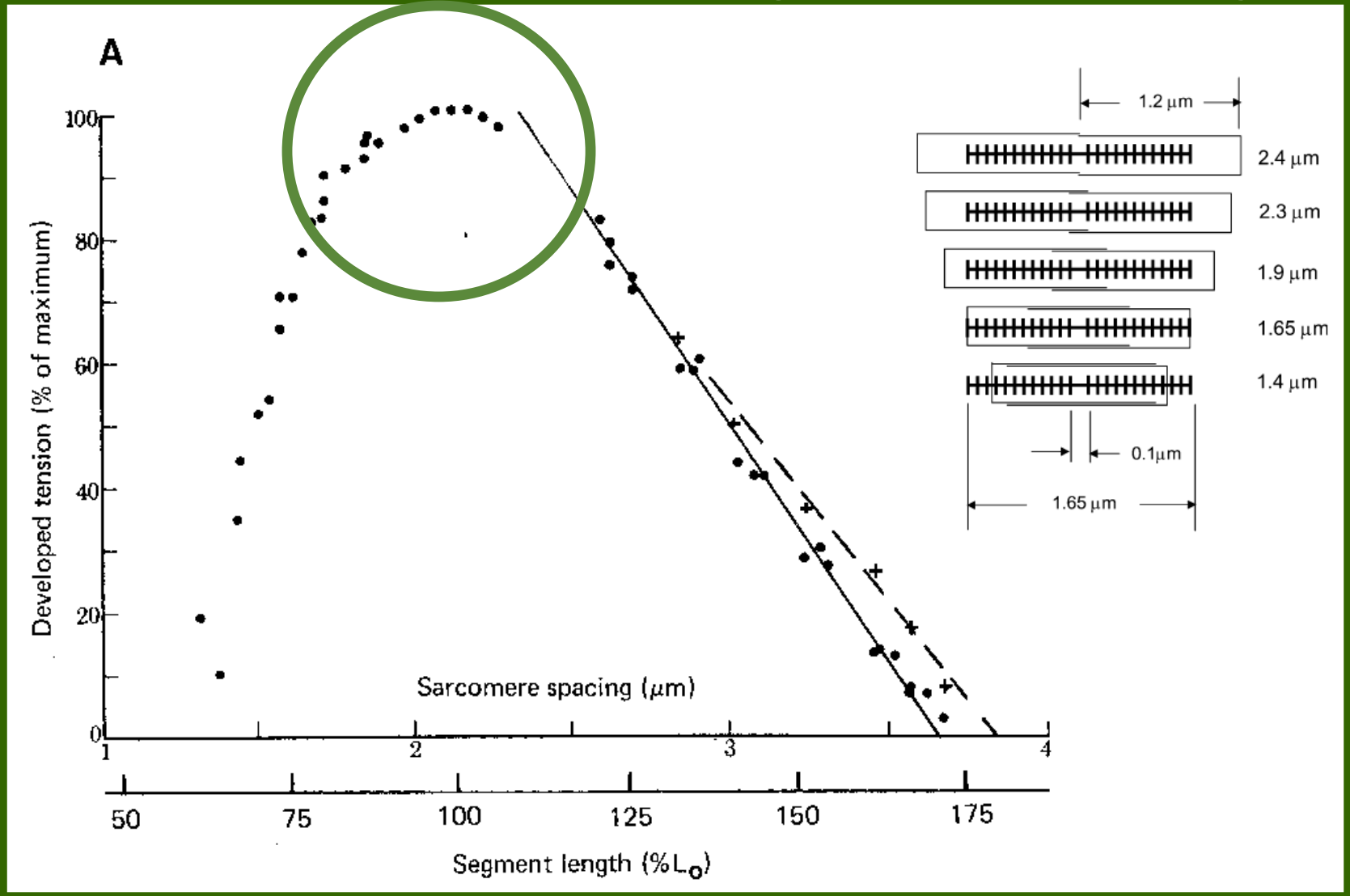
Changes in the Cross-Striations of Muscle during Contraction and Stretch and their Structural Interpretation

By Dr. HUGH HUXLEY* and Dr. JEAN HANSON†

Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts



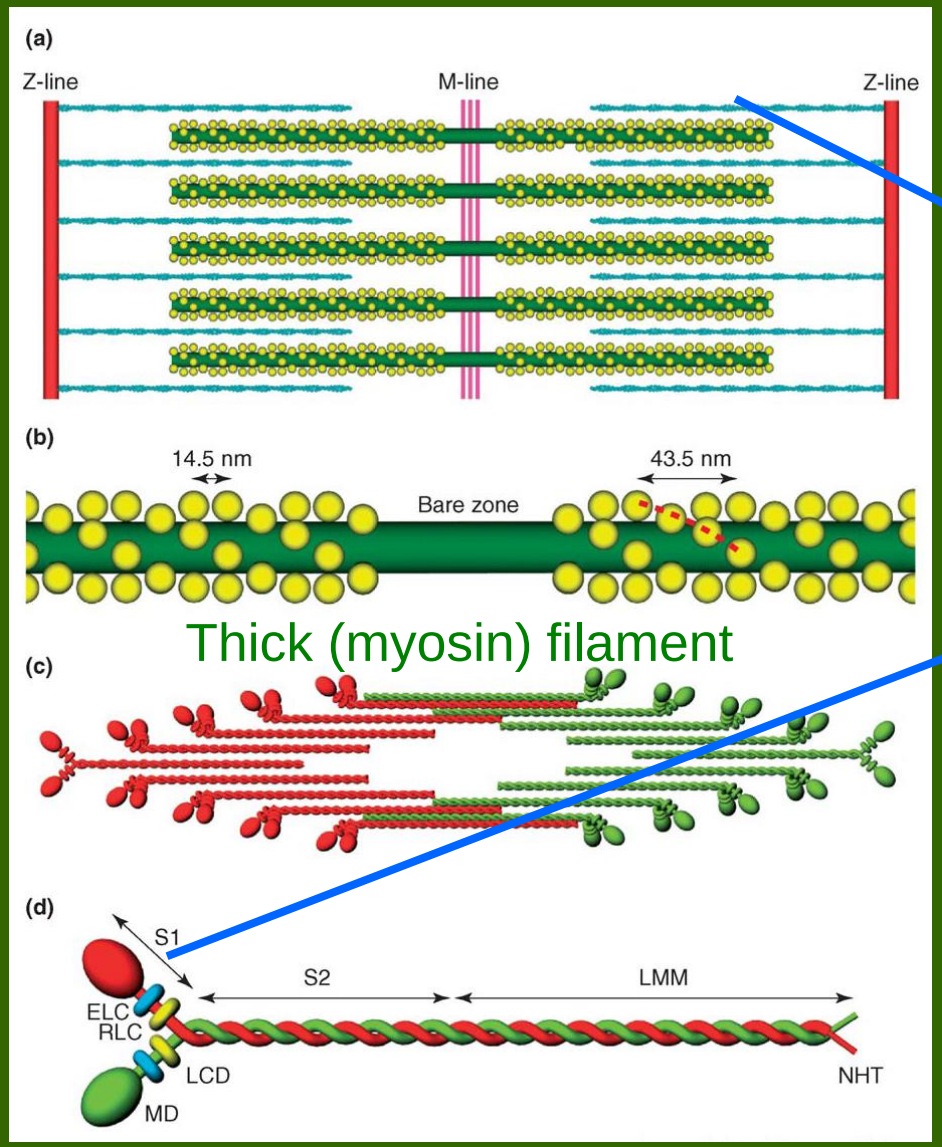
Force at full activation is proportional to filament overlap: evidence for the sliding filament theory



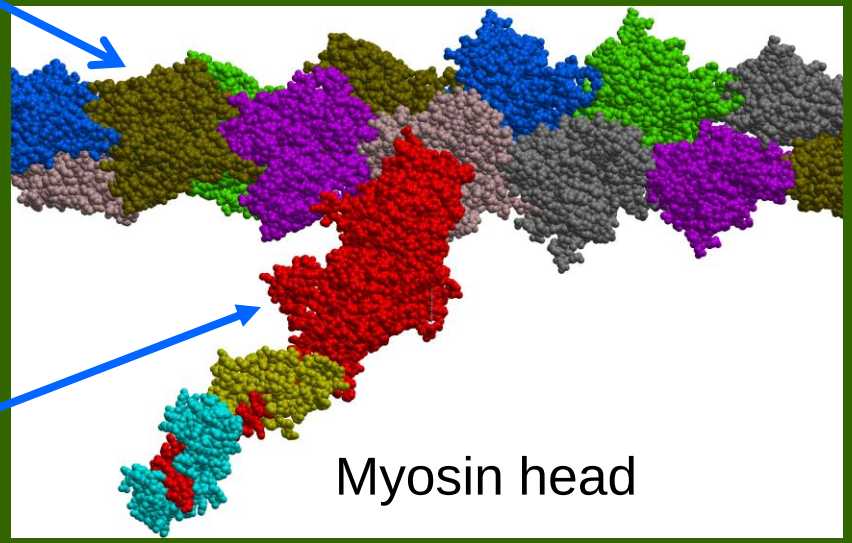
Frog skeletal muscle

(Gordon, Huxley, Julian, *J. Physiol.*, 1966)

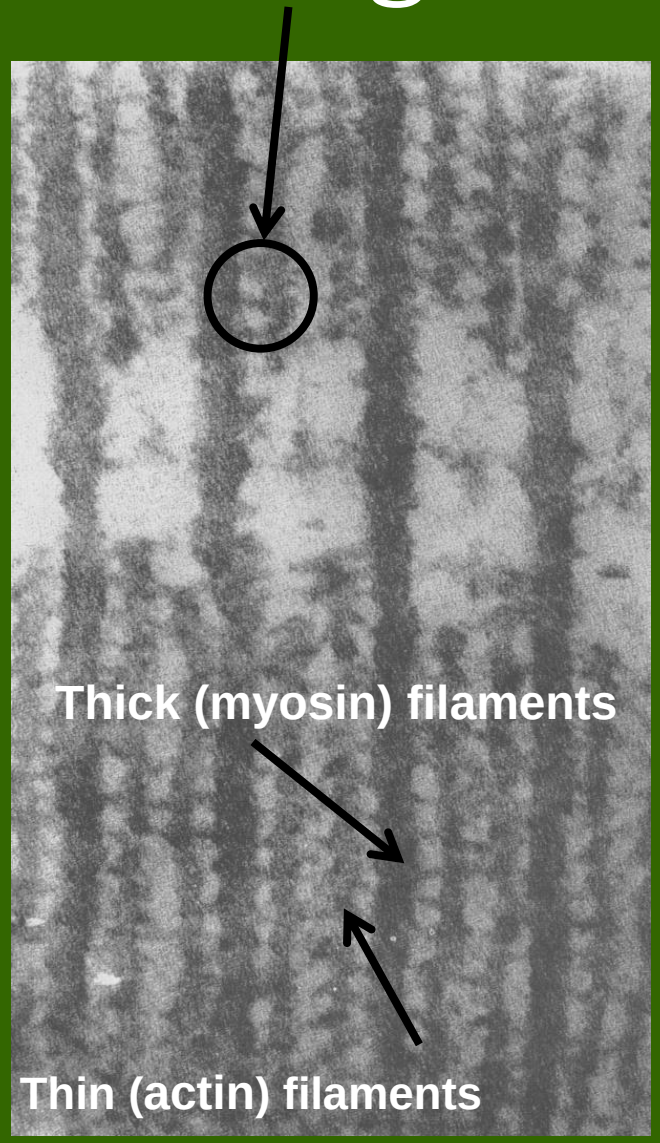
Structure of the thin and thick filaments and of the actin-myosin complex (cross-bridge)



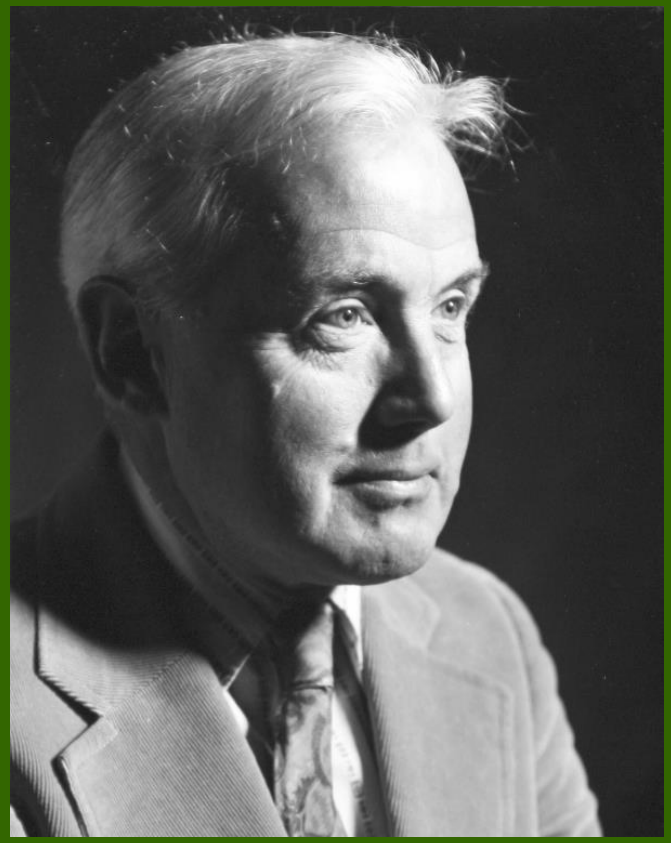
Thin (actin) filament



Cross-bridges: molecular force generators



Electron microscopy (H.E. Huxley, 1957)



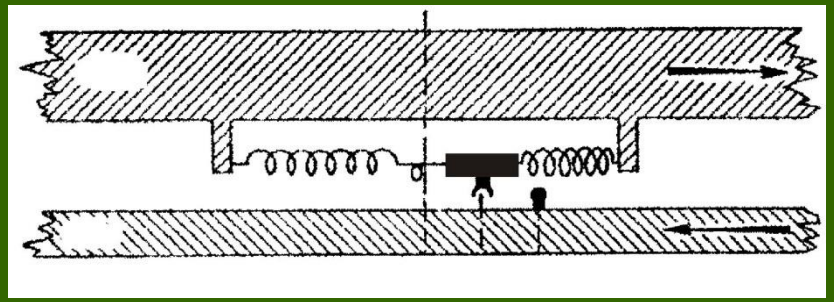
Hugh Esmor Huxley MBE FRS (1924 -2013)

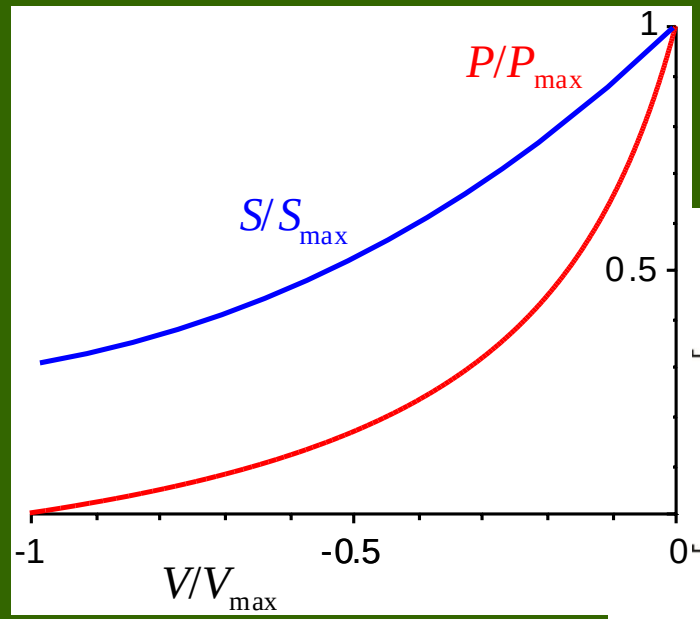
Kinetic model of muscle contraction (A.F. Huxley, 1957)

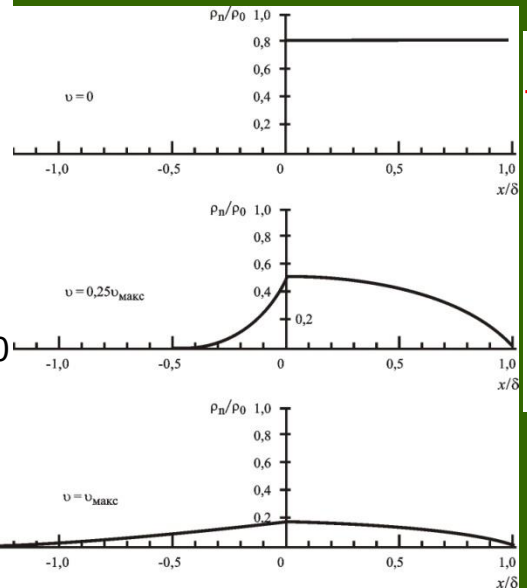
Sir Andrew Fielding Huxley (1917 – 2012)
OM, PRS, Nobel Prize 1963

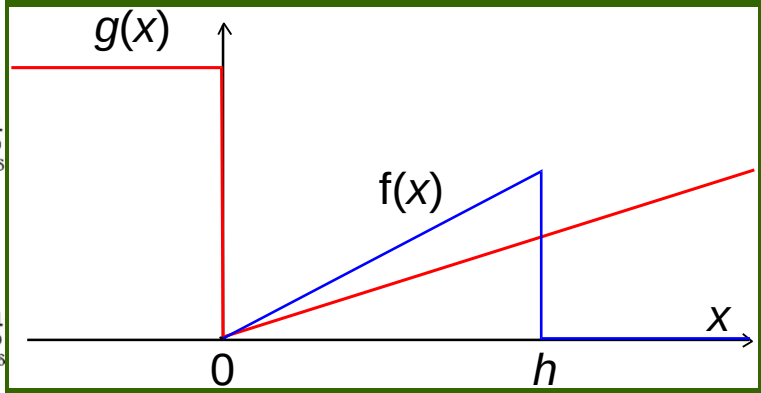
$$\frac{Dn(x,t)}{Dt} = \frac{\partial n(x,t)}{\partial t} + v(t)\frac{\partial n(x,t)}{\partial x} = f(x)\big(1 - n(x,t)\big) - g(x)n(x,t)$$

$$N(t) = \int_{-\infty}^{\infty} n(x,t)dt, \quad F(t) = \int_{-\infty}^{\infty} E\,x\,n(x,t)dt$$



