Computational Modeling of the Cardiovascular System

Modeling of Force Development in Myocytes

CVRTI

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Overview

- Modeling of Force in Skeletal Muscle
- Microscopic Anatomy
- Experimental Studies

Group work & pause

- Modeling of Cellular Force Development
- Cellular Automaton

Group work

Hill's Model of Muscle Contraction (1924/1938)

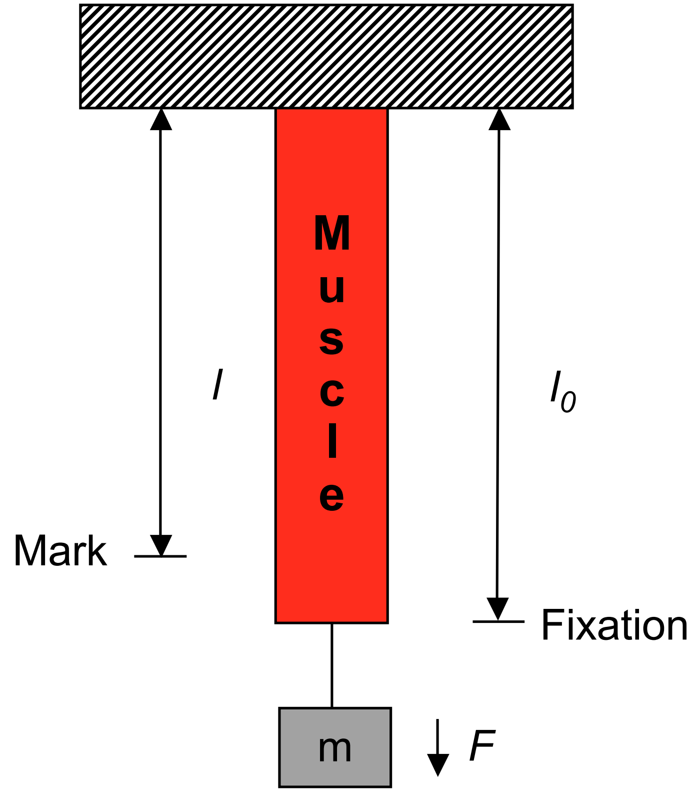
Measurement

- Muscle is fixed at length l_0
- Electrical stimulation

→ Isometric, Tetanus
with max. mechanical tension P_0

- Release of fixation
  Force F is applied with $F=mg$
  g: Gravitational constant
  m: Mass
- Measurement of time t, when muscle passes mark at length l
- Calculation of velocity

$$v = \frac{l_0 - l}{t}$$



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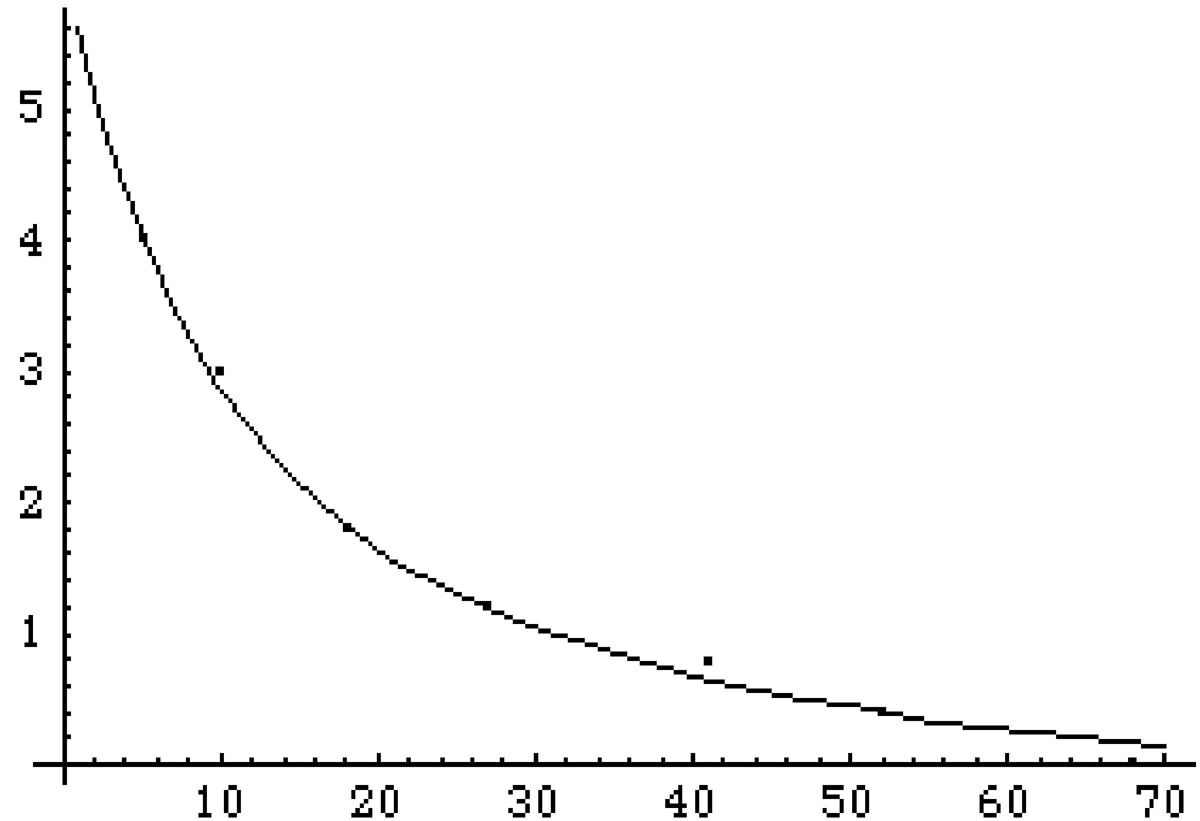
Relationship between Mass and Contraction Velocity

Contraction velocity

v [m/s]

Contraction of skeletal muscle from frog

• measured value



Mass [g]

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Modeling of Muscle Contraction

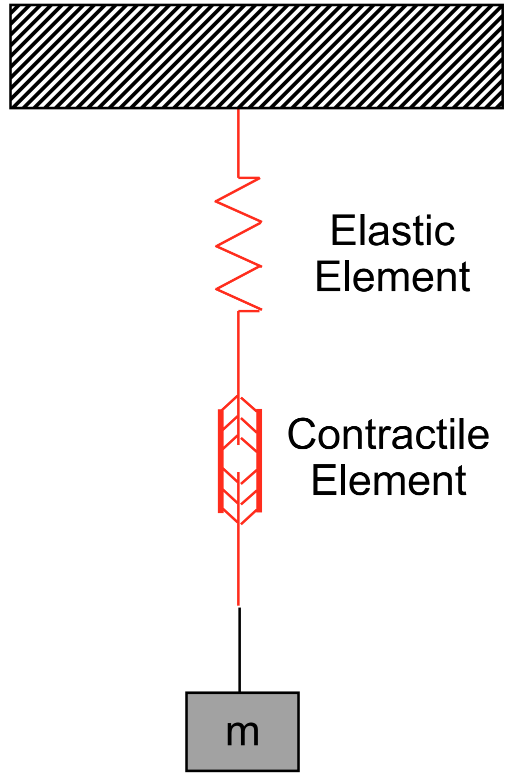
$$(v+b)(P+a)=b(P_0+a)$$

P: Tension of muscle $\left[\frac{N}{m^2}\right]$

P_0: Maximal tension of muscle $\left[\frac{N}{m^2}\right]$

v: Contraction velocity $\left[\frac{m}{s}\right]$

a,b: Constants depending on l_0, temperature, Concentration of Ca, …



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Model Extension: Hill's 3-Element Model (1970)

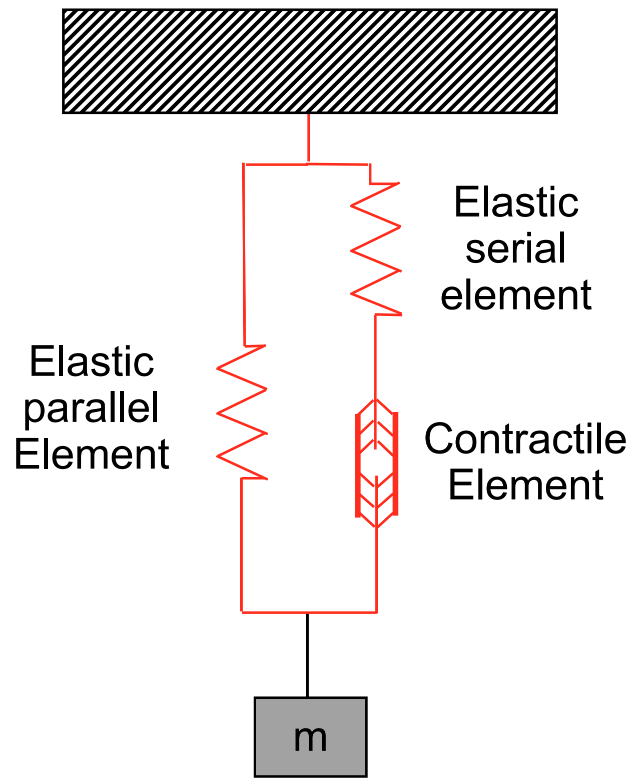
Limitations of Hill's Model

- only force-velocity relationship
- only tetanized muscle, no information of partial or relaxed muscle
- only serial elastic element
- only quick responses

Hills 3-Element Model

- inclusion of parallel elastic element

Further extensions necessary for realistic modeling of cardiac muscles!



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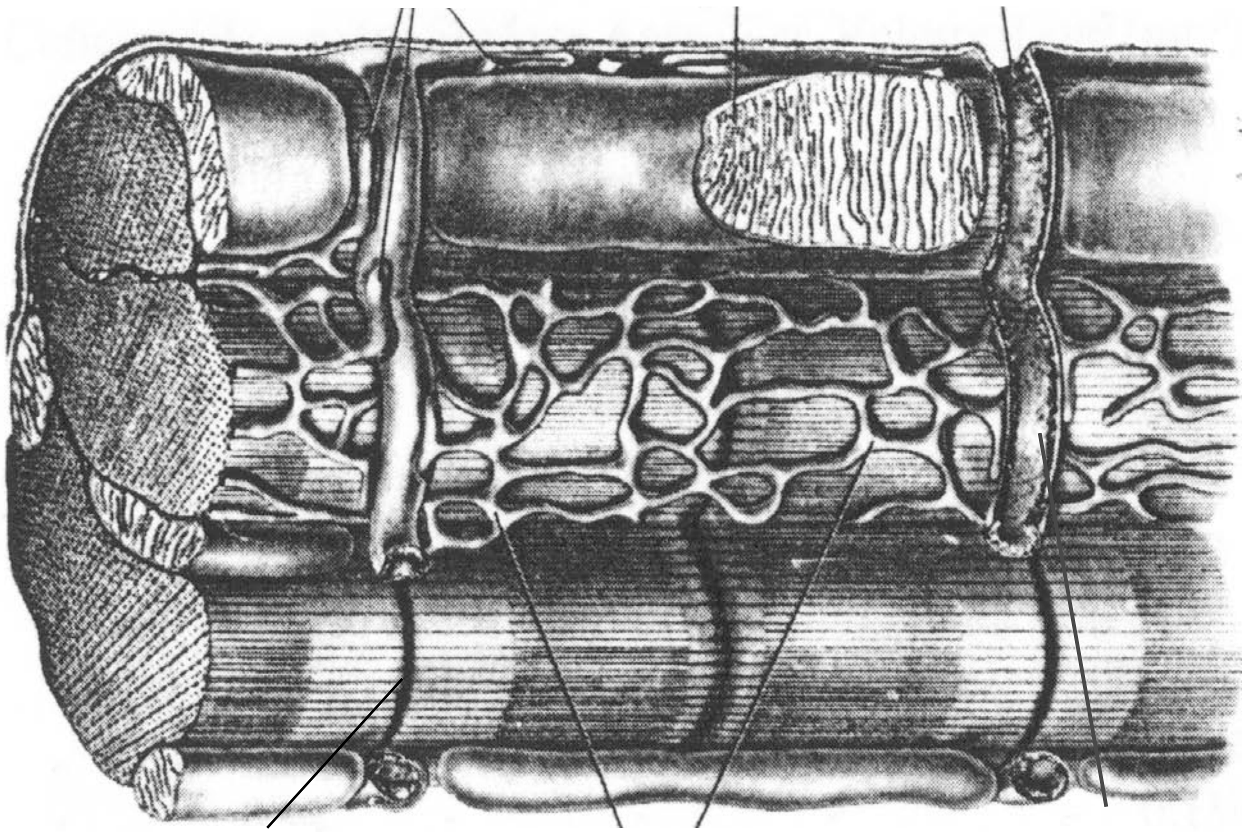
Sarcomeres in Cardiac Muscle (Fawcett & McNutt 1969)



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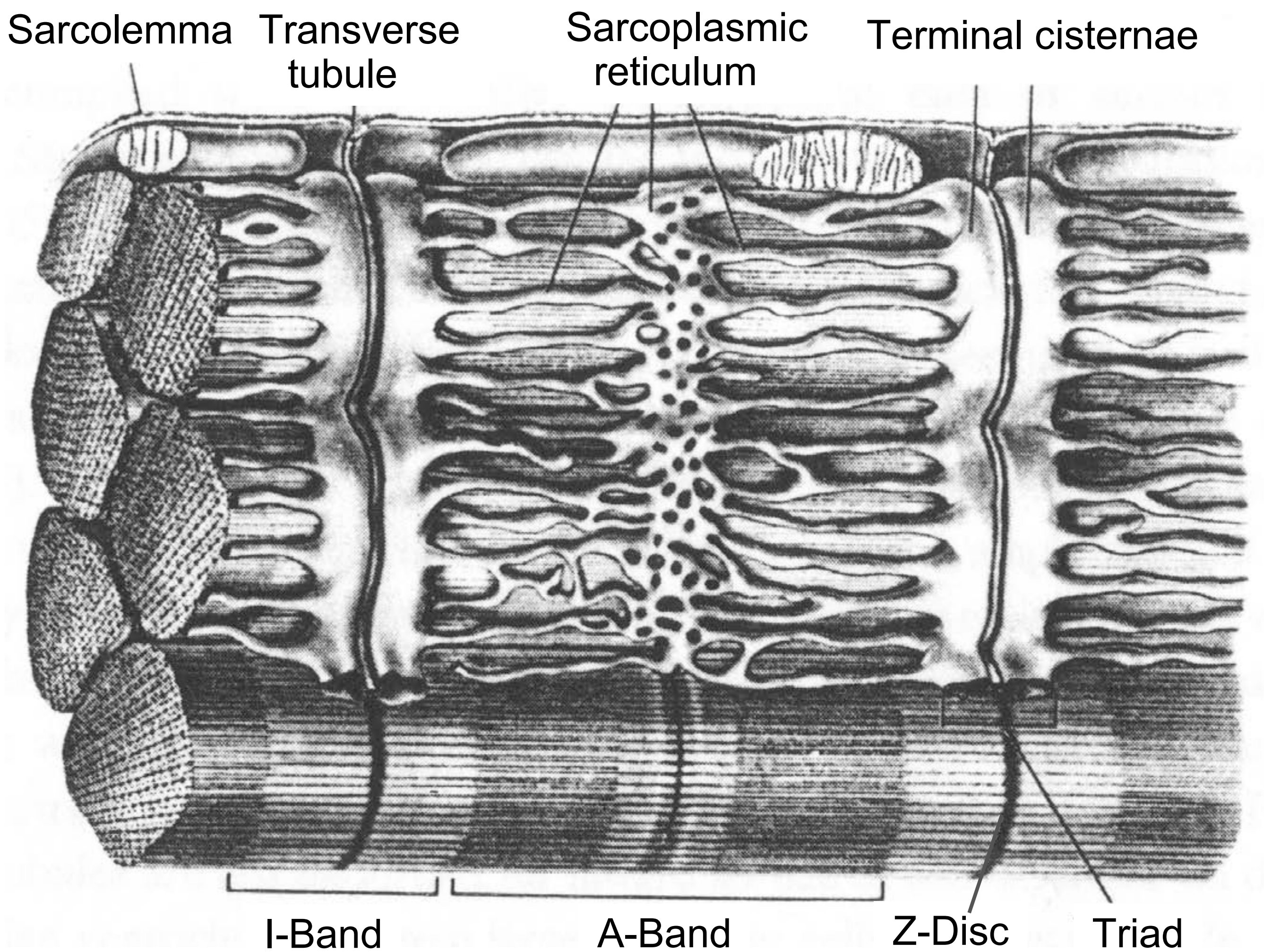
Sarcomeres in Skeletal Muscle (Fawcett & McNutt 1969)



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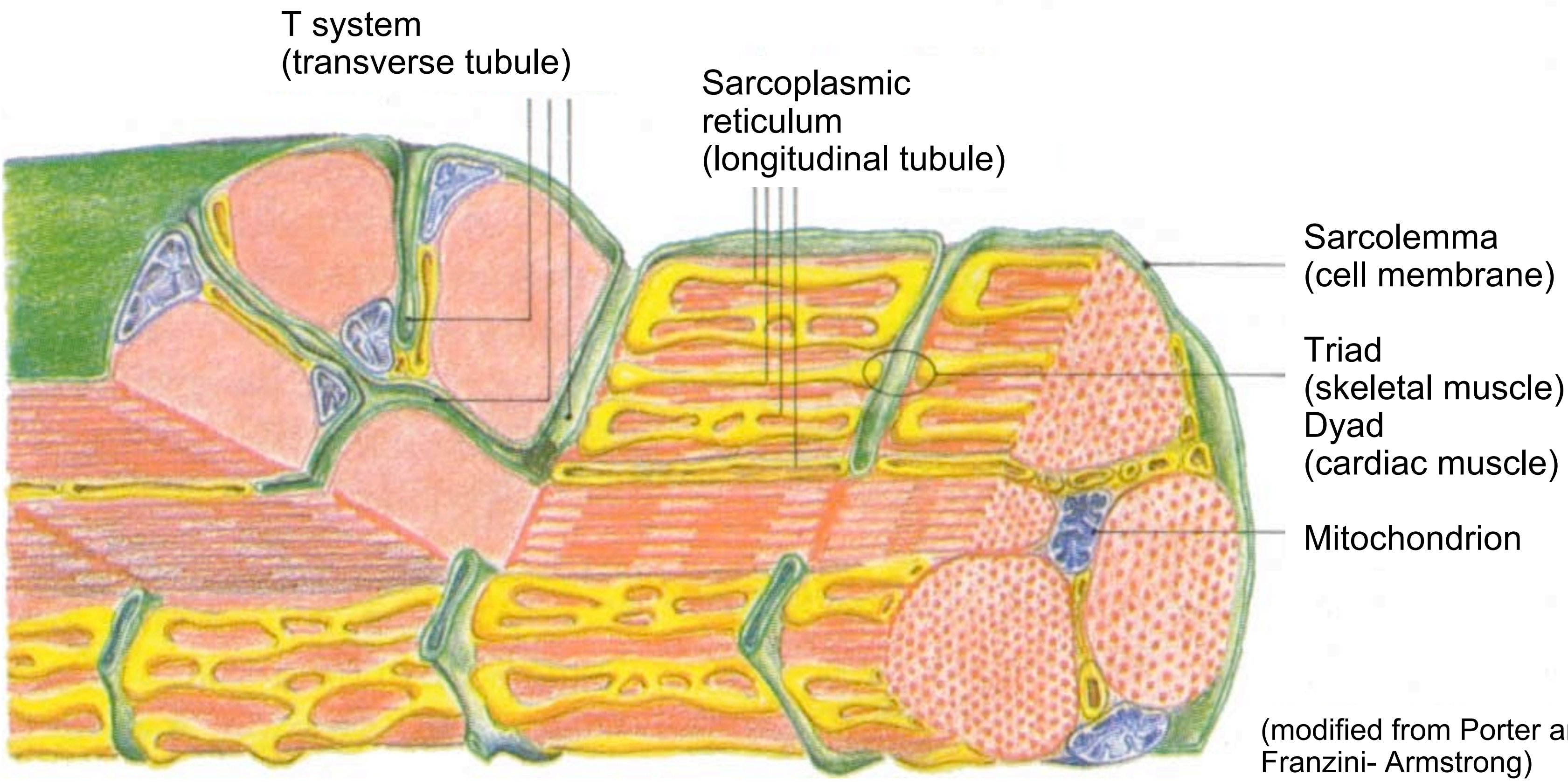
Sarcotubular System