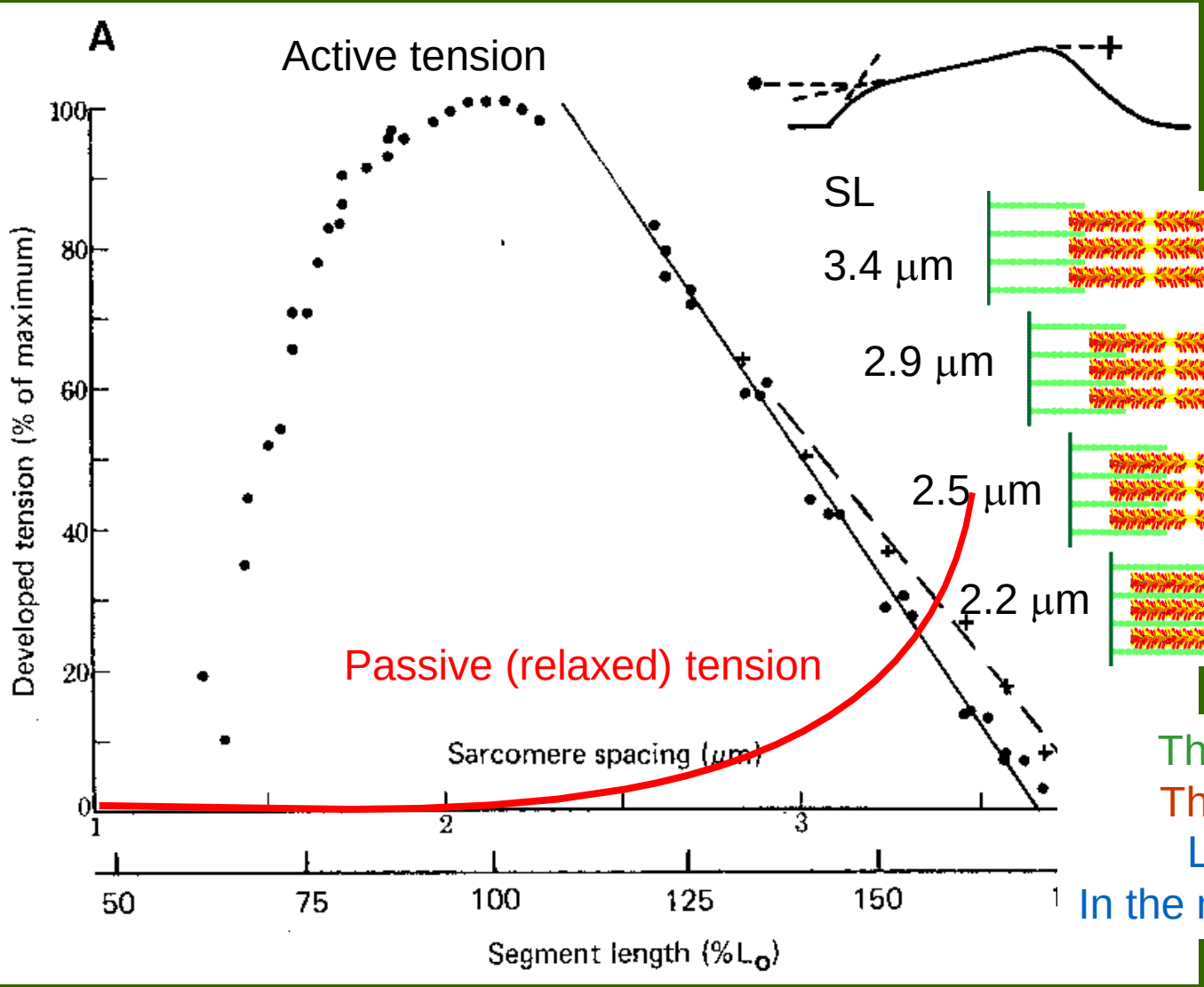






Evidence for the sliding filament theory

(Gordon, A.F.Huxley, Julian, 1966)



Thin filament length 1.05 μm,
Thick filament length 1.6 μm,
Length of the “bare zone”
In the middle of the M-band 0.15 μm

Mechanical approach for studying cross-bridge properties

Sir A.F. Huxley, FRS

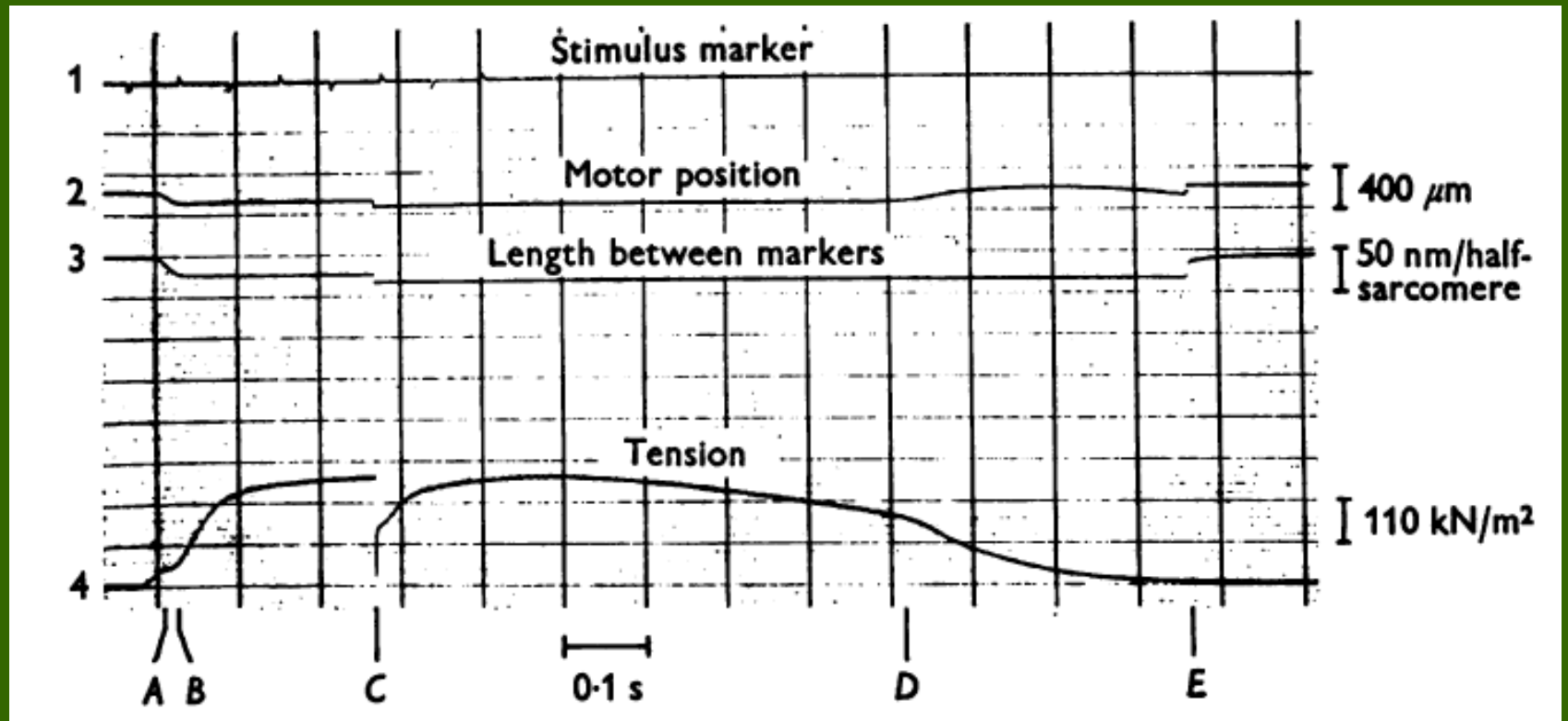
Robert M. Simmons, FRS

NATURE VOL. 233 OCTOBER 22 1971

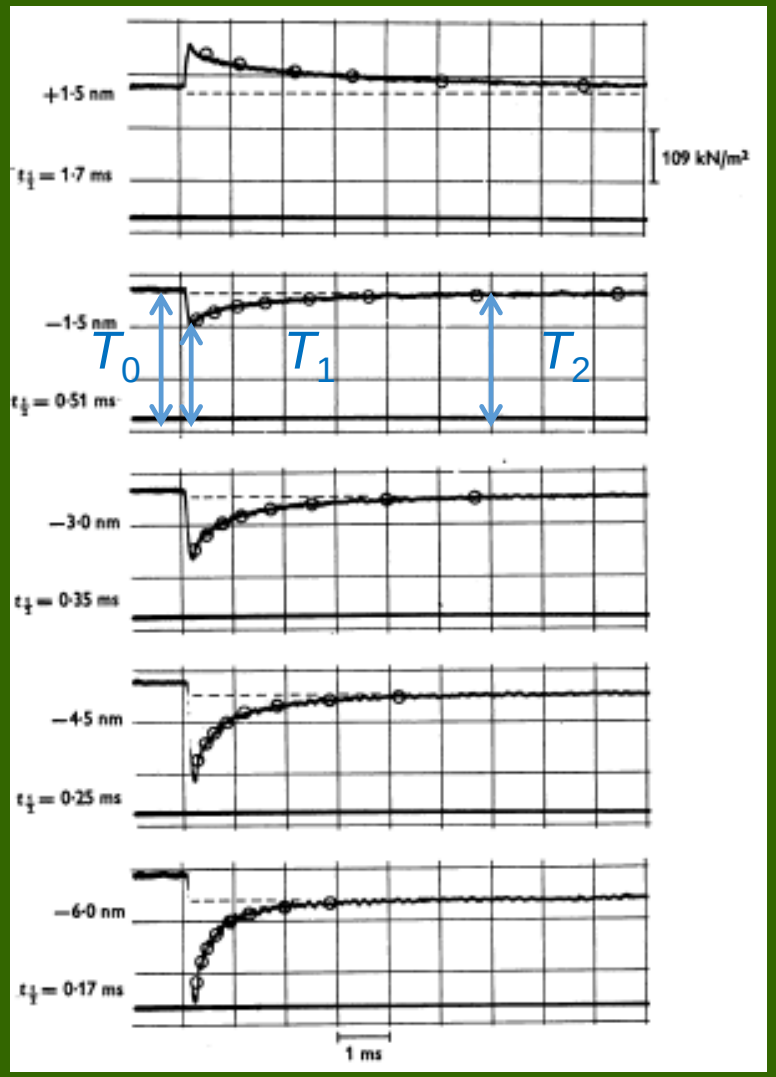
Nature, 1971

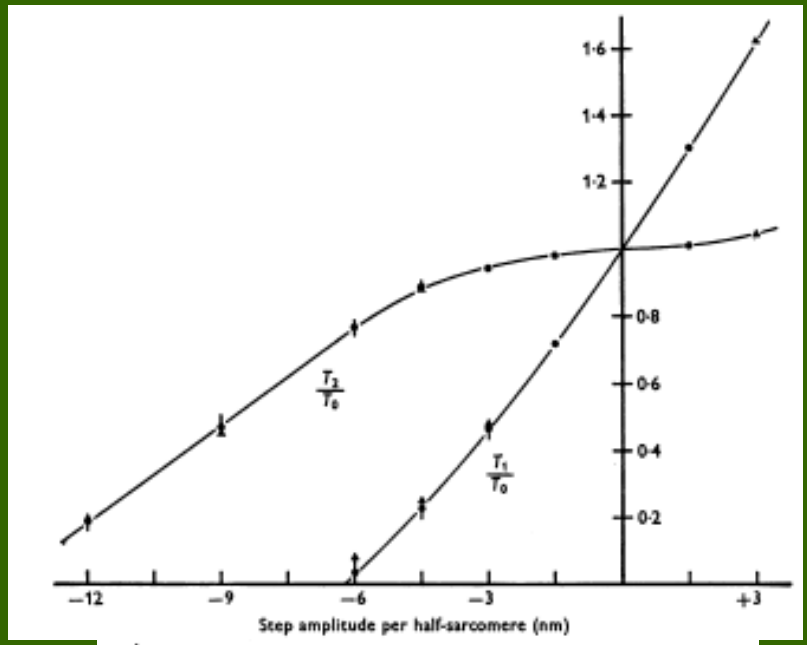
Proposed Mechanism of Force Generation in Striated Muscle

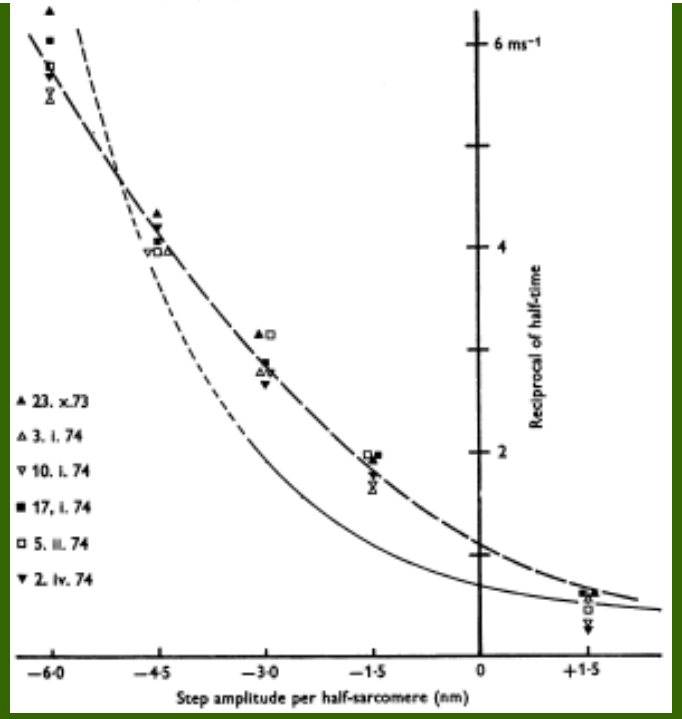
A. F. HUXLEY & R. M. SIMMONS
Department of Physiology, University College London, Gower Street, London WC1



Instantaneous elastic response is Hookean, fast early tension recovery and quasi-steady phase 2 are essentially nonlinear



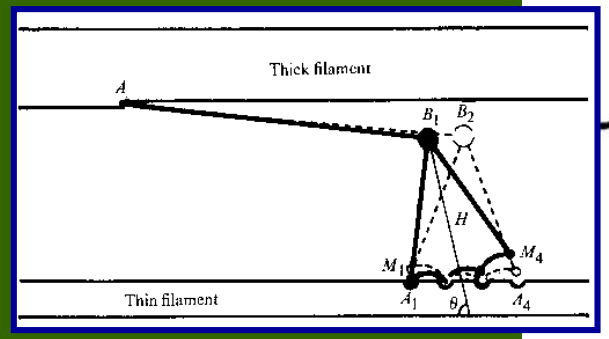


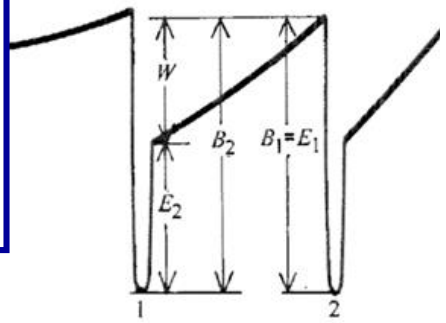


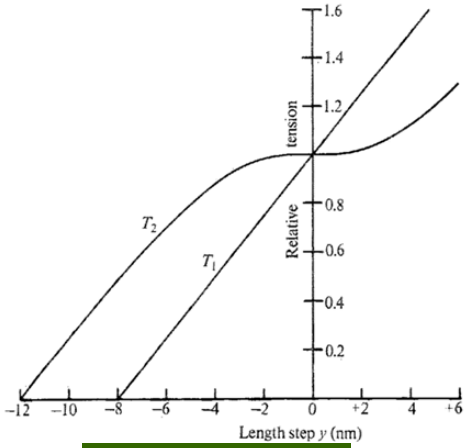
Ford, Huxley, Simmons, 1977

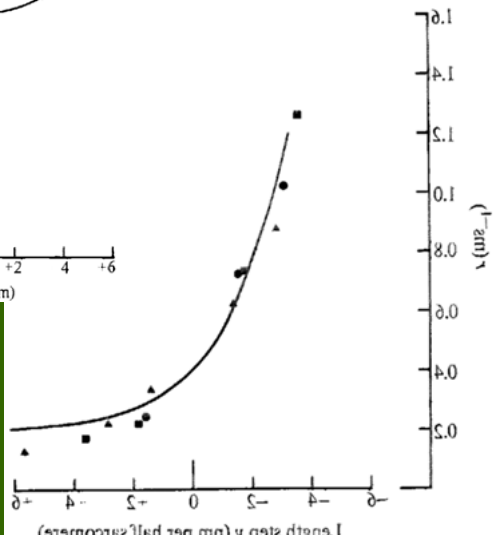
Huxley-Simmons model (1971)

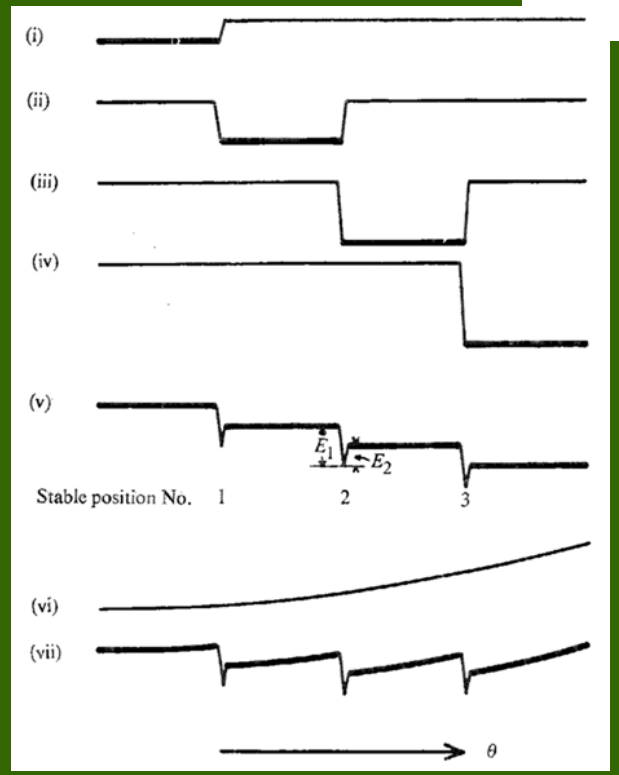
Conformational transition over mechano-chemical barrier











$$\frac{dn_2(t)}{dt} = k_- n_1(t) - k_+(y) n_2(t),$$

$$k_- = const,\ k_+ = k_- \exp\left(\frac{E_1 - E_2 - W(y)}{k_B T}\right),$$

$$n_1 + n_2 \equiv 1,\ \ W = Kh(y + y_0).$$

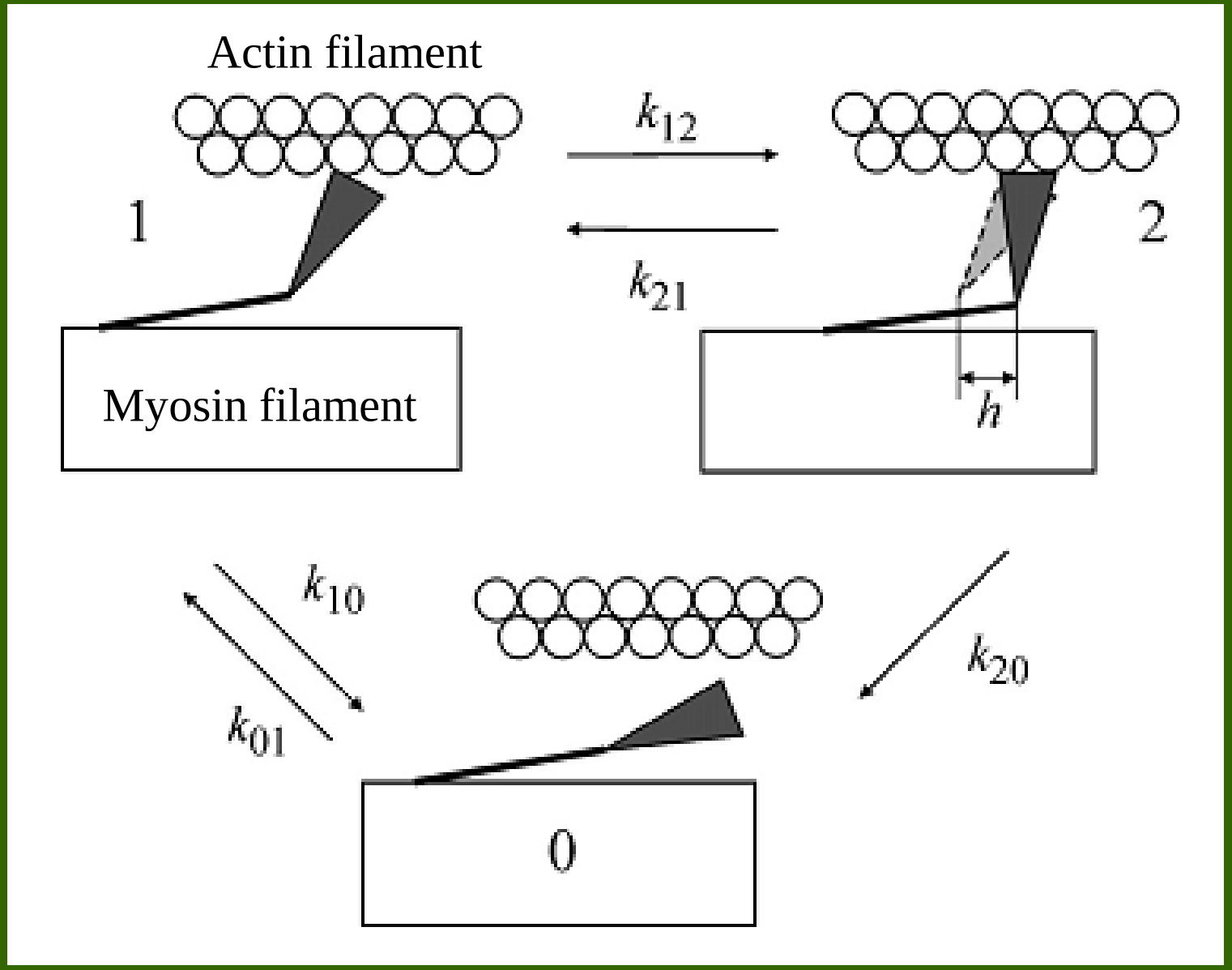
$$\frac{dn_2(t)}{dt} = k_-\left(1 - \exp\left(\frac{E_1 - E_2 - Kh(y + y_0)}{k_B T}\right) n_2(t)\right)$$