(modified from Porter and Franzini- Armstrong)

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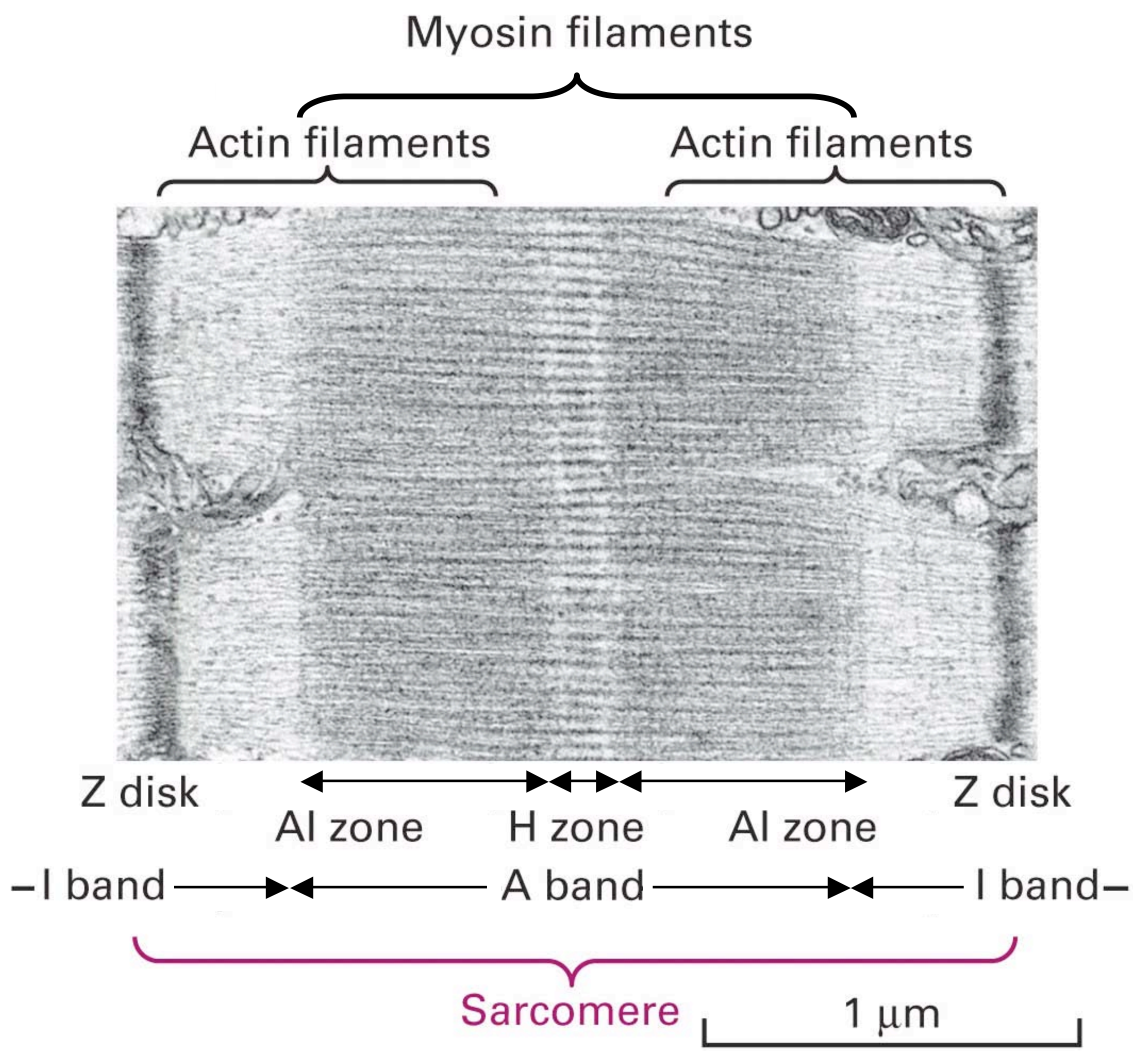
Electron Micrograph of Sarcomere in Striated Muscle

A - anisotrop
I - isotrop



(Modified from Lodish et al., Molecular Cell Biology, 2004)

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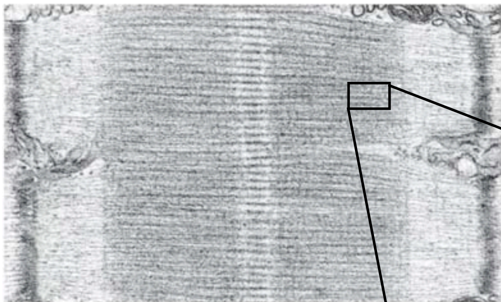
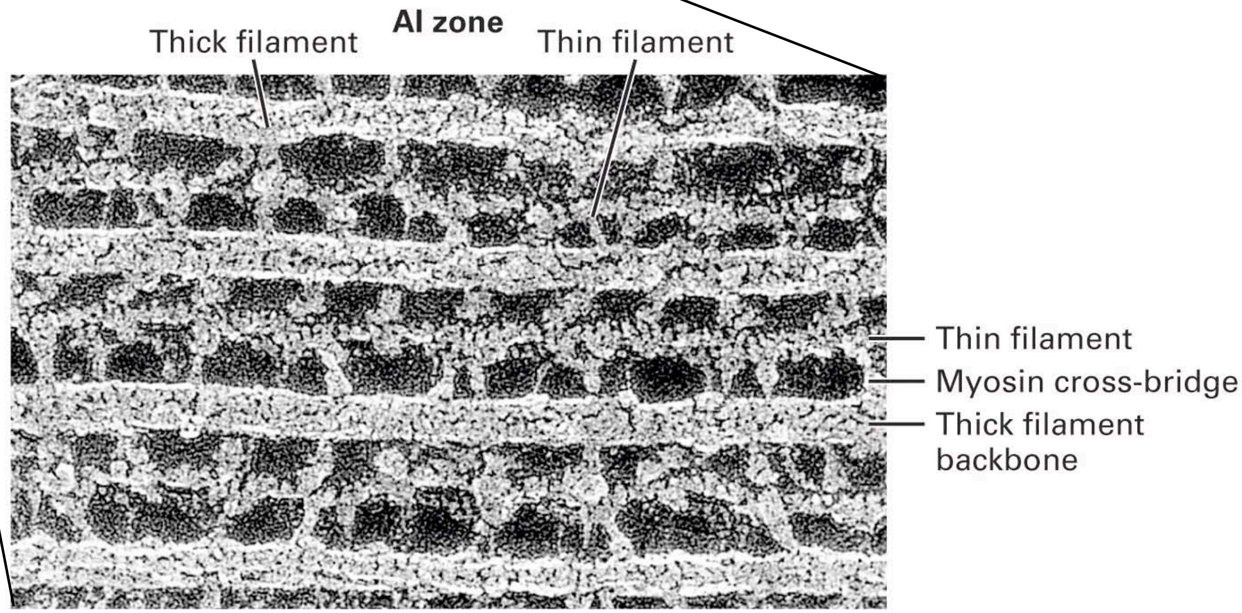
Myofilaments

(Modified from Lodish et al., Molecular Cell Biology, 2004)





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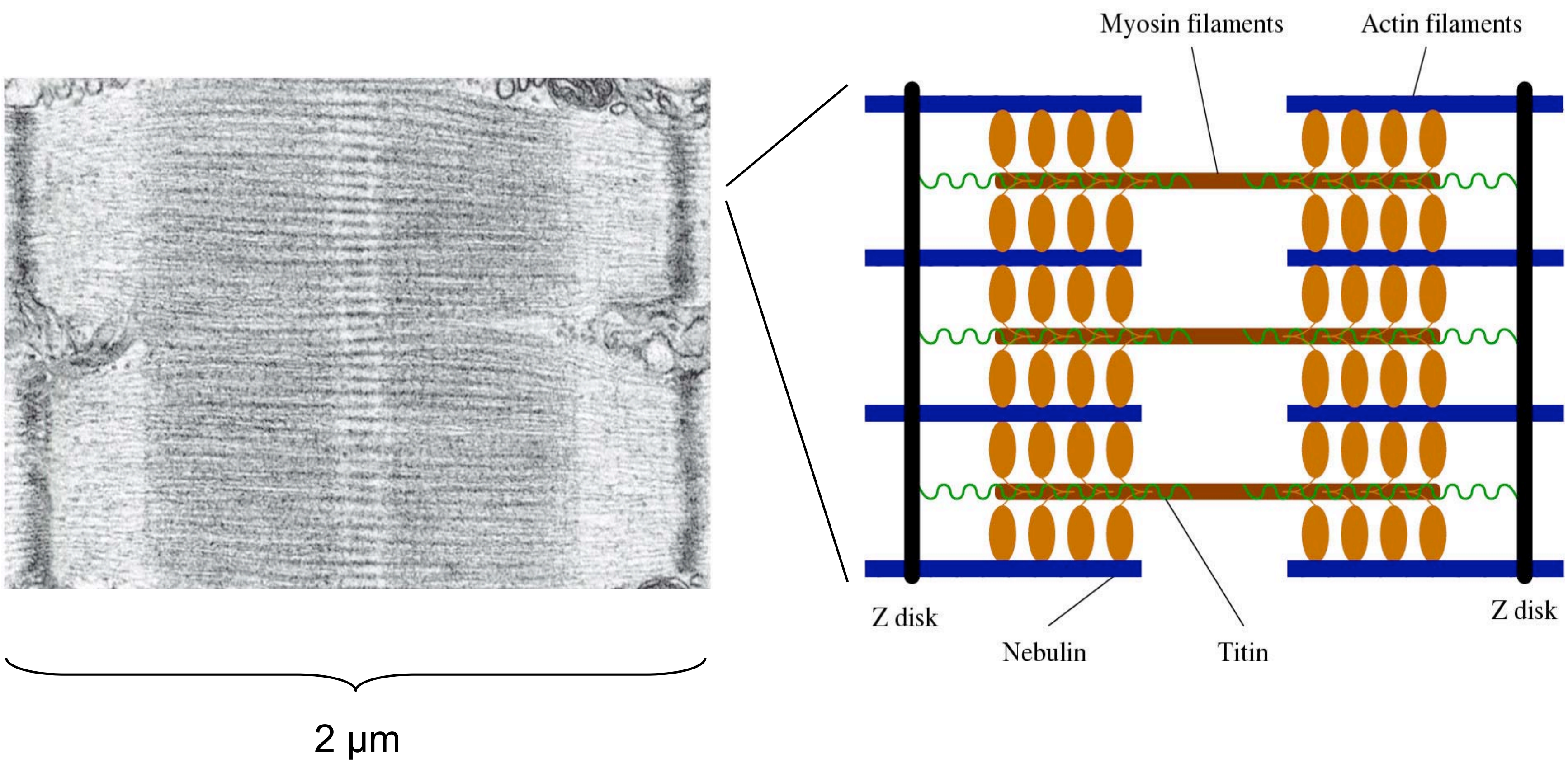
Proteins of Sarcomere



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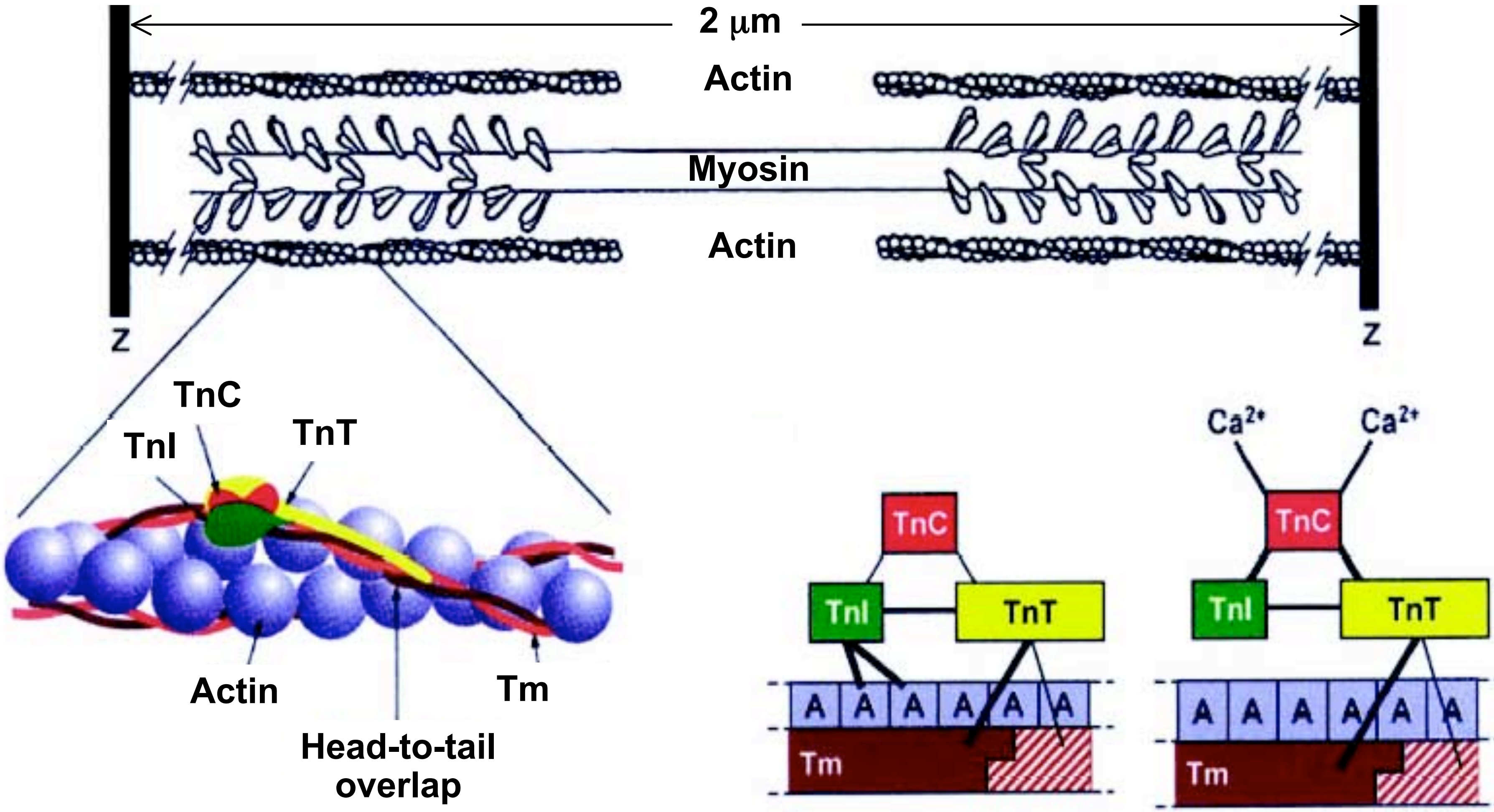
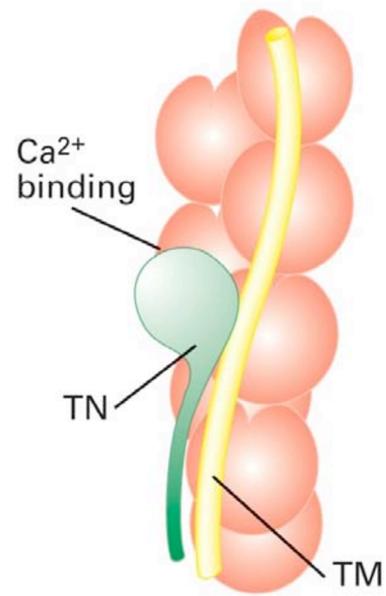
Involved Proteins and Regulation of Force

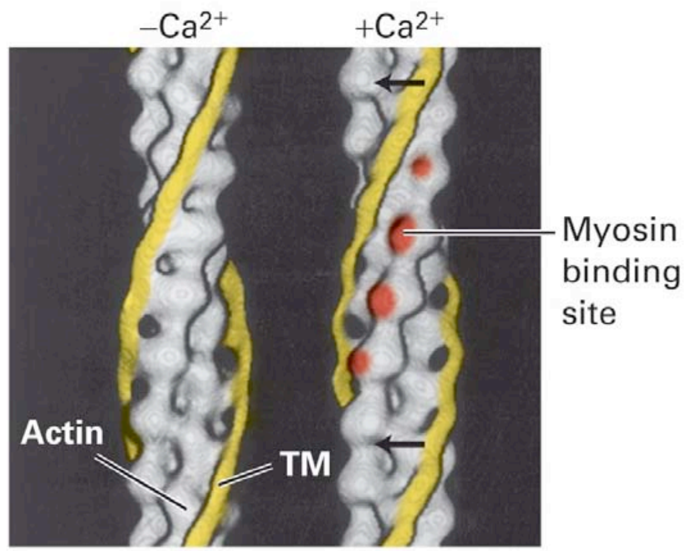


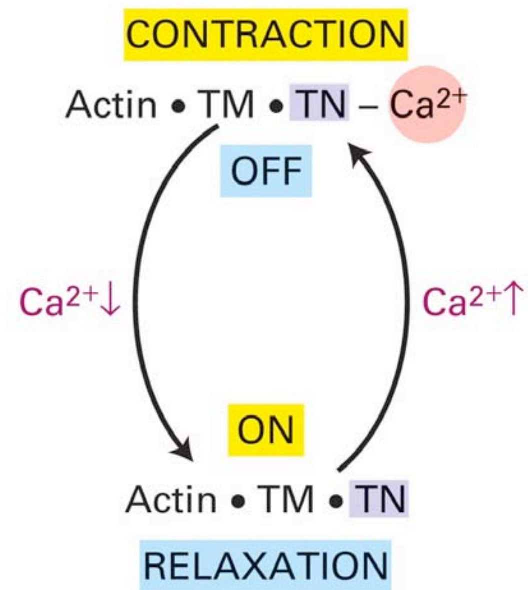
Tn: Troponin Tm: Tropomyosin A: Actin Z: Z-Disk