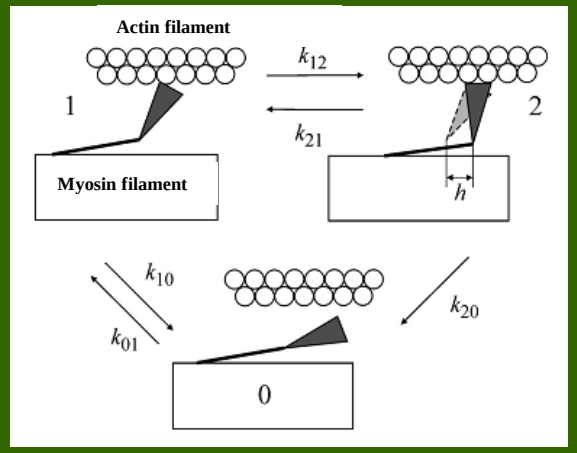
$$F = K(1 + h n_2(t))$$

Data set to be explained
(skeletal muscle at full activation and full filament overlap)

- Force-velocity relationship during shortening (A.V. Hill, 1938)
- Force-velocity relation during stretch (Piazzesi, Lombardi, 1990)
- Dependence of stiffness on shortening/stretch velocity (Ford, Huxley, Simmons, 1985; Piazzesi, Lombardi, 1990)
- Dependence of heat production and ATPase rate on shortening velocity (A.V. Hill, 1938, 1964; … Homsher *et al*., 1984)
- Tension transients induced by length steps (Huxley, Simmons, 1971) and load steps (Podolsky *et al.*, 1960; Piazzesi *et al*., 2002)
- Tension repriming induced by a length step change (Lombardi *et al*., 1992)

Kinetic scheme: a three-state model





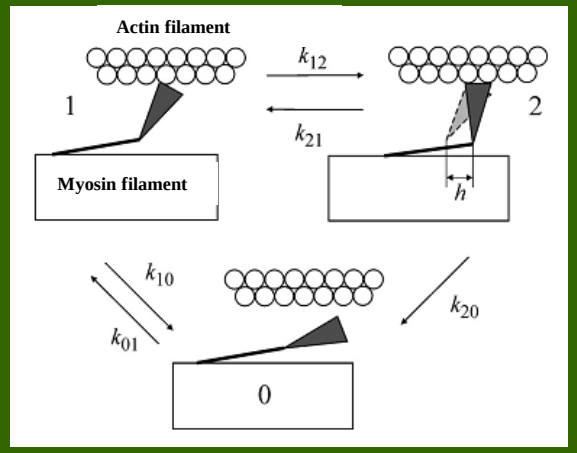
Cross-bridge kinetics

Main assumption (Thorson & White, J Physiol. 1983): the rate constants depend only on the ensemble averaged cross-bridge strain, δ

$$\begin{cases} \dot{n}_1 = k_{01}(\delta)\cdot(1-n_1-n_2)+k_{21}(\delta)\cdot n_2 - k_{12}(\delta)\cdot n_1 - k_{10}(\delta)\cdot n_1 \\ \dot{n}_2 = k_{12}(\delta)\cdot n_1 - k_{21}(\delta)\cdot n_2 - k_{20}(\delta)\cdot n_2 \\ \dfrac{d(\delta\cdot(n_1+n_2))}{dt} = (n_1+n_2)\cdot\dot{u} - \delta\cdot(k_{10}(\delta)\cdot n_1 - k_{20}(\delta)\cdot n_2) \end{cases}$$

- n_1 and n_2 are the probabilities of being in states 1 or 2
- $k_{01,}\ k_{10,}\ k_{12,}\ k_{21,}\ k_{20}$ are the transition rates
- u is the displacement (sliding) of the thin and thick filaments

(Syomin, Tsaturyan, 2012)



$$\frac{d(\delta \cdot (n_1 + n_2))}{dt} = (n_1 + n_2) \cdot \dot{u} - \delta \cdot (k_{10}(\delta) \cdot n_1 - k_{20}(\delta) \cdot n_2)$$

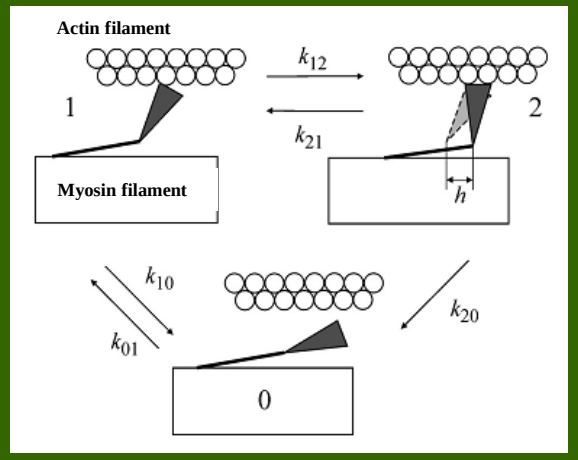
$$\dot{u} = \dot{L} - c \cdot \dot{F}_{Act}$$

$$F_{Act} = E \cdot N \cdot \rho \cdot \left((n_1 + n_2)\delta + n_2 h \right) \cdot W_{ov}(L)$$

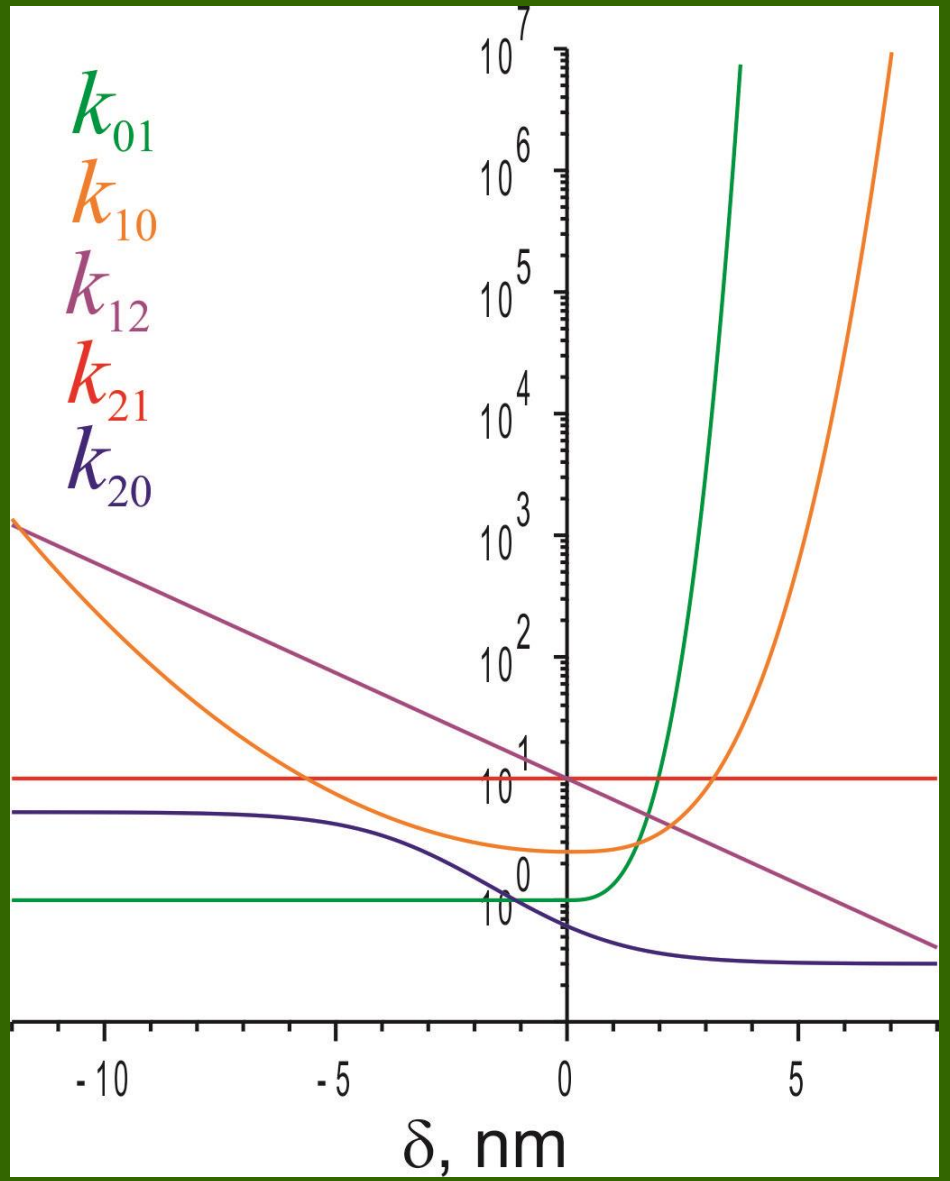
$$F = F_{Act} + F_{\text{titin}}(L) + F_{\text{ct}}(L)$$

- L is sarcomere length;
- F, F_{Act}, F_{titin}, F_{ct} are the total (1D), active, titin and connective tissue tension;
- c is the compliance of the thin and thick filaments;
- E is the cross-bridge stiffness;
- $N\rho$ is the number of the cross-bridges in a half-sarcomere per cross-section area;
- h is the displacement during the force-generating working stroke (transition 1 to 2);
- W_{ov} is the normalized length of the filament overlap zone;

Strain dependence of the rate constants at full activation

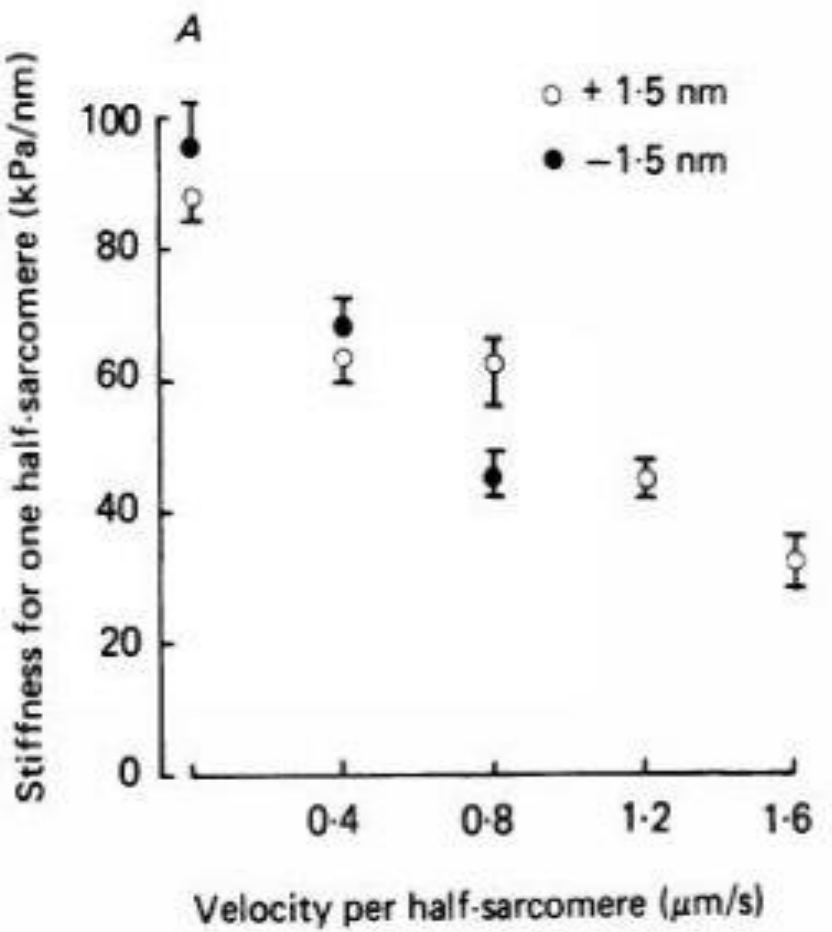


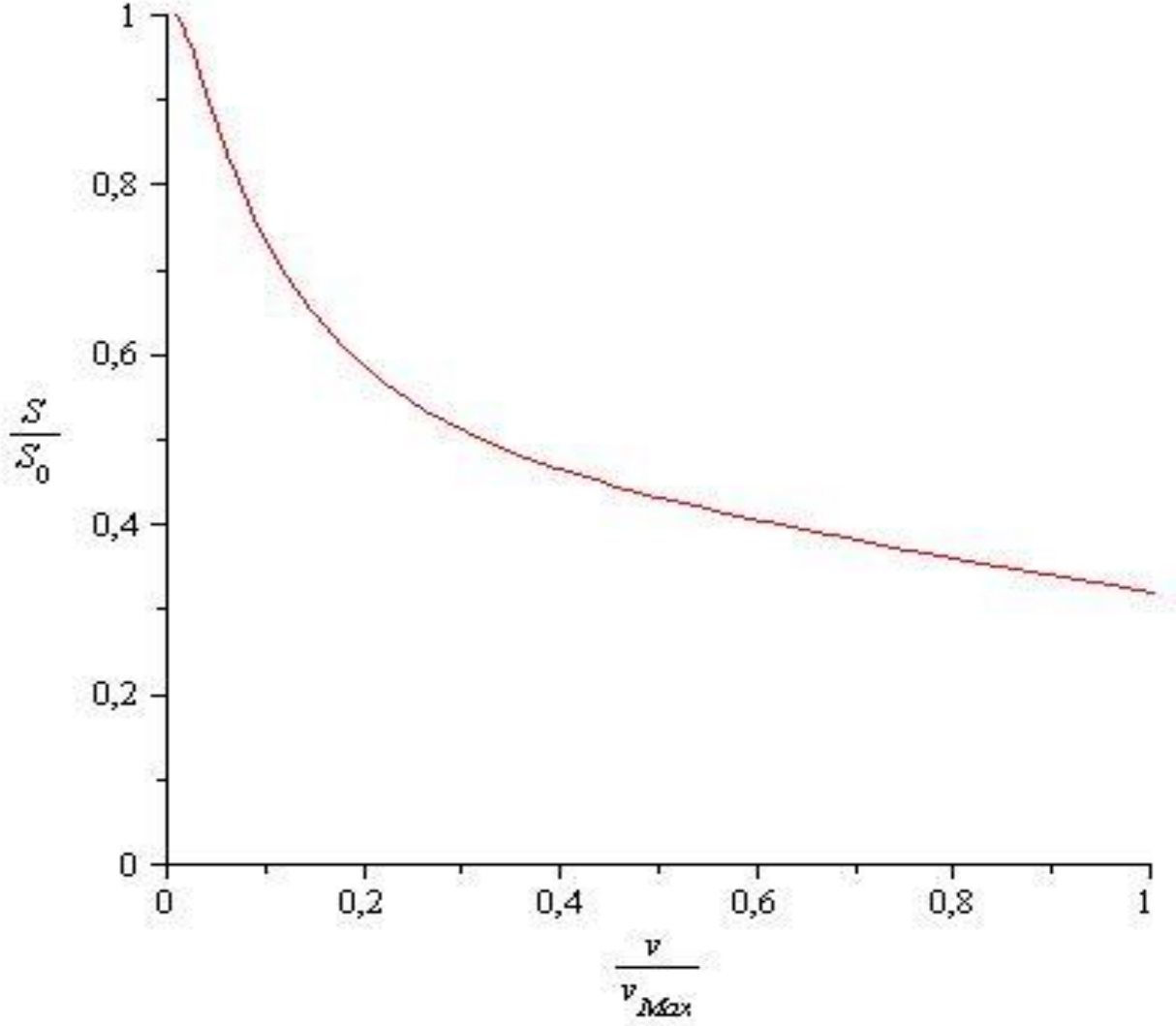
h = 10 nm



(Syomin, Tsaturyan, 2012)

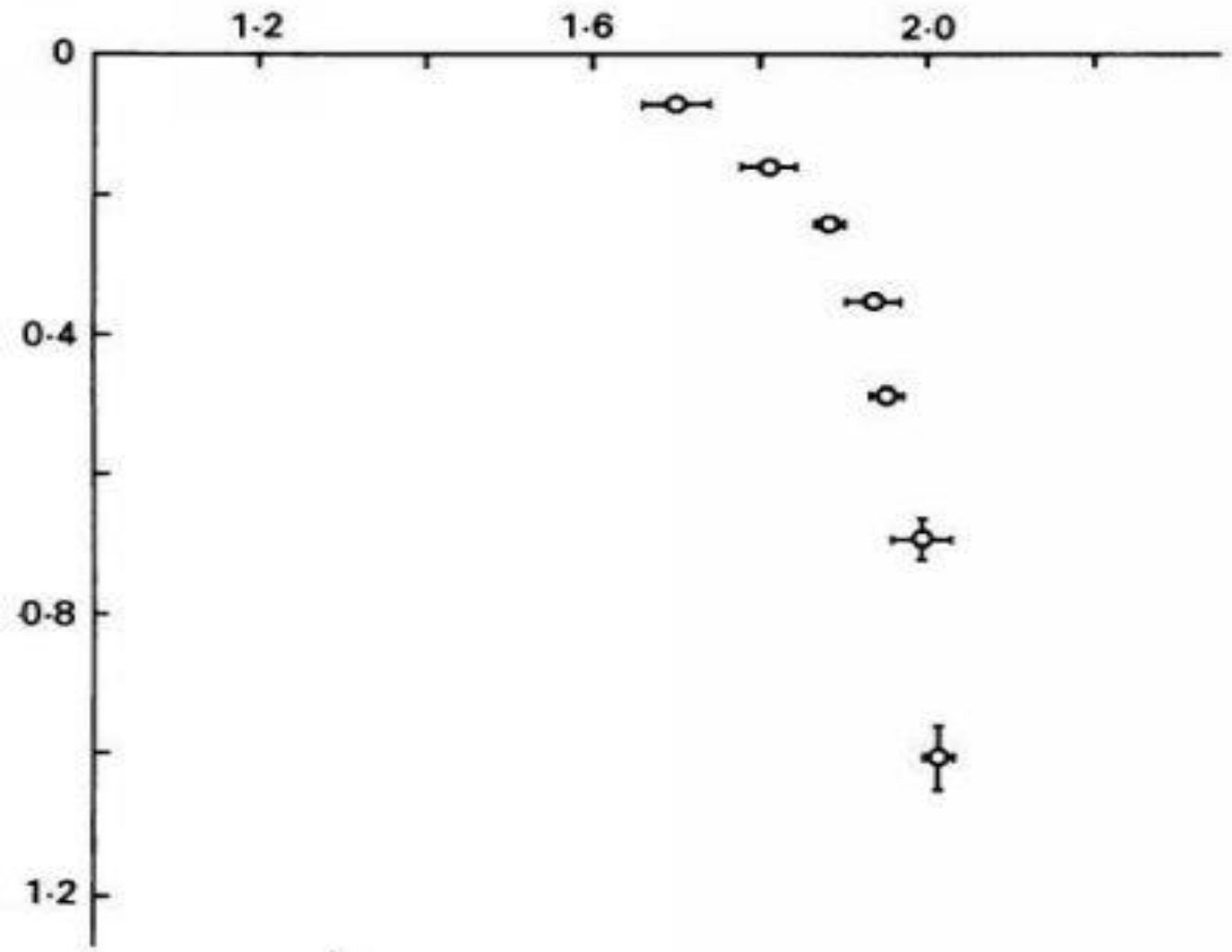
Stiffness-velocity relation

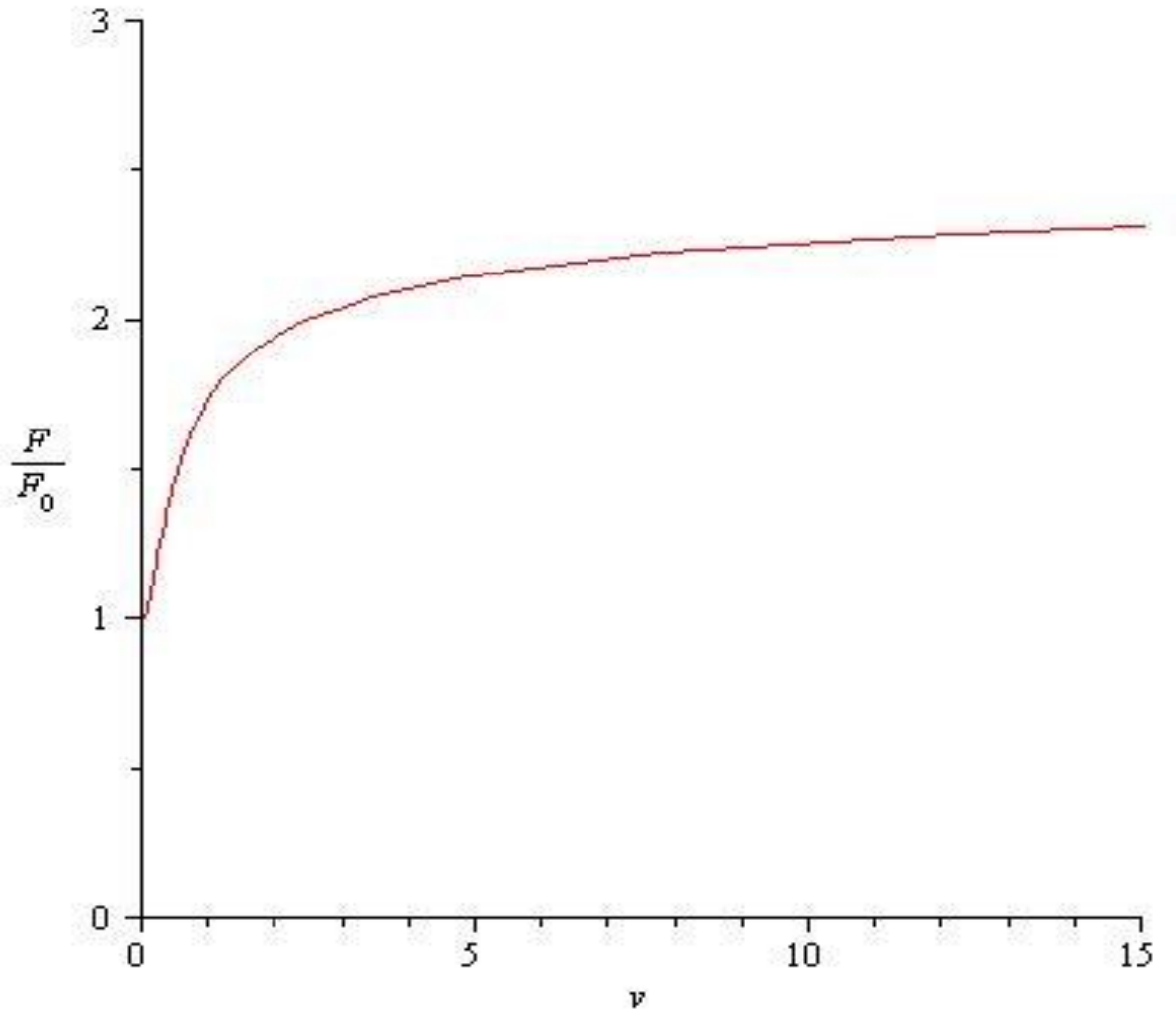




(Ford, Huxley, Simmons, J. Physiol., 1985)

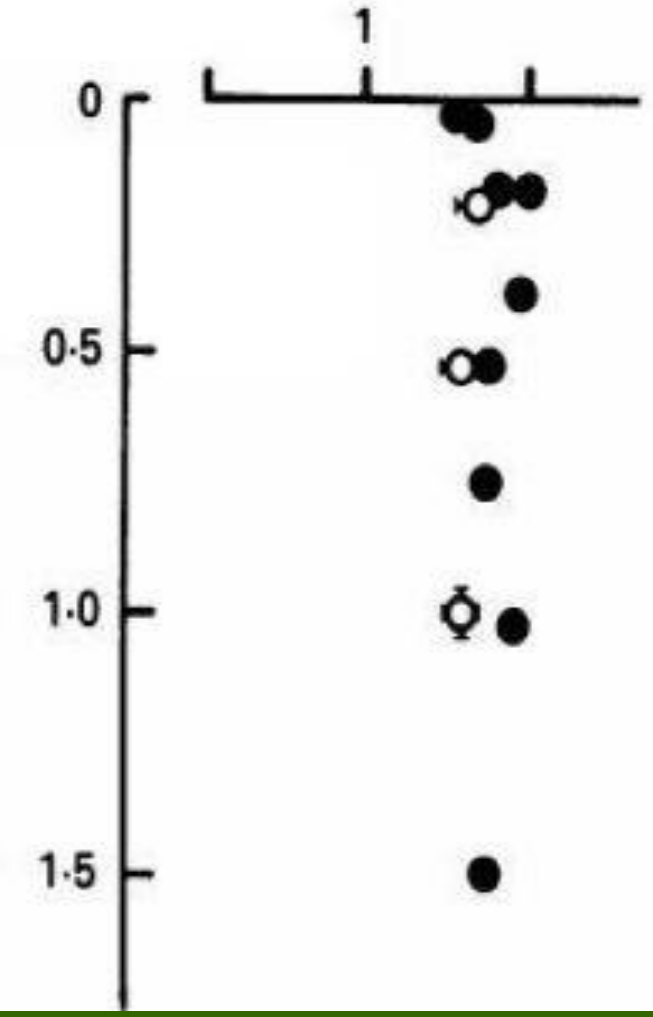
Force-velocity relation during stretch

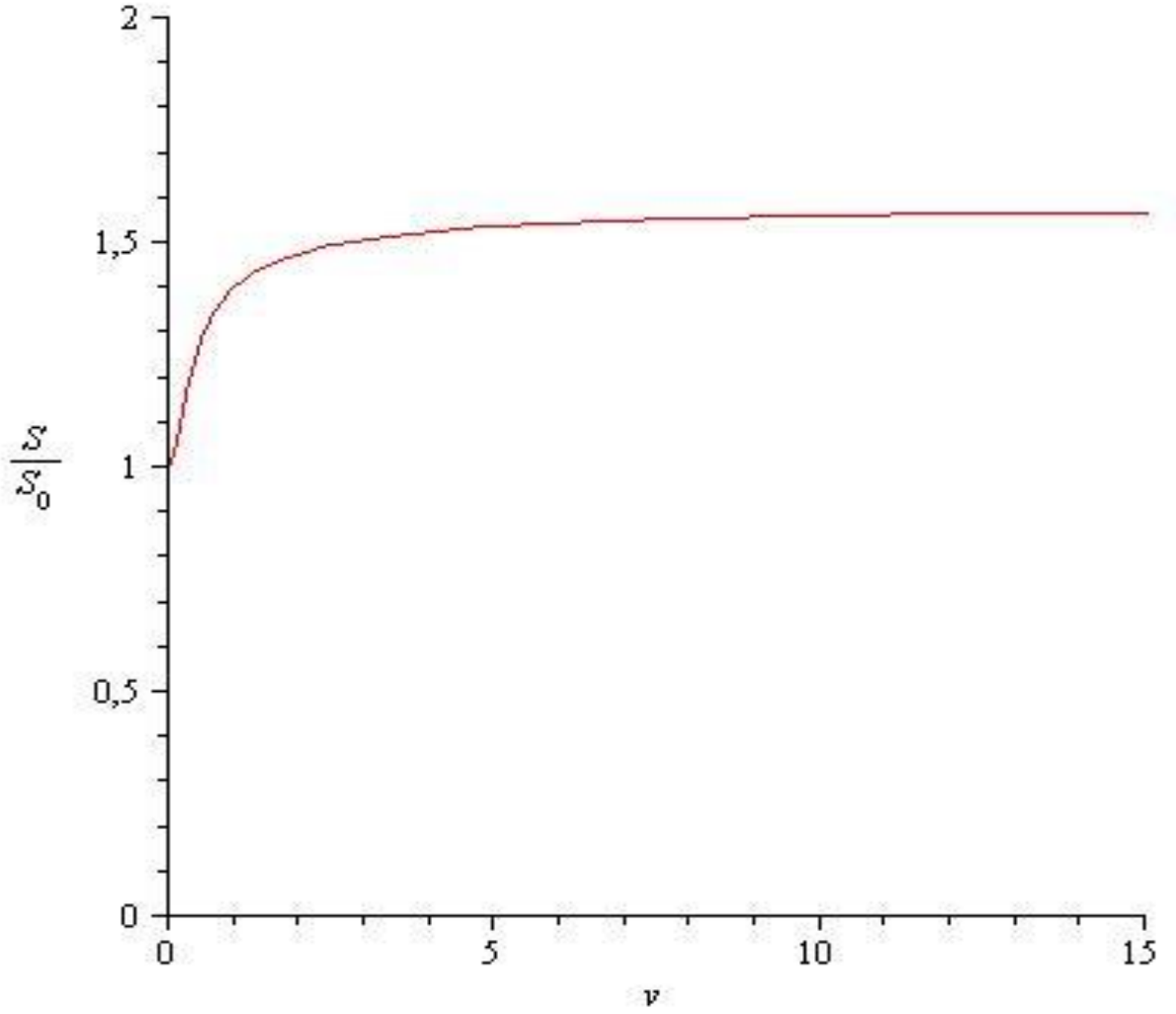




(Piazzesi, Lombardi, 1990)

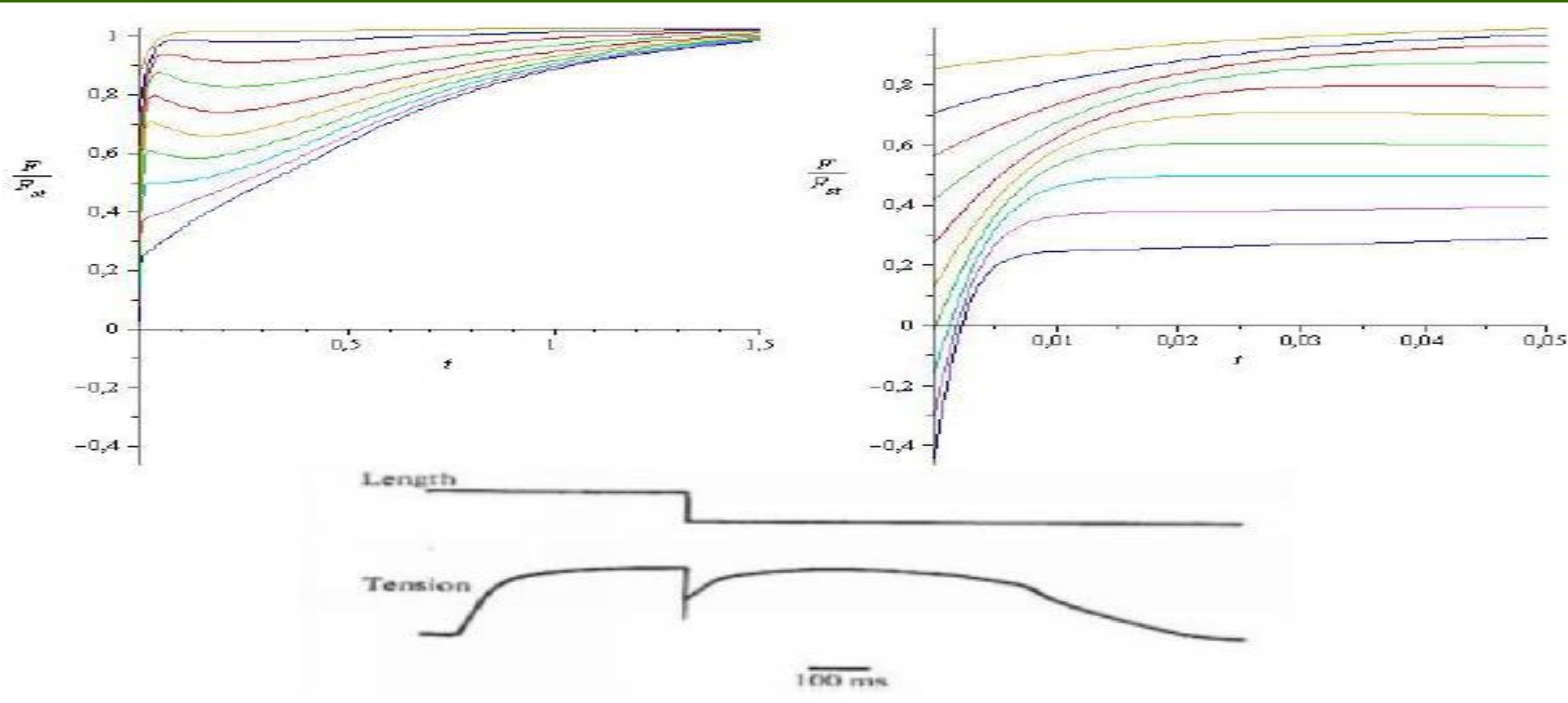
Force-velocity relation during stretch





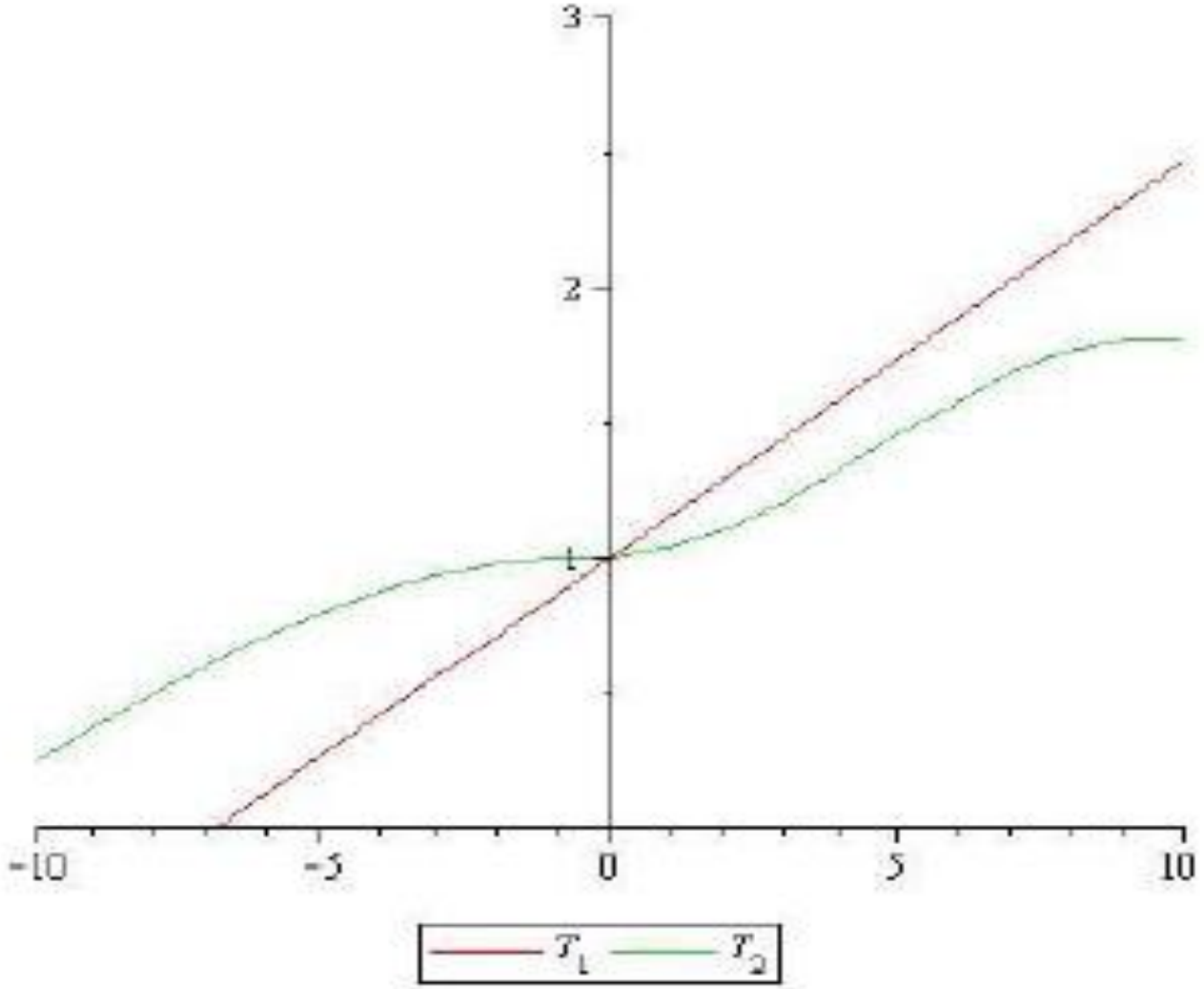
(Piazzesi, Lombardi, 1990)