(adapted from Gordon et al. 2001)

Regulation of Force







Tn: Troponin   Tm: Tropomyosin

(Modified from Lodish et al., Molecular Cell Biology, 2004)

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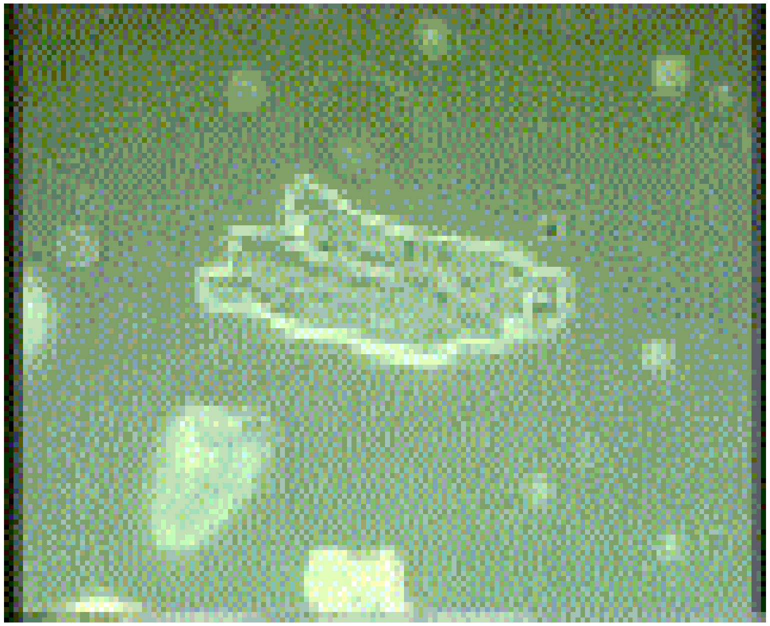
Contraction of Myocyte by Electrical Stimulation



Microscopic imaging of isolated ventricular cell from guinea pig
http://www-ang.kfunigraz.ac.at/˜schaffer

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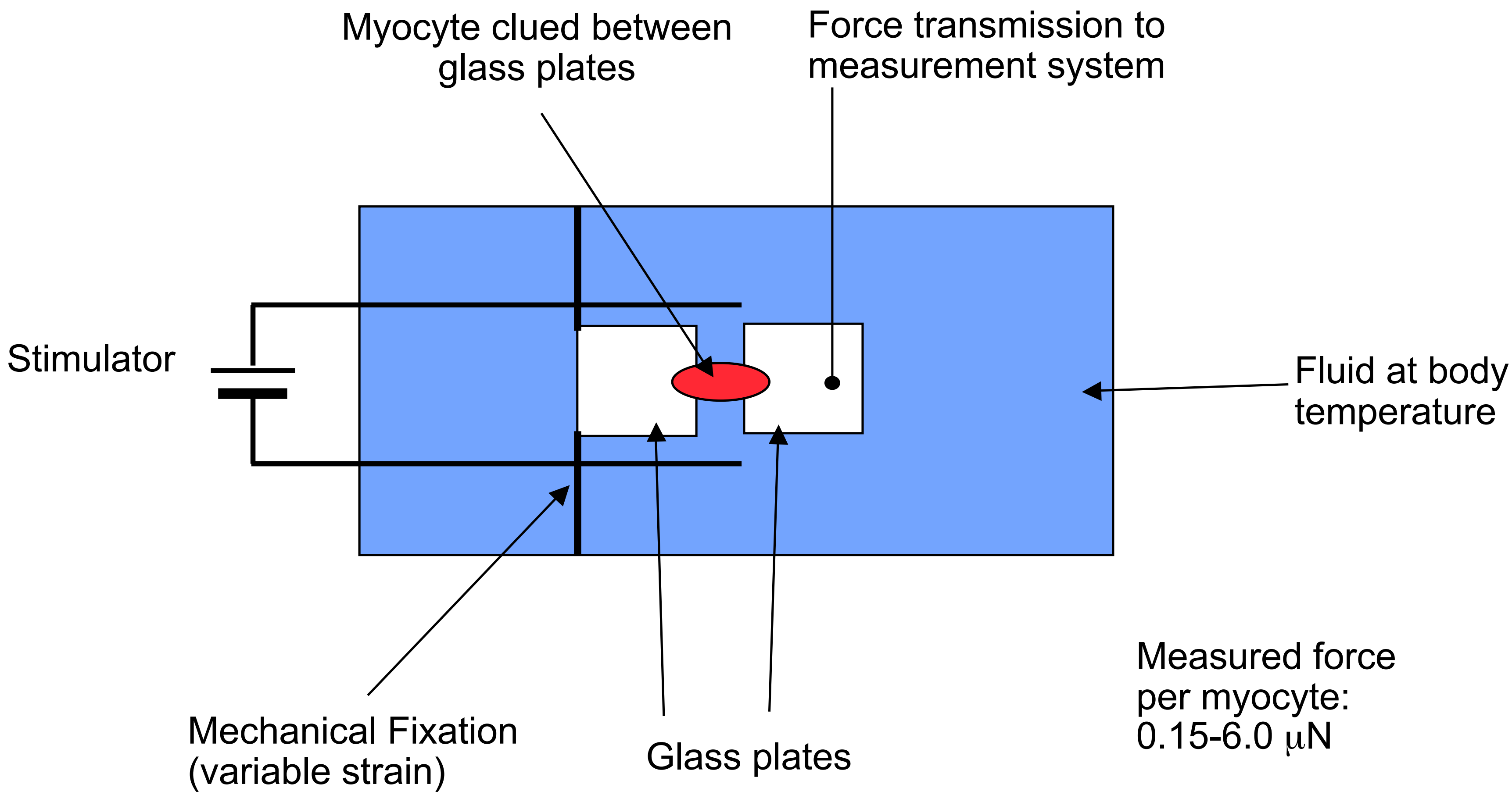
Measurement of Force Development in Single Cell



Measured force per myocyte: 0.15-6.0 μN

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Measurement Techniques

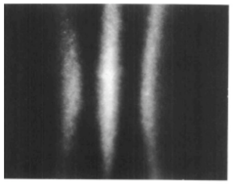
Permeabilization of sarcolemma/**skinning** of myocytes by saponin or Triton X-100

Direct control of intracellular concentrations of ions, drugs etc.

$$\left[Ca^{2+}\right]_i = \left[Ca^{2+}\right]_o$$

Transillumination of myocyte or muscle strands with laser light

Diffraction pattern ~ sarcomere length



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Sarcomere Length Measurement via Laser Diffraction

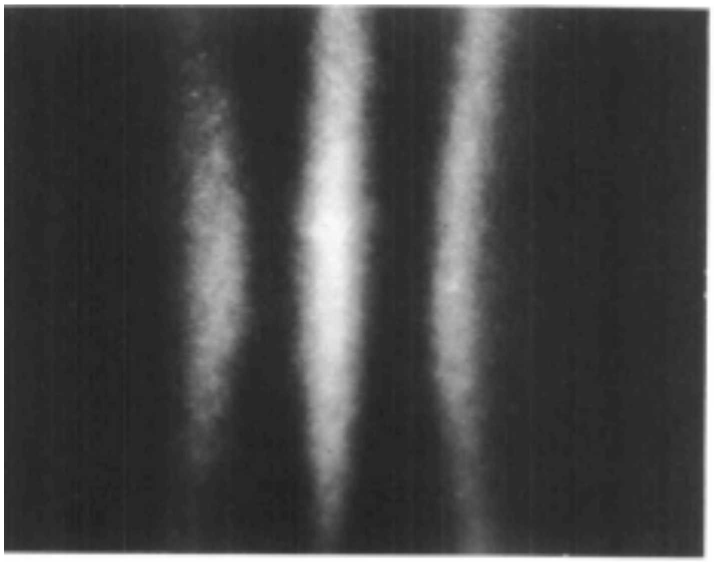

FIGURE 2. *Diffraction spectra obtained from a thin, right-ventricular rat trabecula. The two first-order diffracted lines (±1) were symmetrically spaced on either side of the central bright line of nondiffracted light (zero order). The distance between the zero-order line and the first-order lines are inversely related to sarcomere length.*

(Figures from Lecarpentier et al., Real-Time Kinetics of Sarcomere Relaxation by Laser Diffraction, AJP, 1985)