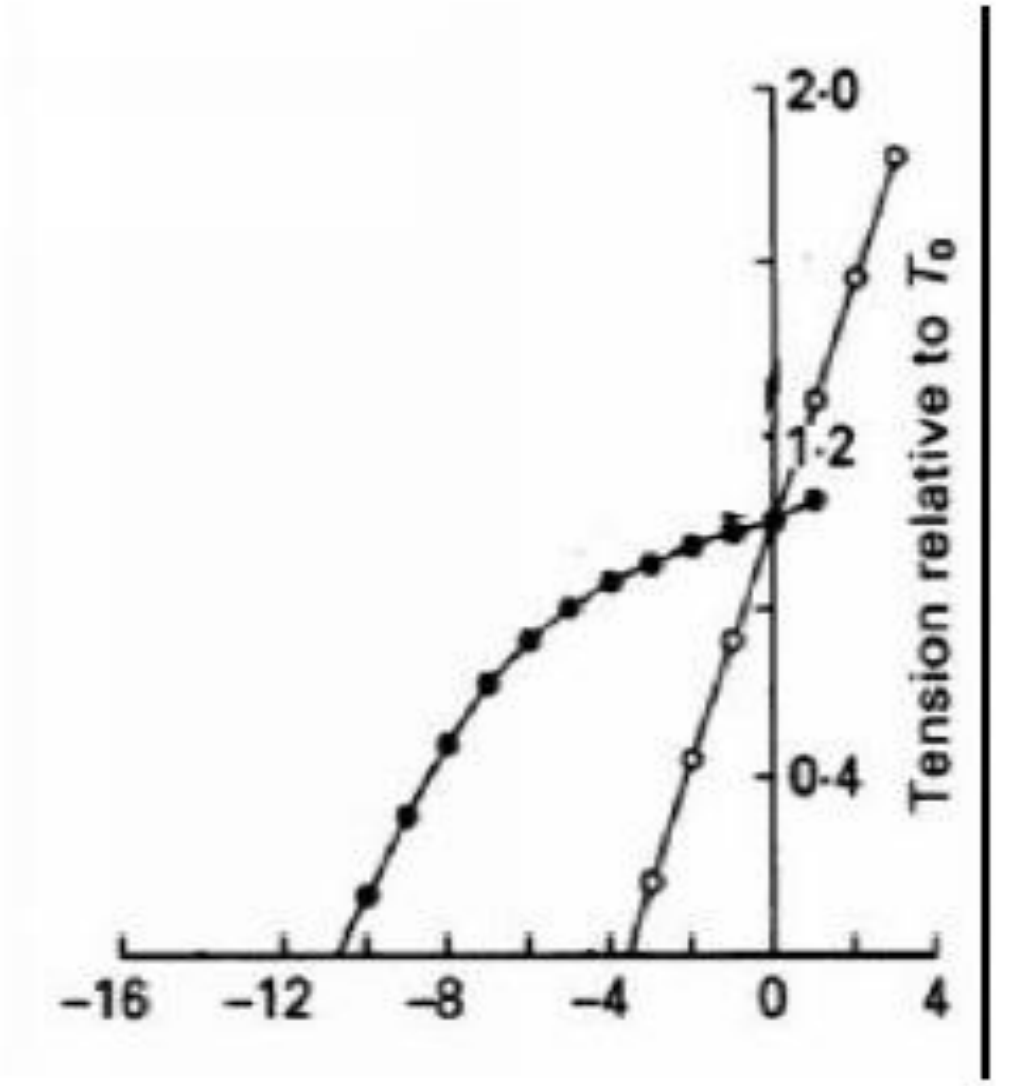
Tension responses to step length changes



(Huxley, Simmons, 1971; Ford, Huxley, Simmons, 1977)

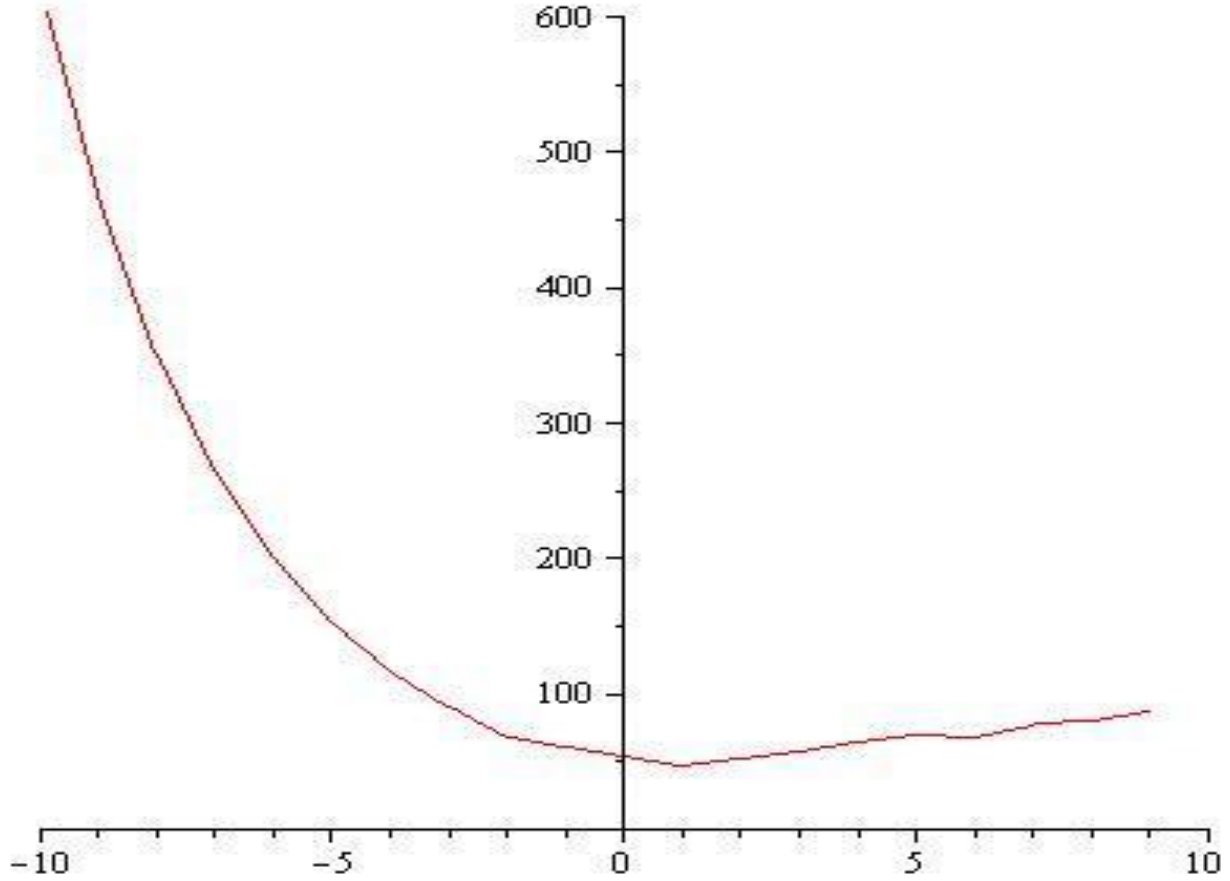
Strain-dependence of tension responses to step length changes

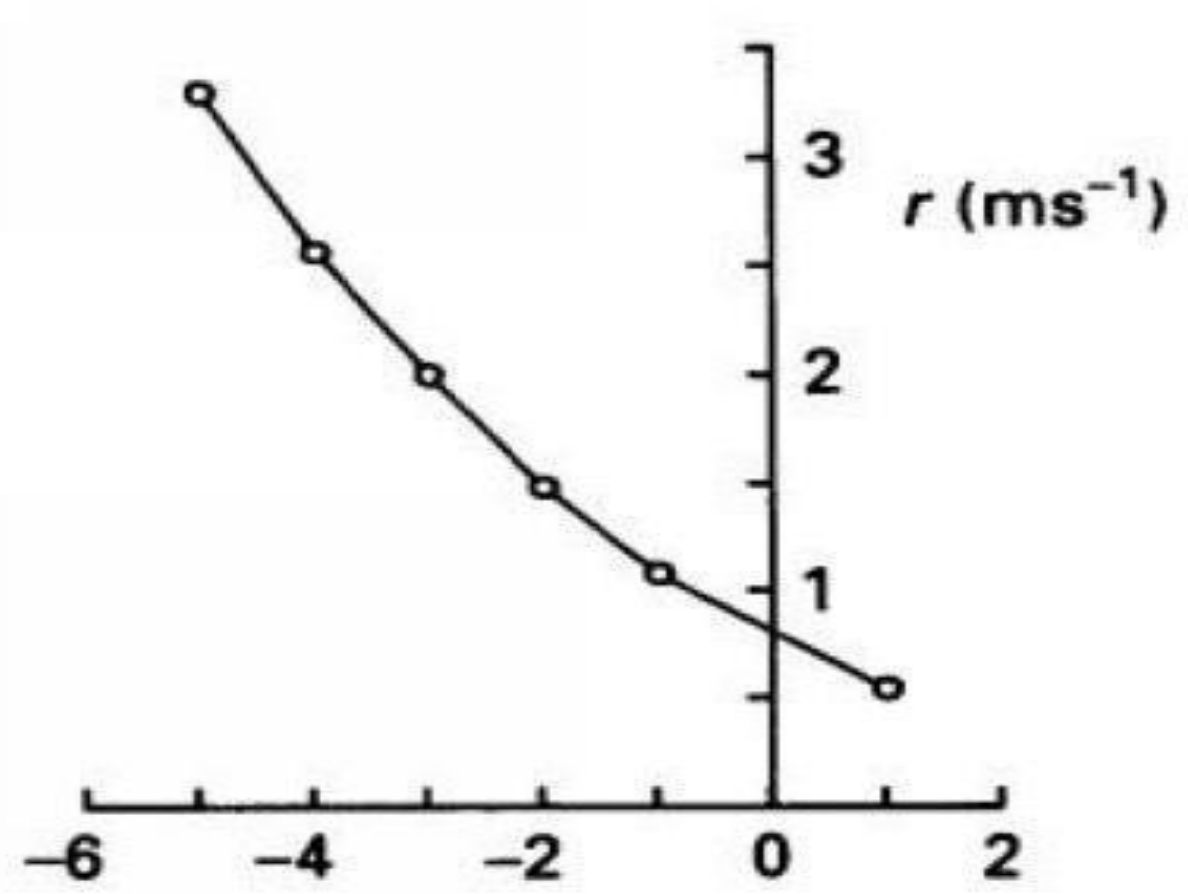




(Piazzesi et al, 1992)

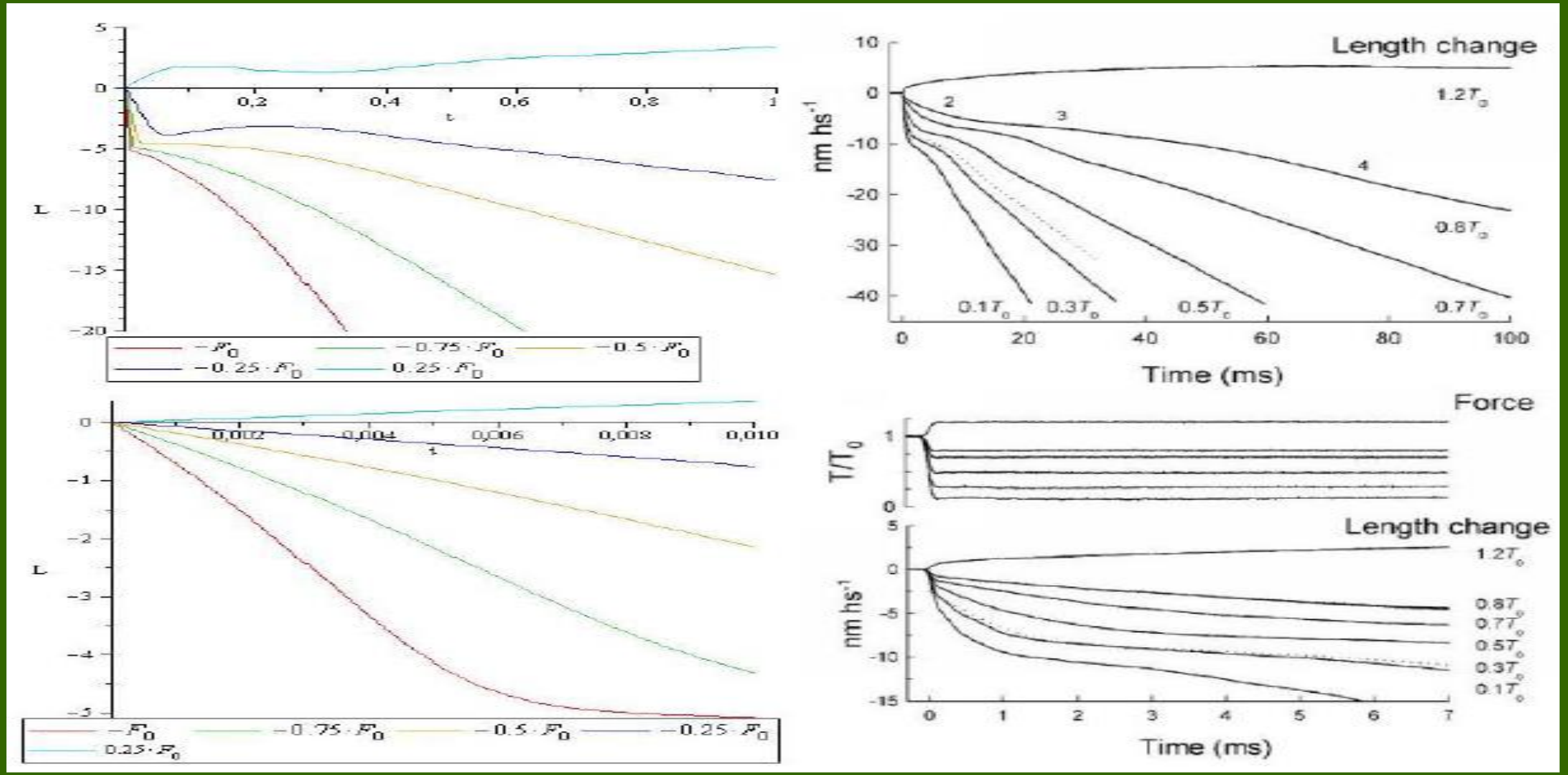
Strain-dependence of rate of early partial tension recovery





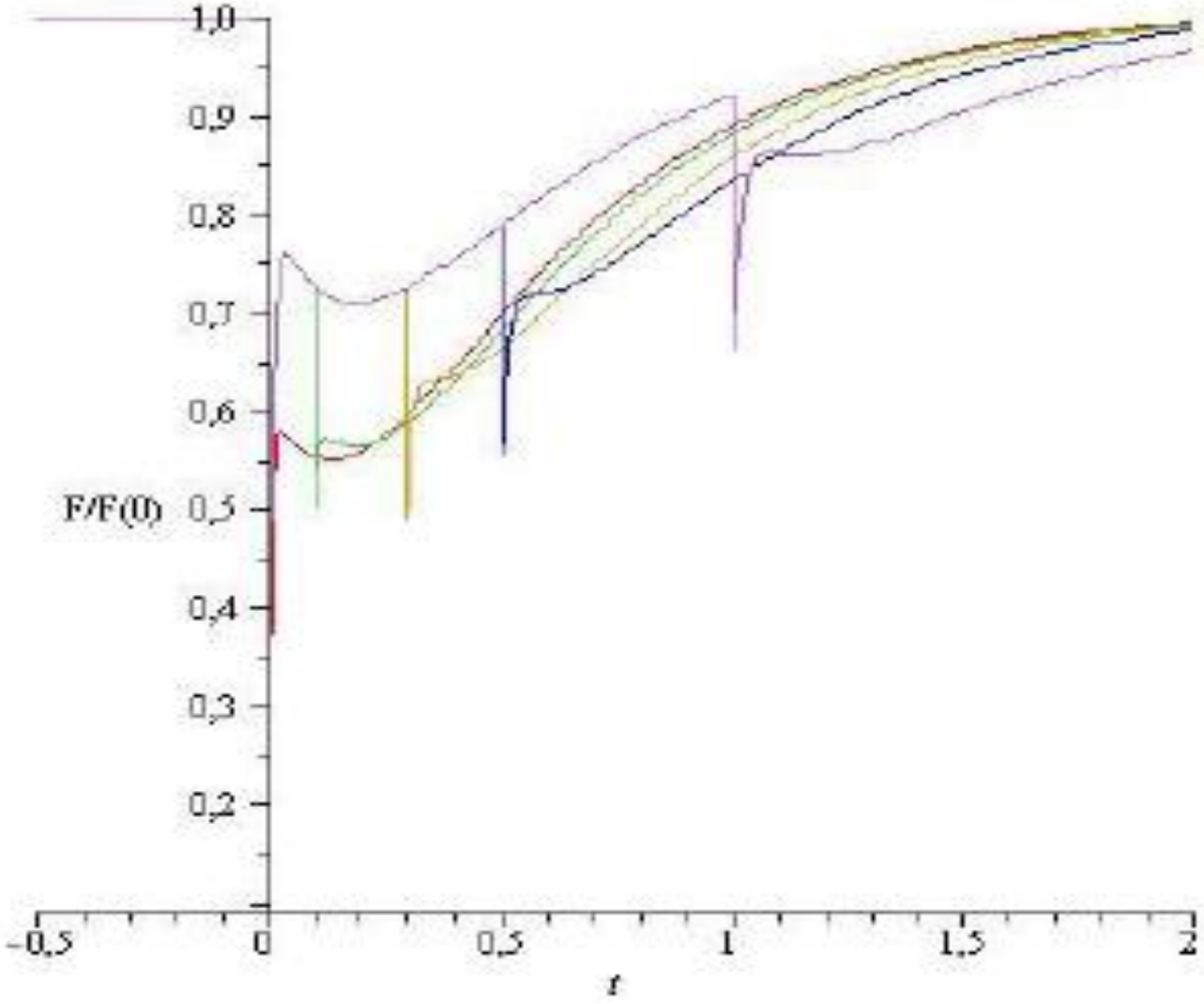
(Piazzesi et al, 1992)