More information:
http://muscle.ucsd.edu/musintro/diffraction.shtml

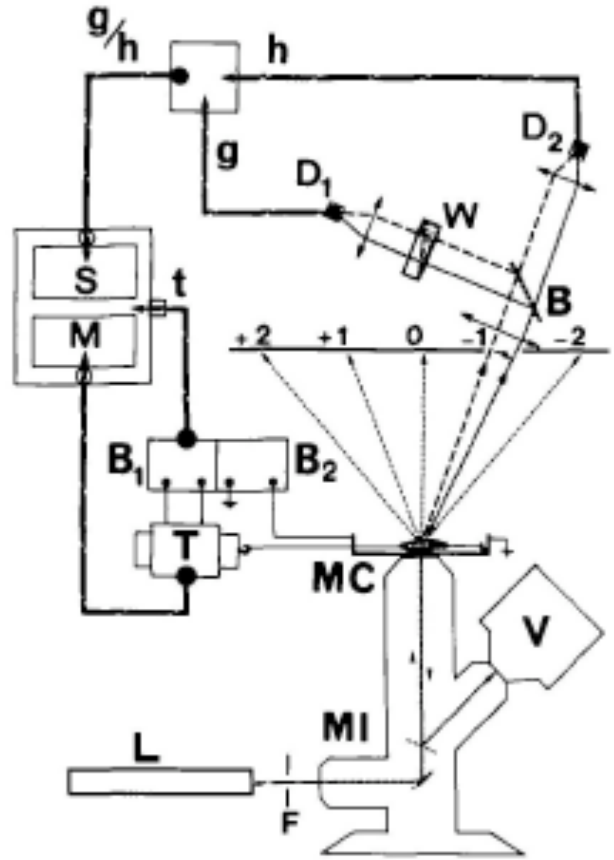

FIGURE 1. *Experimental set-up. Abbreviations are: L, laser; MI, microscope; V, video camera; MC, muscle chamber; B, beam splitter; W, densitometric wedge; F, split; D_1 and D_2, diodes; g and h, optical signals electronically converted by D_1 and D_2 respectively; g/h, signal function of sarcomere length; T, electromagnetic transducer; B_1, stimulator; M, muscle tension and shortening curves vs. time (t); S, instantaneous sarcomere length curve vs. time (t).*

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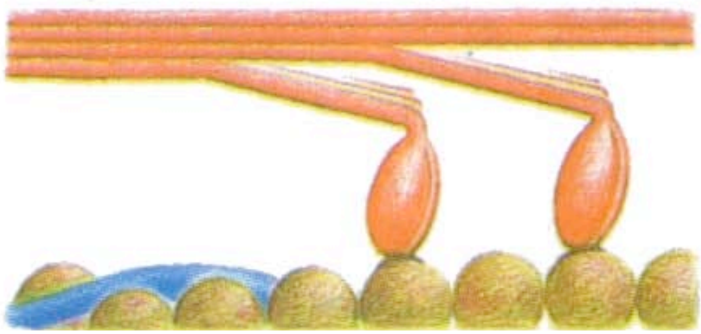
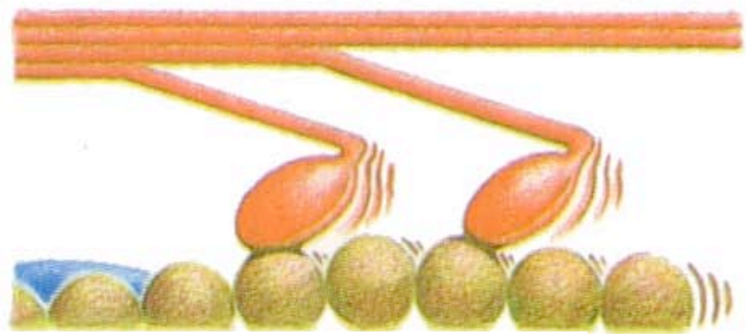
Force Development: Sliding Filament Theory

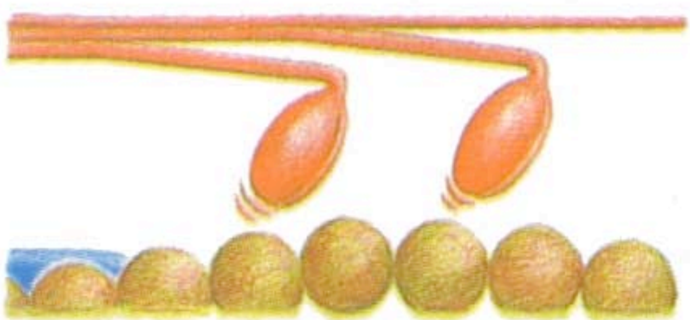
Cellular force development by sliding myofilaments (Huxley 1957), i.e. actin and myosin, located in sarcomere



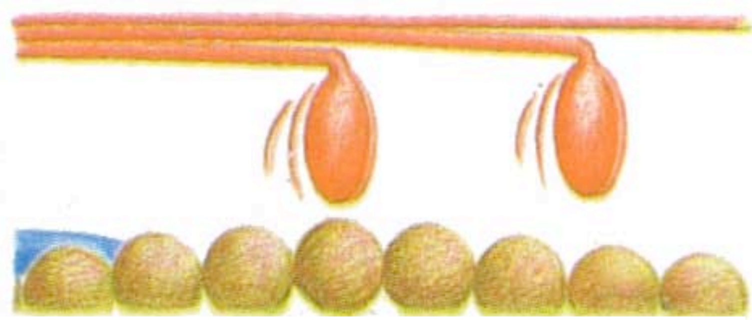
Attachment of myosin heads to actin



Filament sliding



Detachment



Spanning of myosin heads

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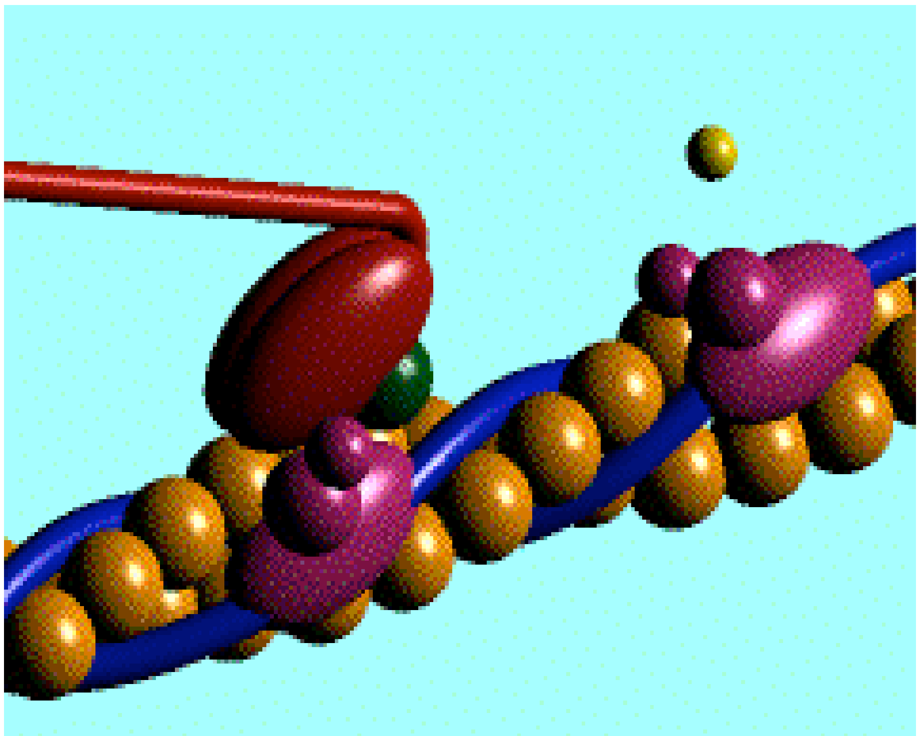
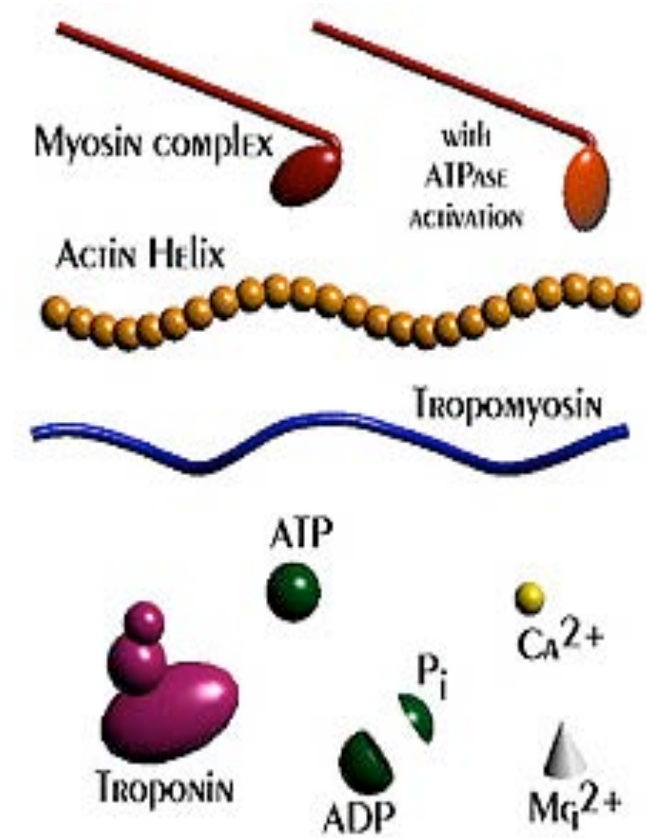
Force Development: Sliding Filament Theory