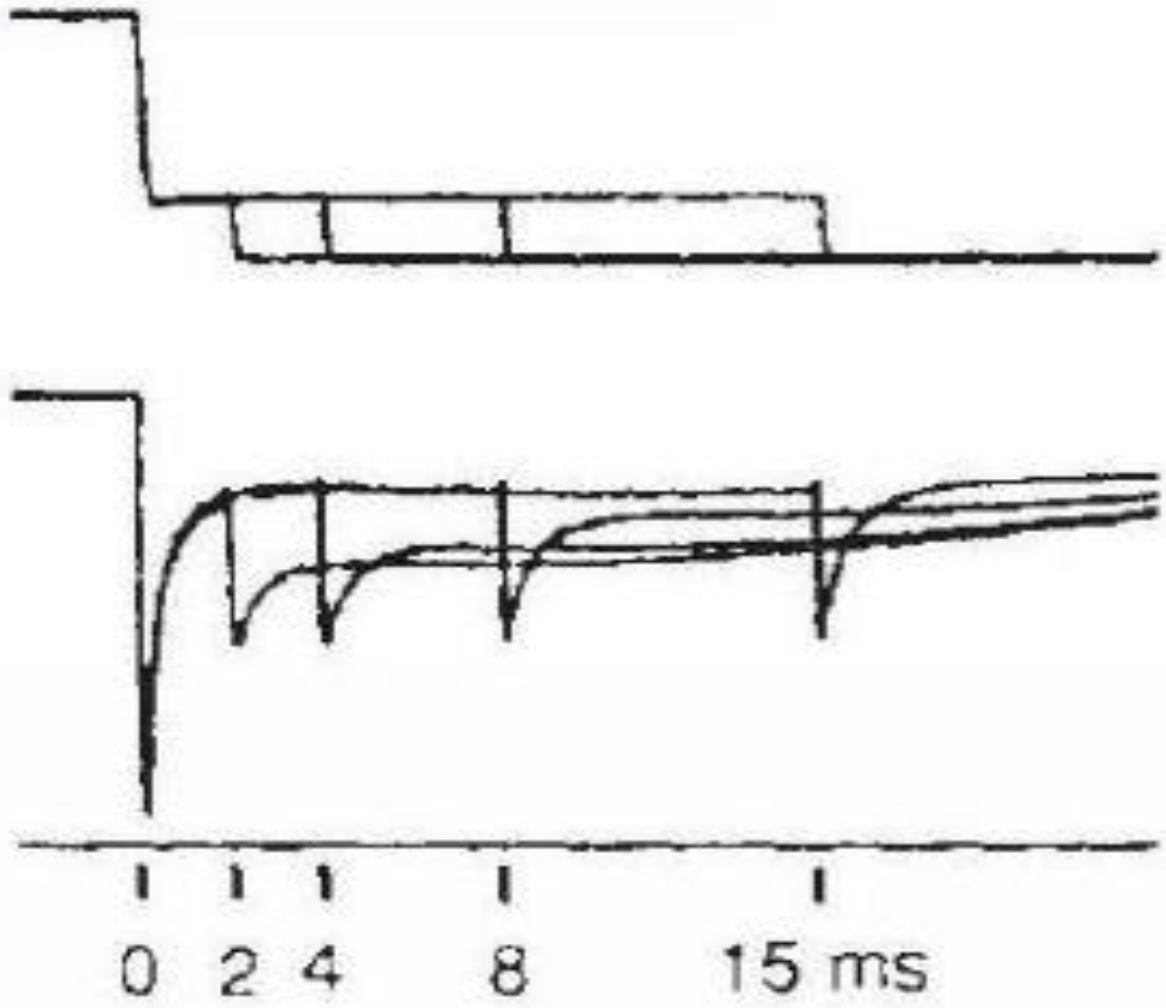
Length responses to step changes in load



(Piazzesi et al, 2002)

Repriming of the working stroke

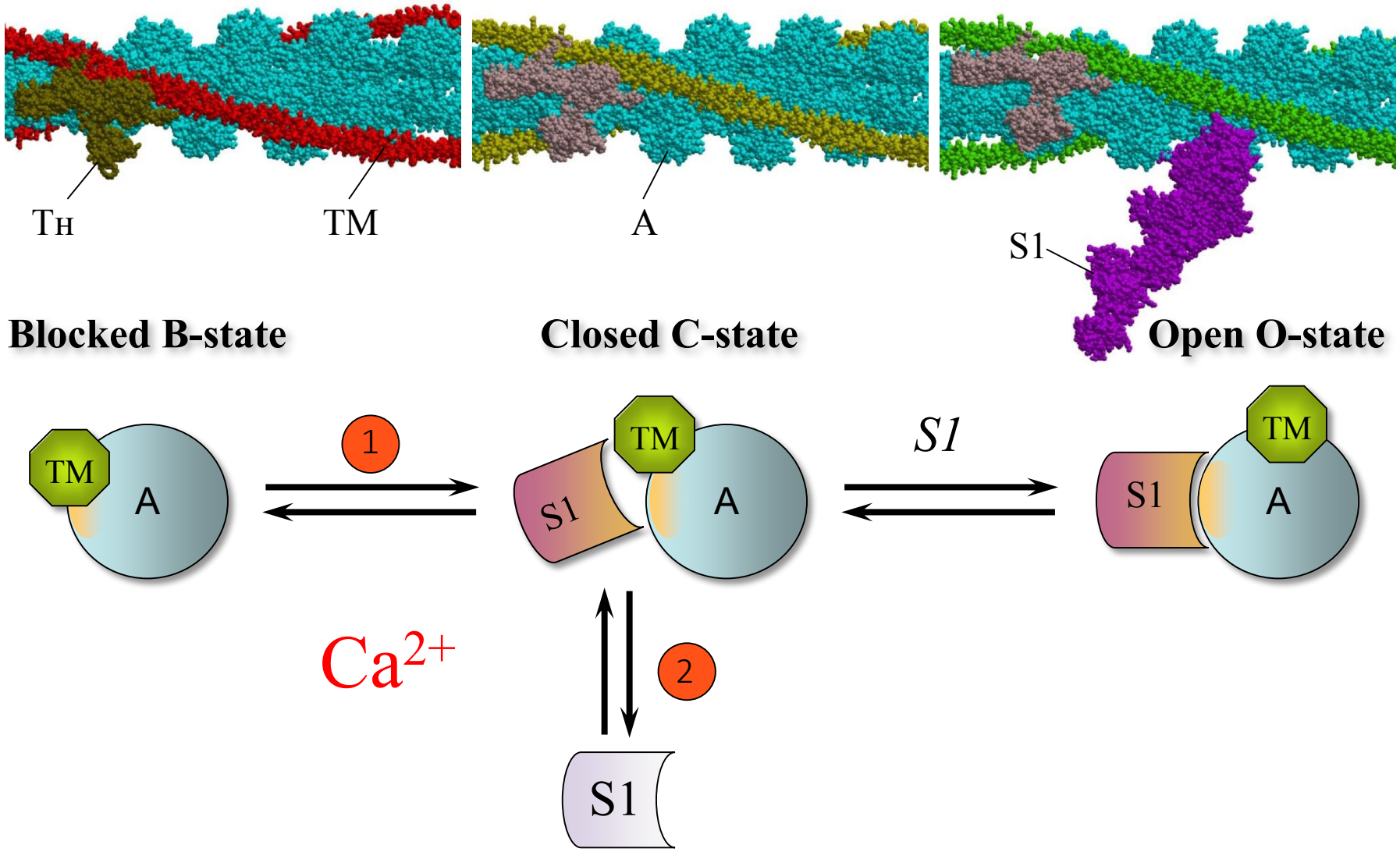




(Lombardi et al., *Nature*, 1992)

Troponin-tropomyosin regulation of muscle contraction

3-state model (McKillop, Geeves, 1993)



Cooperativity of Ca activation

TnC affinity for Ca^{2+} increases when:

- sarcomere length increases

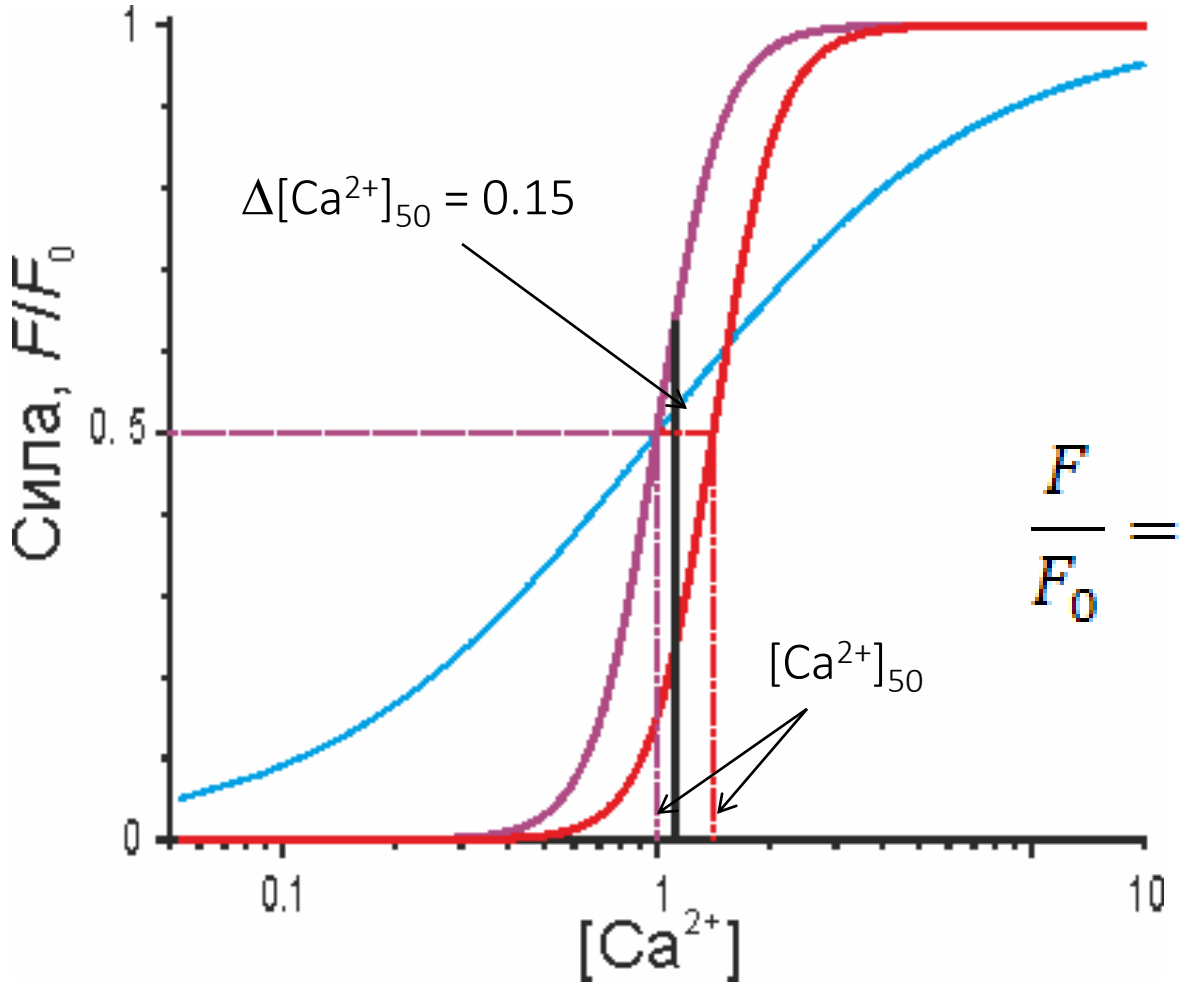
or

- myosin head binds actin

or

- neighbour TnC molecules bind Ca^{2+}

Calcium-tension curve is steep



Hill coefficient

$n = 1$,

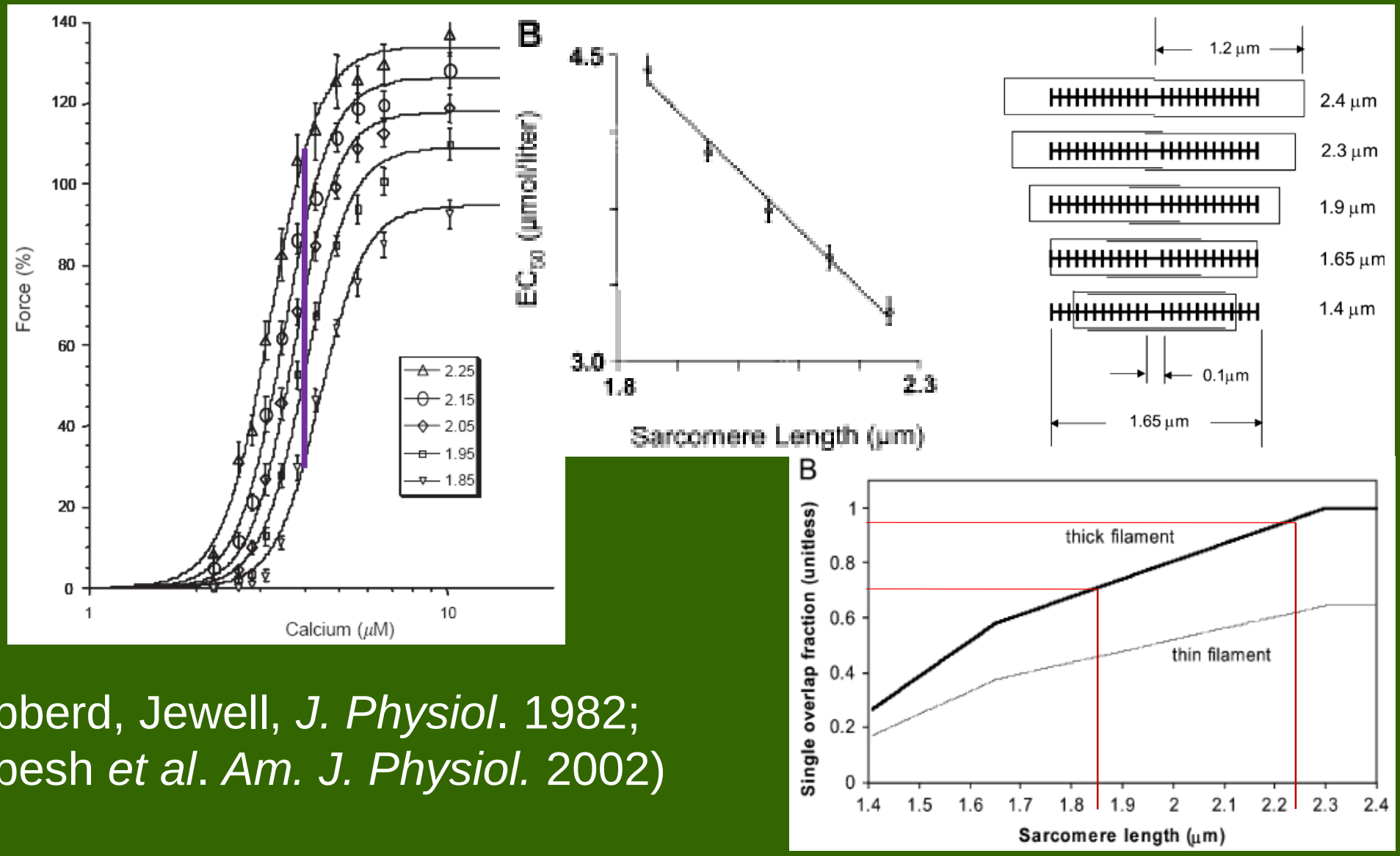
$n = 5$

$$nCa^{2+} + TnC = Ca_nTn$$

$$\frac{F}{F_0} = \frac{[Ca^{2+}]^n}{[Ca^{2+}]_{50}{}^n + [Ca^{2+}]^n}$$

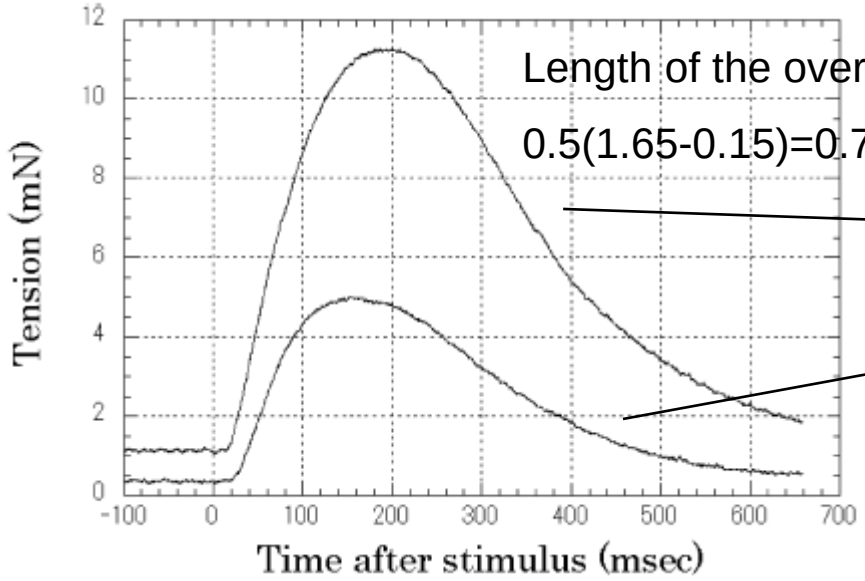
$pCa = -\lg[Ca^{2+}]$, $[Ca^{2+}]$

The “Starling law of the heart” is based on length-dependent activation



(Hibberd, Jewell, *J. Physiol*. 1982;
Dobesh *et al*. *Am. J. Physiol.* 2002)

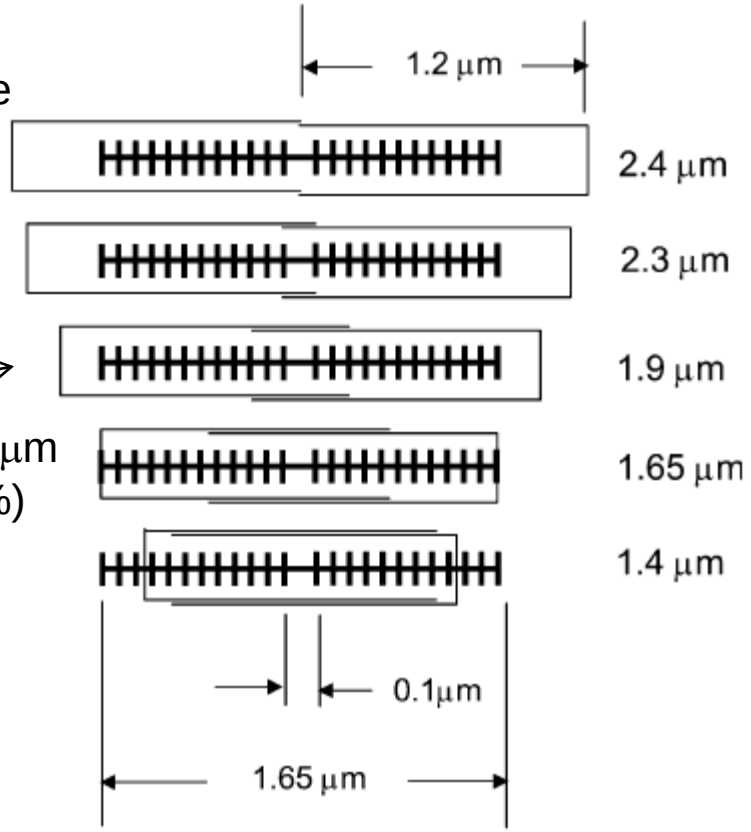
The Frank-Starling law of the heart on tissue level