http://www.sci.sdsu.edu/movies/actin_myosin.html

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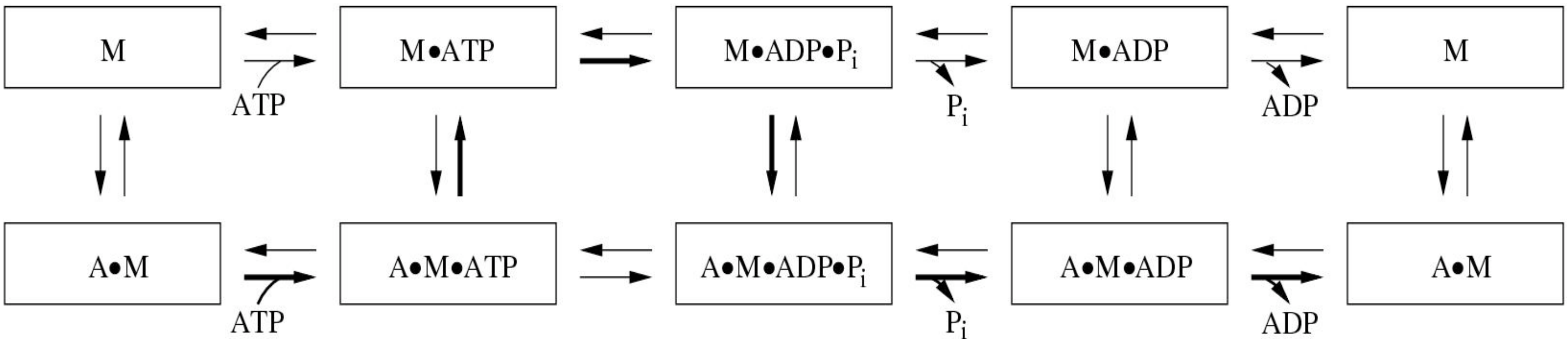
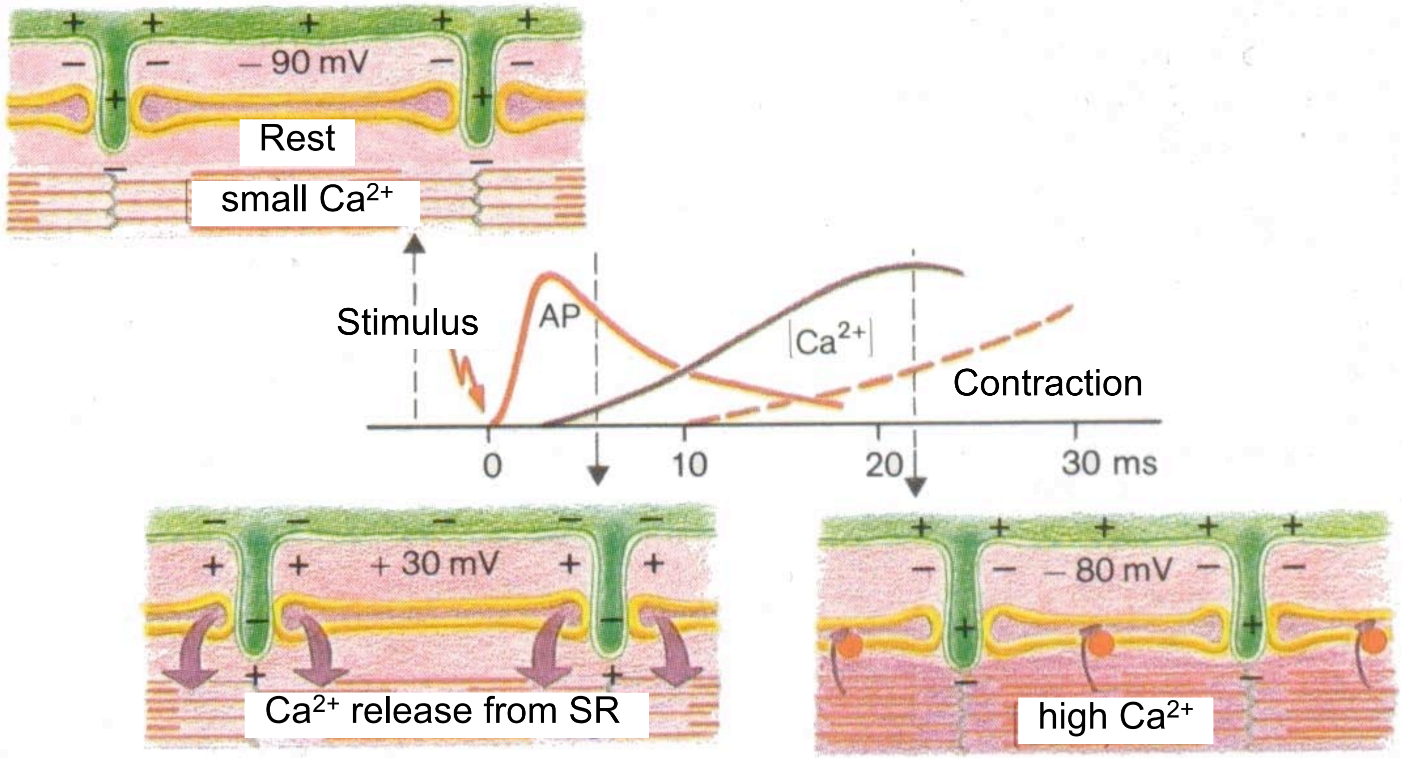
Actin-Myosin Interaction



A	Actin	**M**	Myosin
ADP	Adenosine diphosphate	**ATP**	Adenosine triphosphate
P_i	Phosphate		

(modified from Bers, Excitation-Contraction Coupling and Cardiac Contractile Force, 1991)

Coupling of Electrophysiology and Force Development



High concentration of intracellular Ca^{2+} → Force development Contraction of sarcomere/cell

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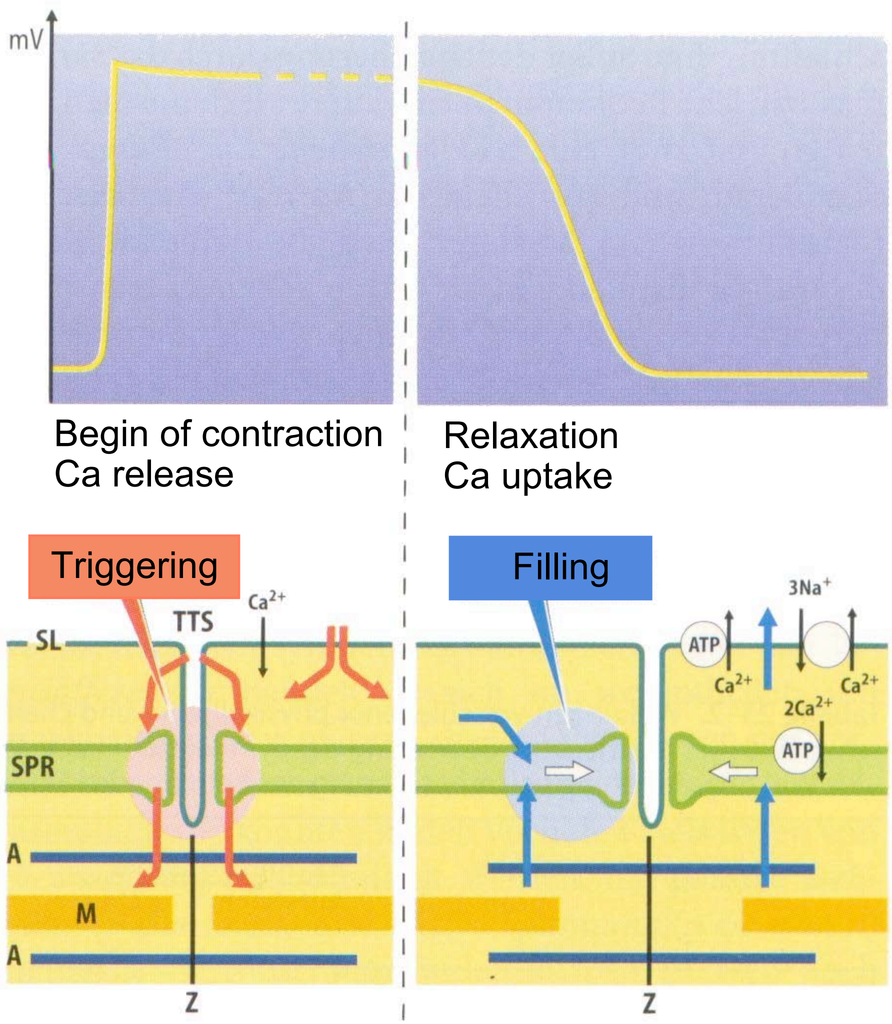
Phases of Force Development