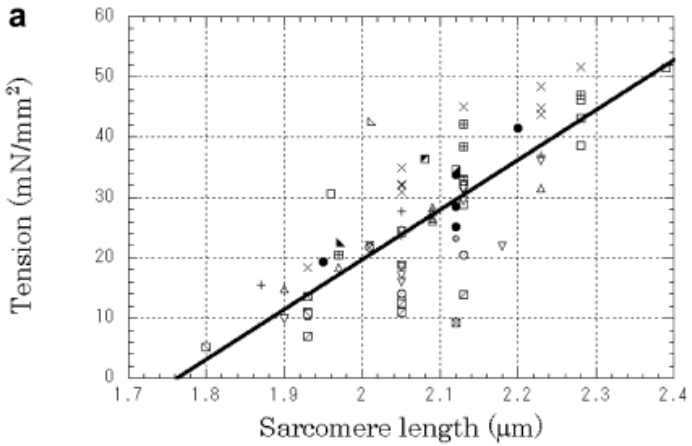


Length of the overlap zone

0.5(1.65-0.15)=0.75 μm

0.675 μm
(90%)





Kinetics of Ca binding to troponin-C

$$\dot{A}_1 = \begin{cases} \alpha_{01}(1-A_1) - \alpha_{101}A_1, \dot{W}_{act} \le 0 \\ \alpha_{01}(1-A_1) - \alpha_{101}A_1 + \dot{W}_{act}\dfrac{A_2 - A_1}{W_{act}}, \dot{W}_{act} > 0 \end{cases}$$

$$\dot{A}_2 = \begin{cases} \alpha_{01}(1-A_2) - \alpha_{102}A_2 - \dot{W}_{act}\dfrac{A_1 - A_2}{1-W_{act}}, \dot{W}_{act} \le 0 \\ \alpha_{01}(1-A_2) - \alpha_{102}A_2, \dot{W}_{act} > 0 \end{cases}$$

$$\frac{d[Ca^{2+}]}{dt} = I_{Ca}(t) - Y_{Ca}[Ca^{2+}] - [Tn]\cdot\frac{d(A_1W_{act} + A_2(1-W_{act}))}{dt}$$

The rate ‘constants’ depend on sarcomere length and CaTnC concentration

$$\alpha_{01} = \alpha_0 \frac{[Ca^{2+}]}{[Ca_0]}$$

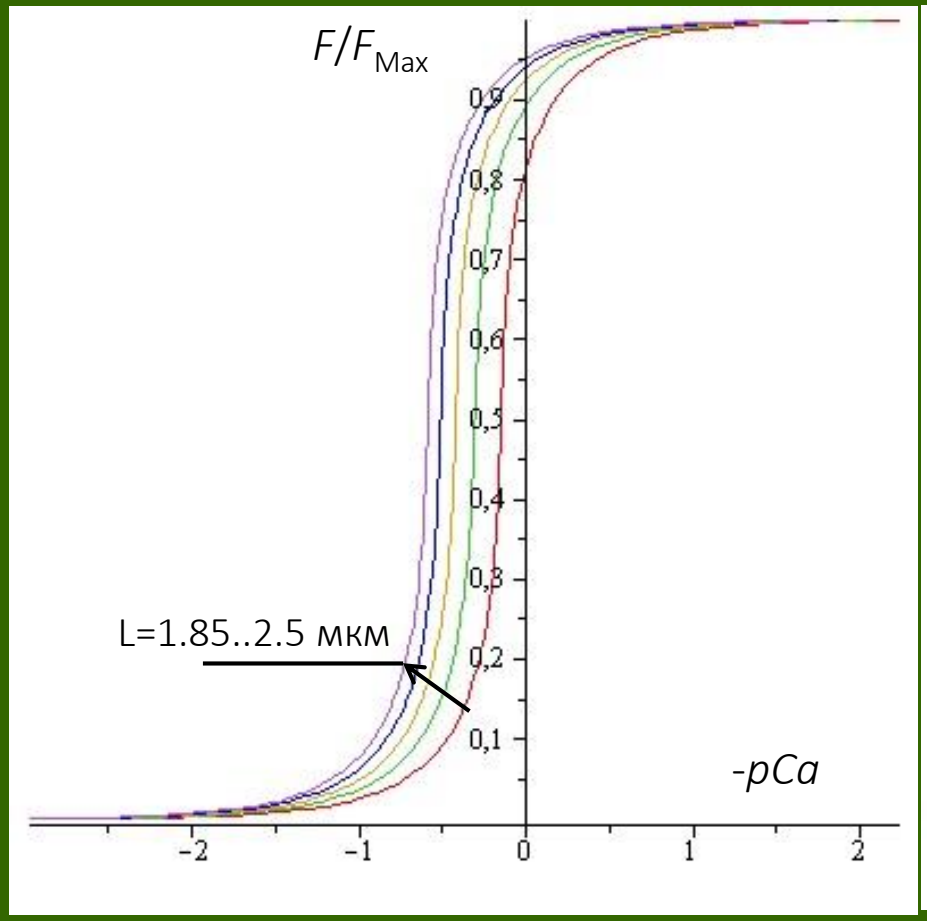
$$\alpha_{101} = \alpha_0 \cdot \frac{\alpha_{10}^{n_2} \cdot \alpha_{10}^{A}(A_1)}{\alpha_{10}^{L}}, \; \alpha_{102} = \alpha_0 \cdot \frac{\alpha_{10}^{A}(A_2)}{\alpha_{10}^{L}}$$

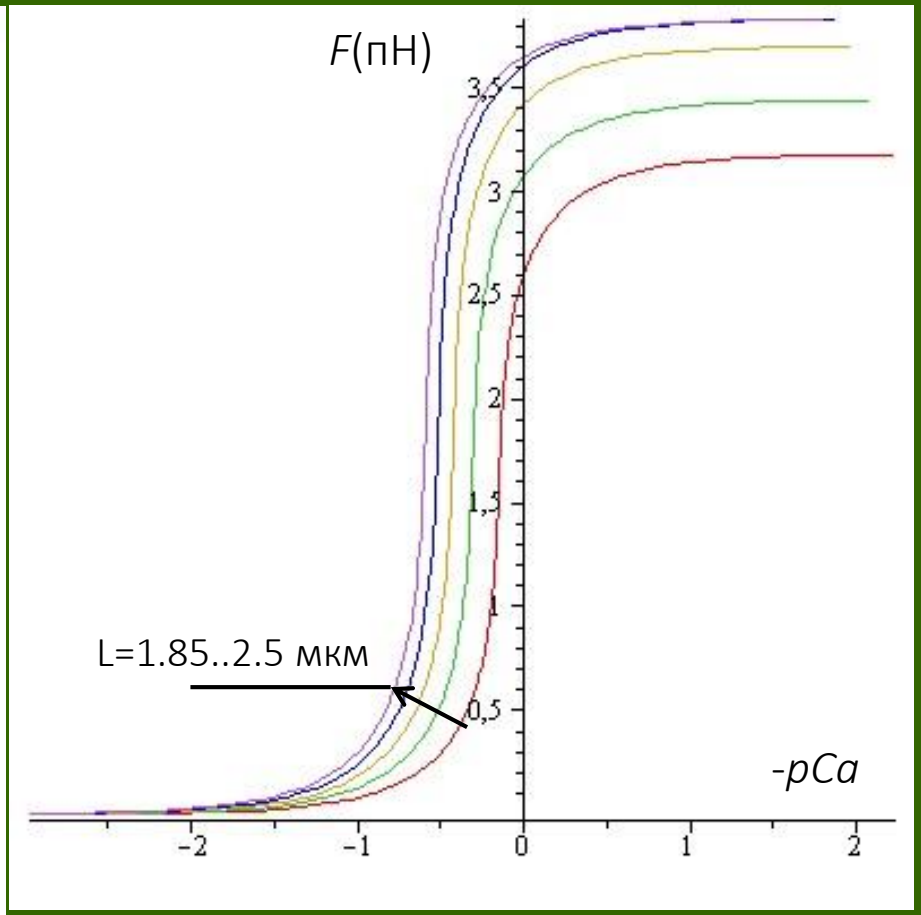
$$\alpha_{10}^{n_2} = \gamma_1^{n_2}, \; \alpha_{10}^{A}(A) = e^{-\gamma_2 A}, \; \alpha_{10}^{L} = \frac{L - L_{Min}}{L_{Max} - L_{Min}}$$

The set of model equations

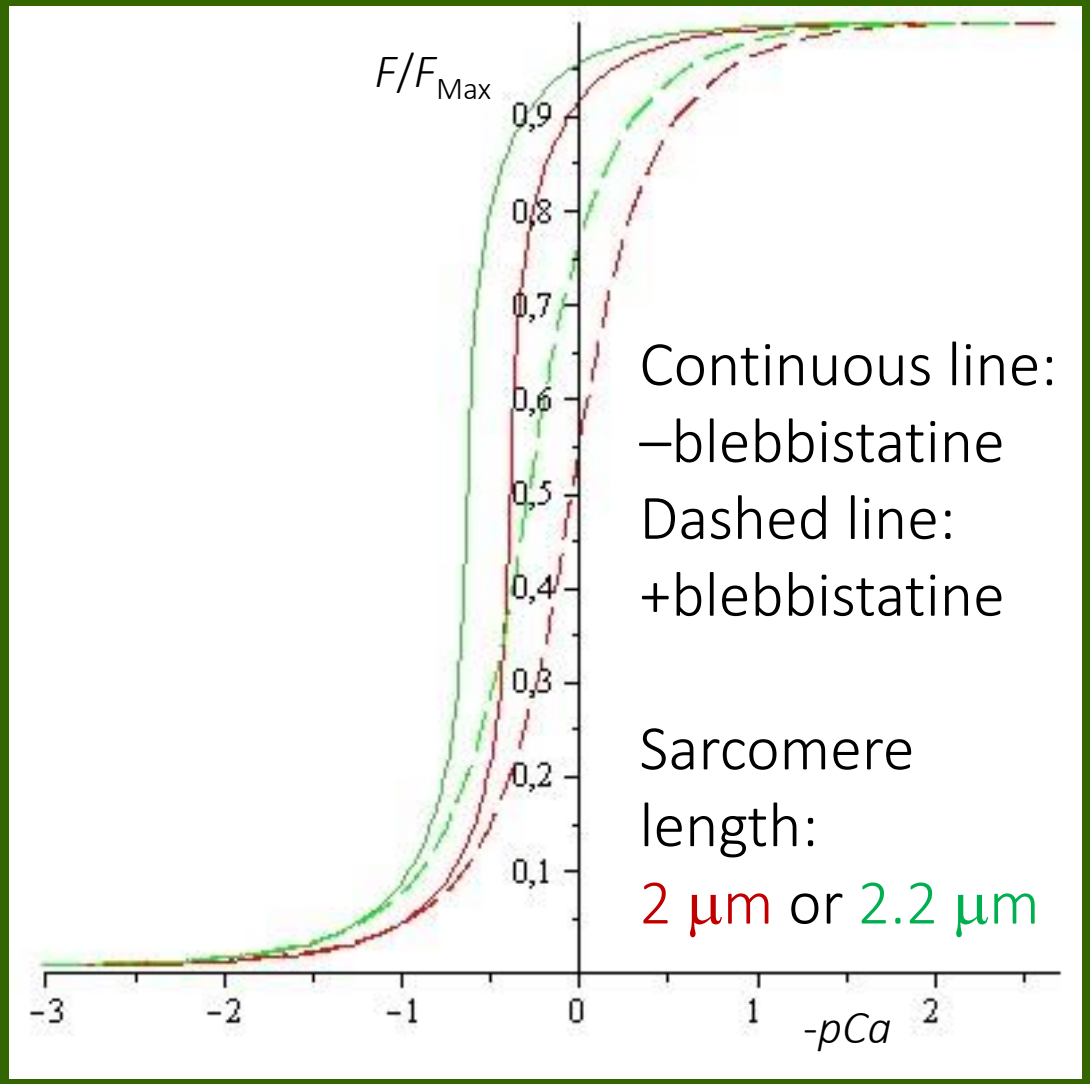
$$
\begin{cases}
\dot{n} = k_{01}(A_1 - n) - k_{10} n(1-\Theta) - k_{20} n\Theta \\
\dot{n}\Theta + n\dot{\Theta} = k_{12} n(1-\Theta) - k_{21} n\Theta - k_{20} n\Theta \\
\dfrac{d(\delta n)}{dt} = n(\dot{L} - c \cdot \dot{F}_{Act}) - \delta(k_{10} n(1-\Theta) + k_{20} n\Theta) \\
\dfrac{d[Ca^{2+}]}{dt} = I_{Ca}(t) - Y_{Ca}[Ca^{2+}] - [Tn] \cdot \dfrac{d(A_1 W_{act} + A_2(1-W_{act}))}{dt} \\
\dot{A}_1 = \begin{cases} \alpha_{01}(1-A_1) - \alpha_{101} A_1, \dot{W}_{act} \le 0 \\ \alpha_{01}(1-A_1) - \alpha_{101} A_1 + \dot{W}_{act} \dfrac{A_2 - A_1}{W_{act}}, \dot{W}_{act} > 0 \end{cases} \\
\dot{A}_2 = \begin{cases} \alpha_{01}(1-A_2) - \alpha_{102} A_2 - \dot{W}_{act} \dfrac{A_1 - A_2}{1-W_{act}}, \dot{W}_{act} \le 0 \\ \alpha_{01}(1-A_2) - \alpha_{102} A_2, \dot{W}_{act} > 0 \end{cases} \\
\dot{L} = \Phi(t) \text{ или } \dot{F} = \Psi(t)
\end{cases}
$$

Steady-state calcium-tension relation depends on sarcomere length (Starling law)



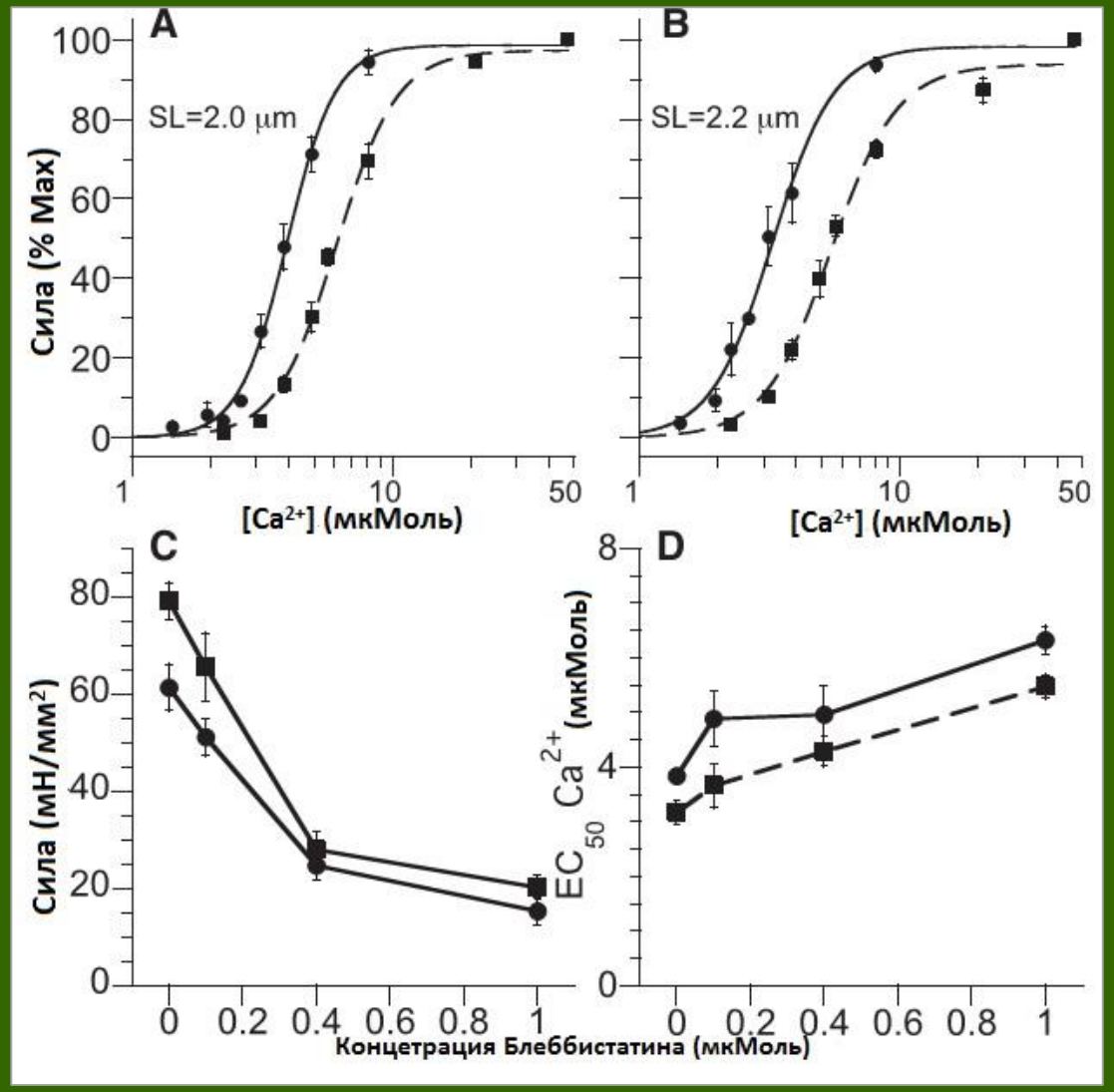


Effect of blebbistatine on calcium-tension relation

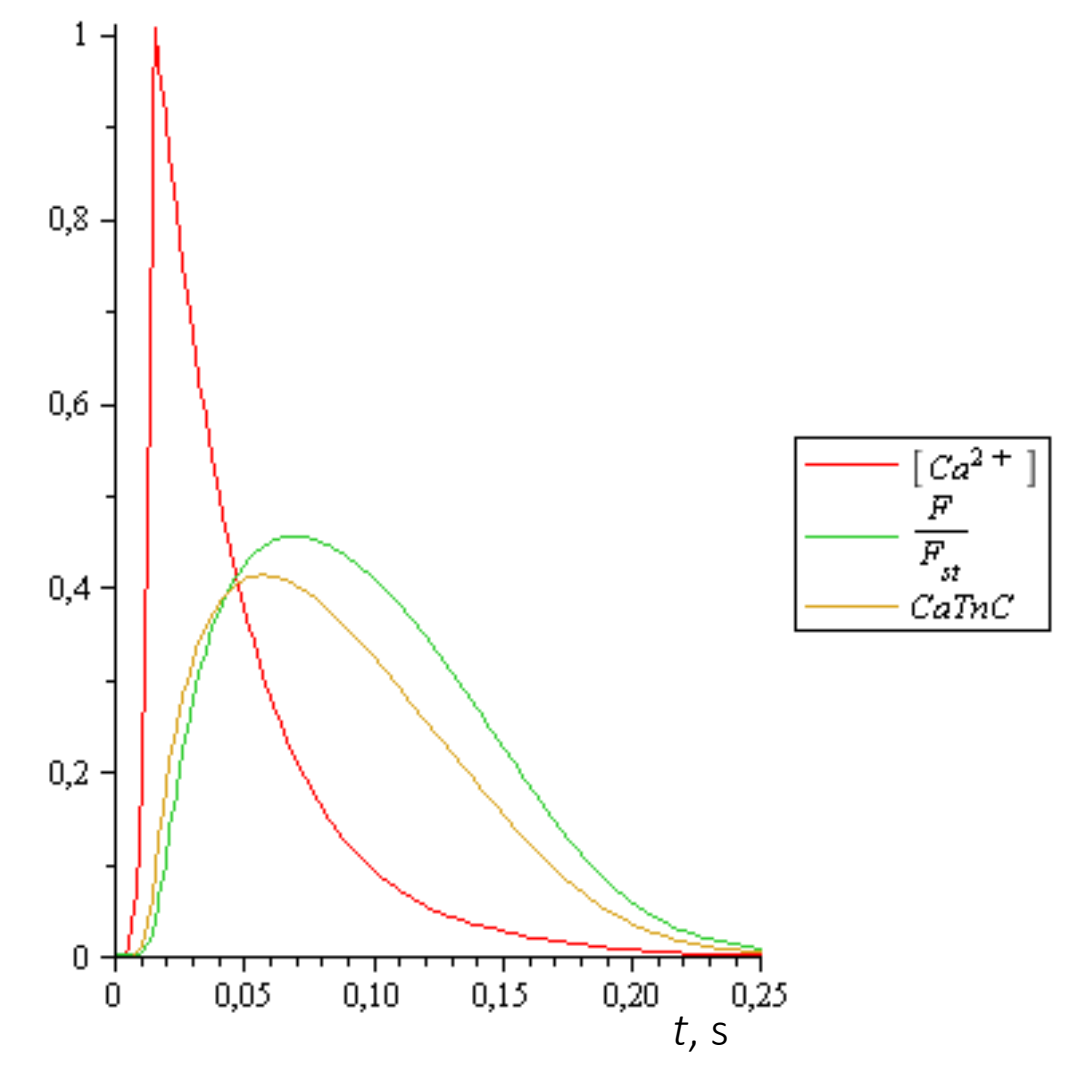


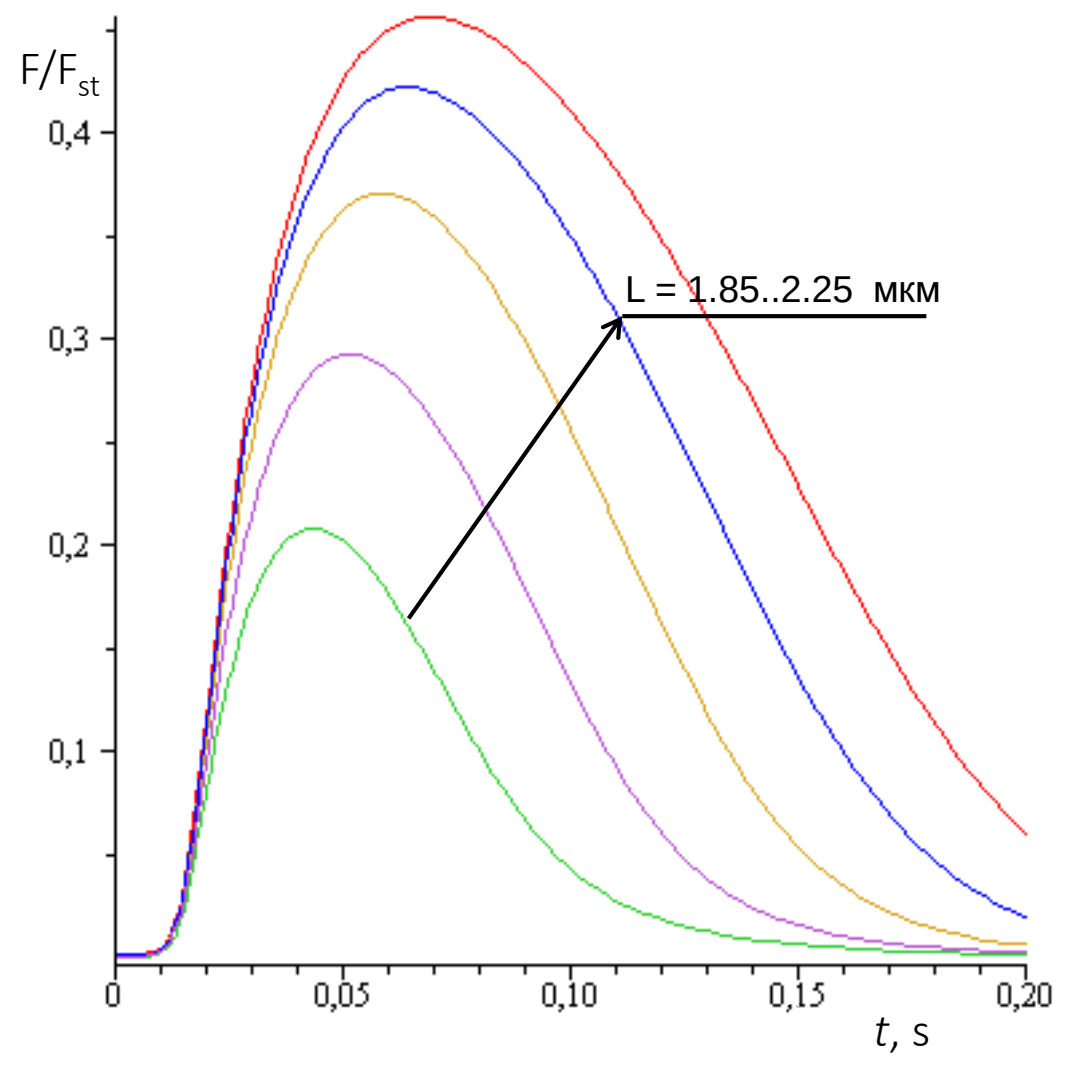
Continuous line:
–blebbistatine
Dashed line:
+blebbistatine

Sarcomere length:
2 μm or 2.2 μm

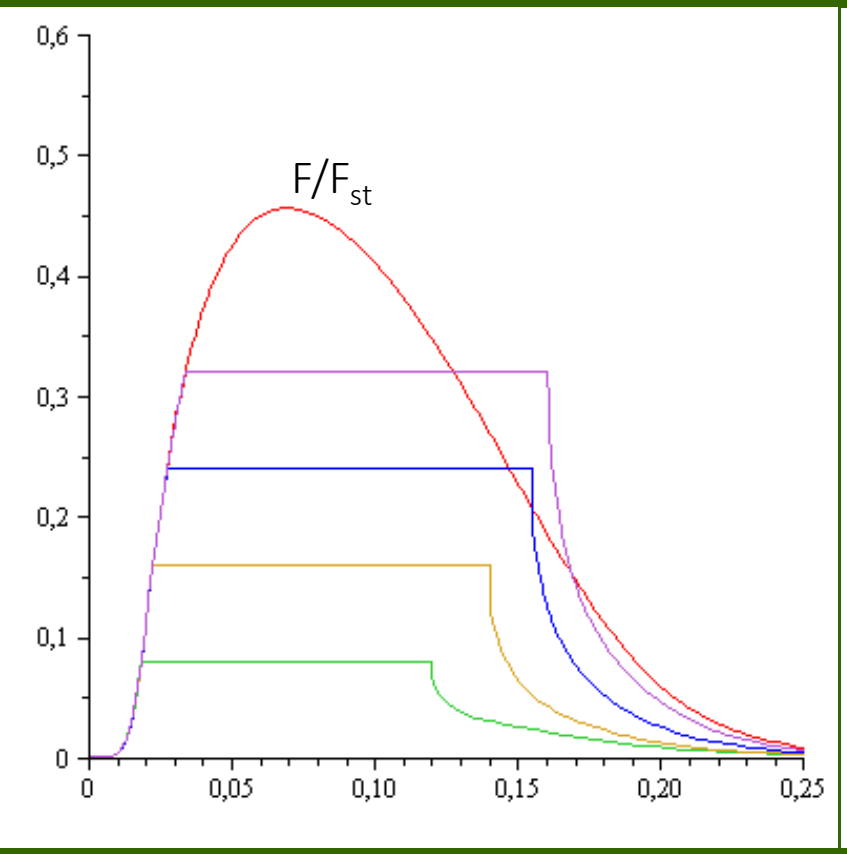


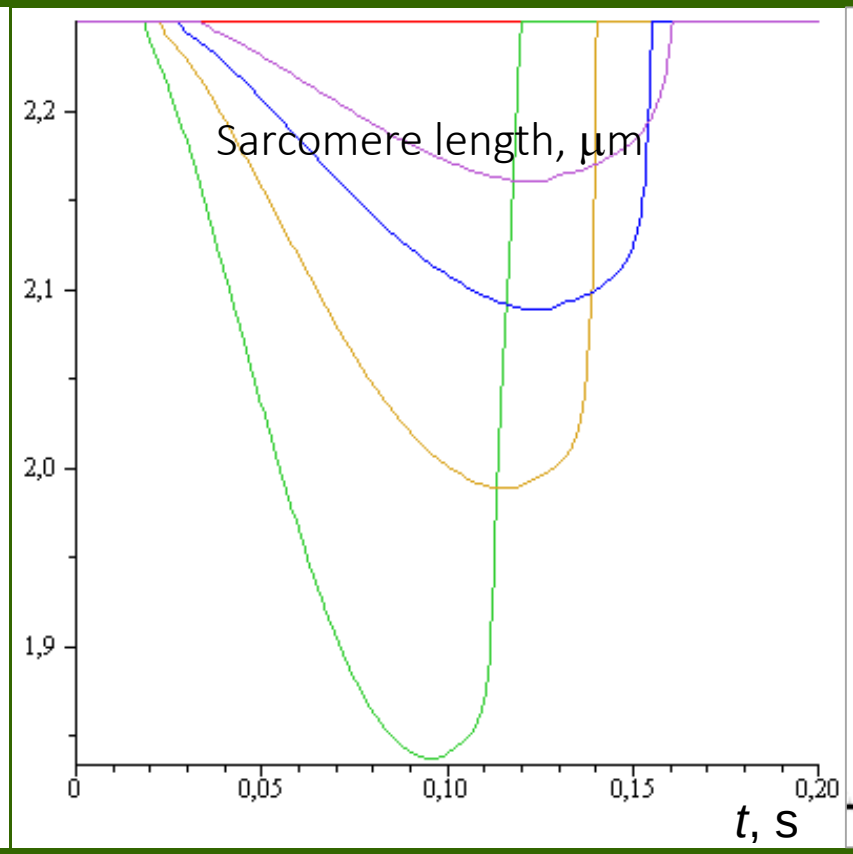
Time course of twitch contractions

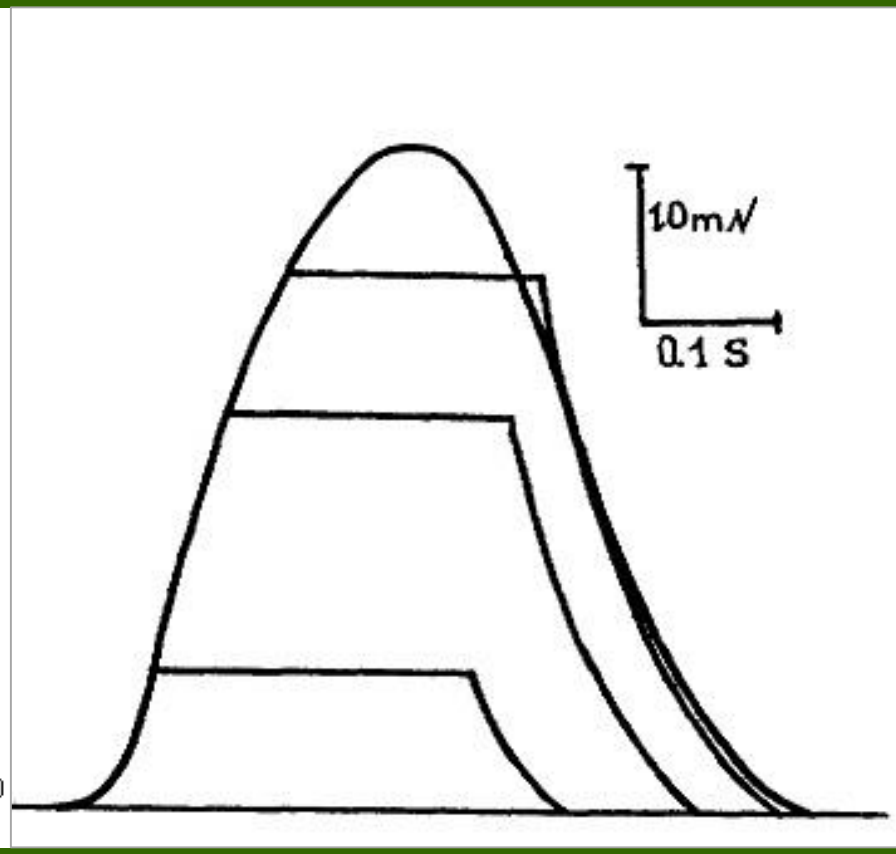




Length-dependent relaxation of cardiac muscle



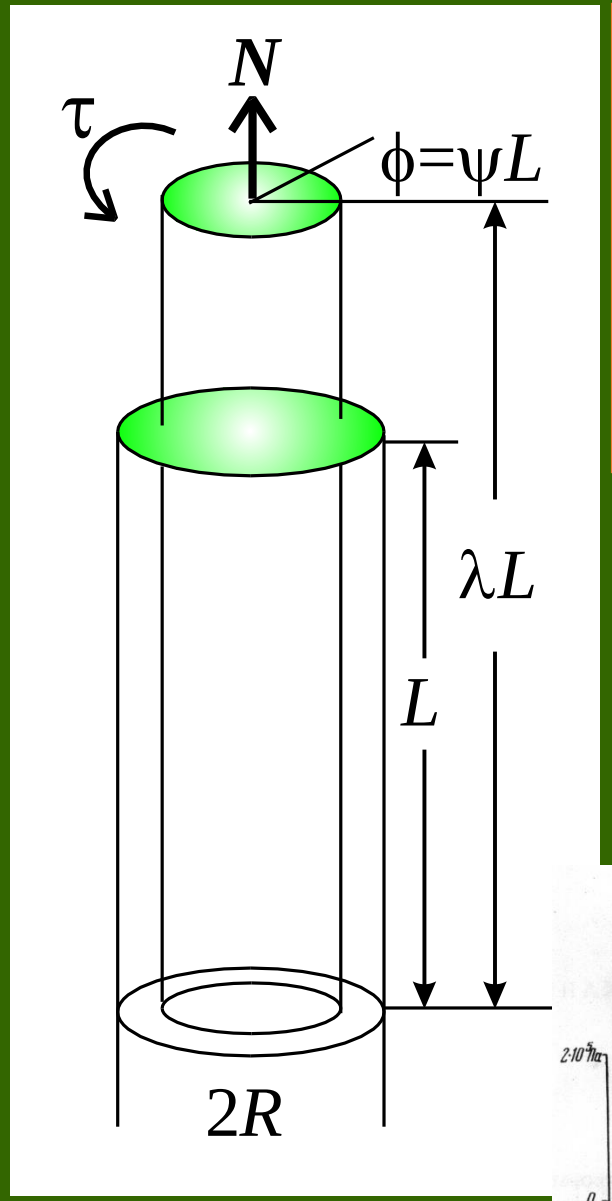




Summary

- A simple kinetic mechano-chemical model of muscle contraction is proposed. The model is based on the idea of J. Thorson and D.C. White (J. Physiol. 1983) that strain-dependent kinetics can be described as a dependence of the rate constants on the ensemble averaged strain of the myosin cross-bridges.
- The model describes a set of experimental data concerning muscle mechanics and energetics as well as basic details of calcium regulation including length-dependent activation (Frank-Starling law of the heart).
- The model can be used for simulation of mechanics of the heart beat and muscle work during locomotions.

Striated muscle is quazi-1D: active tension is directed along muscle fibres

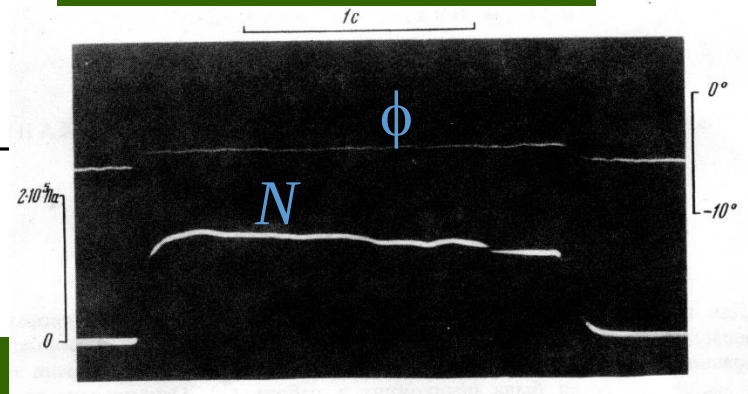


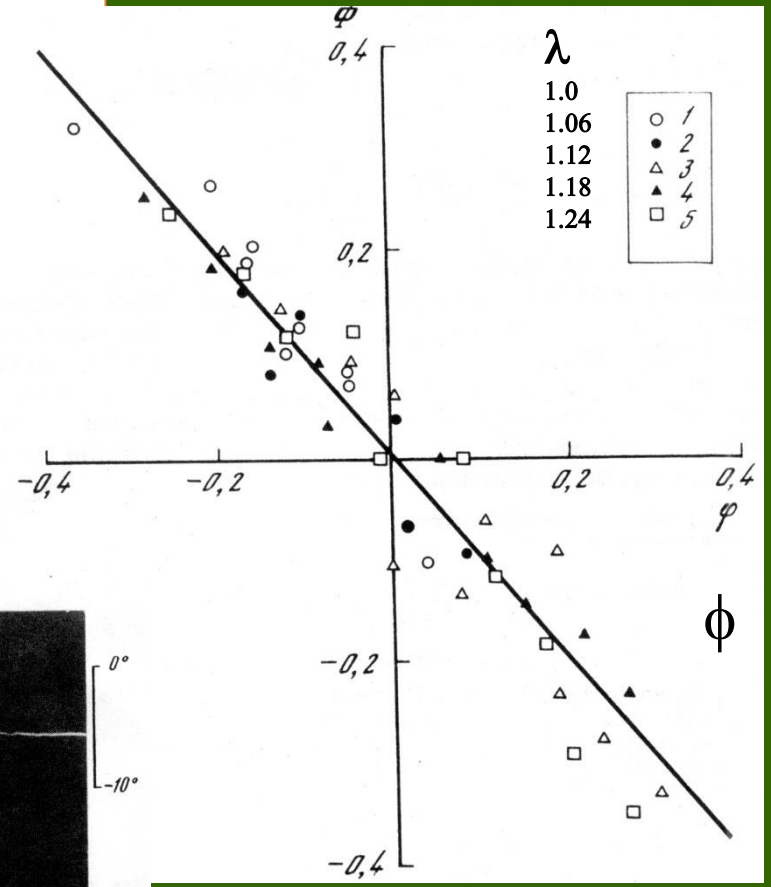
$$N = N_0 + \frac{\pi R^2}{\lambda} P + O(\psi R),$$

$$\tau = \tau_0 + \frac{\pi R^4}{2\lambda^3} P\psi + o(\psi R),$$

$$\lim_{\psi \to 0} \frac{\tau - \tau_0}{(N - N_0)\psi} = \frac{R^2}{2\lambda^2}$$

M. gracilis of the frog





(Bershitsky, Tsaturyan, 1981)