A: Actin

M: Myosin

Z: Z-Disc

SL: Sarcolemma

TTS: Transverse tubule

SPR: Sarcoplasmic Reticulum

Ca^{2+} Release

Ca^{2+} Uptake

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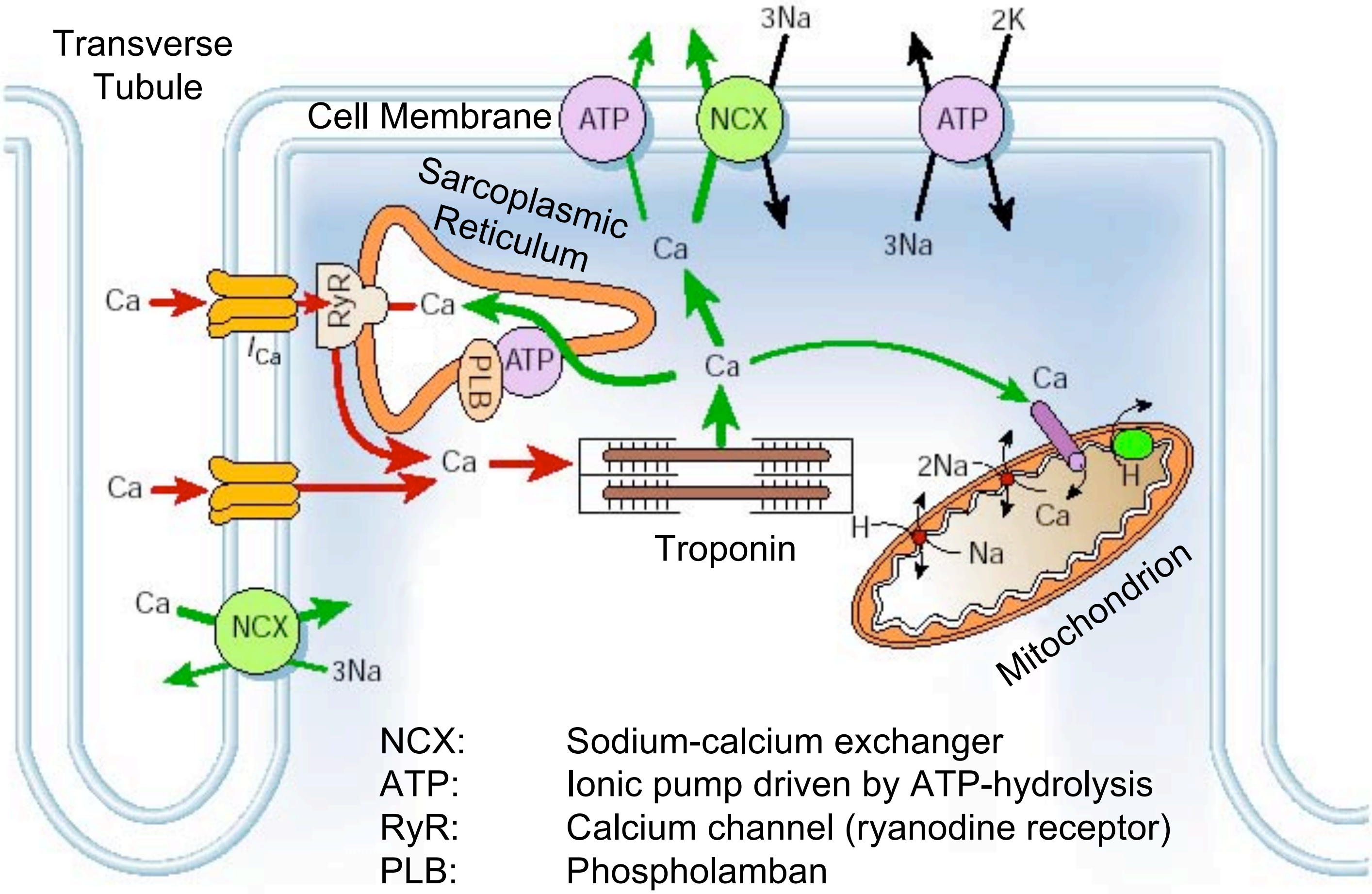
Calcium Handling and EC-Coupling



NCX:	Sodium-calcium exchanger
ATP:	Ionic pump driven by ATP-hydrolysis
RyR:	Calcium channel (ryanodine receptor)
PLB:	Phospholamban

(modified from Bers, Nature Insight Review Articles, 2002)

Group Work

Which states are important for a detailed modeling of force in myocytes?

Which states can be neglected for an efficient model?

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Models of Force Development

1938 → today

• Hill	Skeletal muscle	Frog
• Huxley	Skeletal muscle	-
• Wong	Cardiac muscle	-
• Panerai	Papillary muscle	Mammalian
• Peterson, Hunter, Berman	Papillary muscle	Rabbit
• Landesberg, Sideman	Skinned cardiac myocytes	-
• Hunter, Nash, Sands	Cardiac Muscle	Mammalian
• Noble, Varghese, Kohl, Noble	Ventricular Muscle	Guinea pig
• Rice, Winslow, Hunter	Papillary muscle	Guinea pig
• Rice, Jafri, Winslow	Cardiac muscle	Ferret
• Glänzel, Sachse, Seemann	Ventricular myocytes	Human

…

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Mathematical Modeling of Myofilament Sliding (Huxley)

$$A + M \overset{f}{\underset{g}{\Leftrightarrow}} A - M$$

$A + M$: Number of myosins not bound to actin

$A - M$: Number of myosins bound to actin

f,g: Rate constants for binding and unbinding

$$\frac{d\,[A-M]}{dt} = f\left(Max[A-M] - [A-M]\right) - g[A-M]$$

$Max[A-M]$: Maximal number of myosin proteins bound to actin filament

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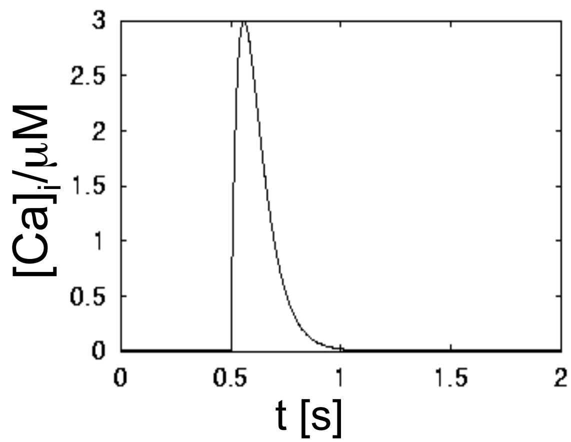
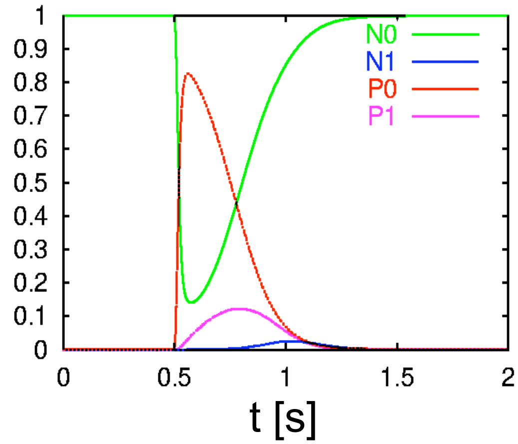
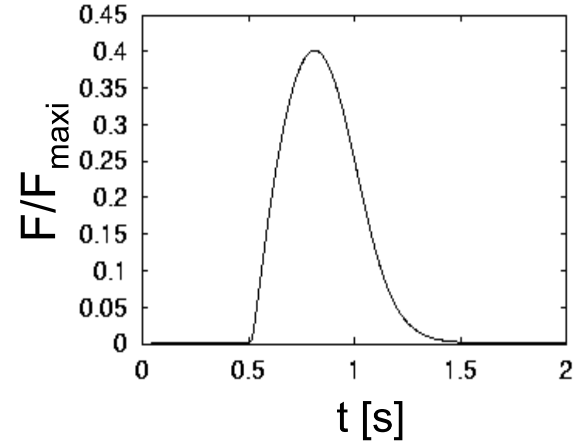
Modeling of Cellular Force Development







Intracellular concentration of calcium

Calculated with electrophysiological cell models

System of coupled ordinary differential equations

Processes in myofilaments

State of troponins, tropomyosins and cross bridges

System of coupled ordinary differential equations

Force Development

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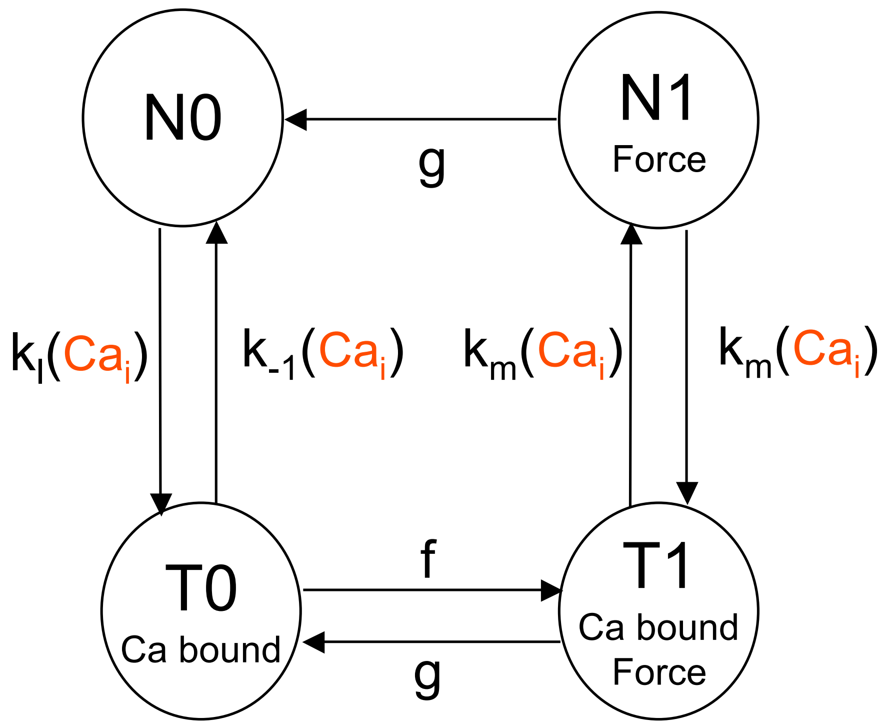
4-State Model of Force Development: State Diagram



Description by set of 1st order ODEs

- Transfer of states N0, N1, T0, and T1 is dependent of rate coefficients
- Rate coefficients are partly function of intracellular calcium $[Ca^{2+}]_i$

(Model 1 of Rice 1999 et al./ Landesberg et al.1994)

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4-State Model of Force Development

Several states contribute to force development:

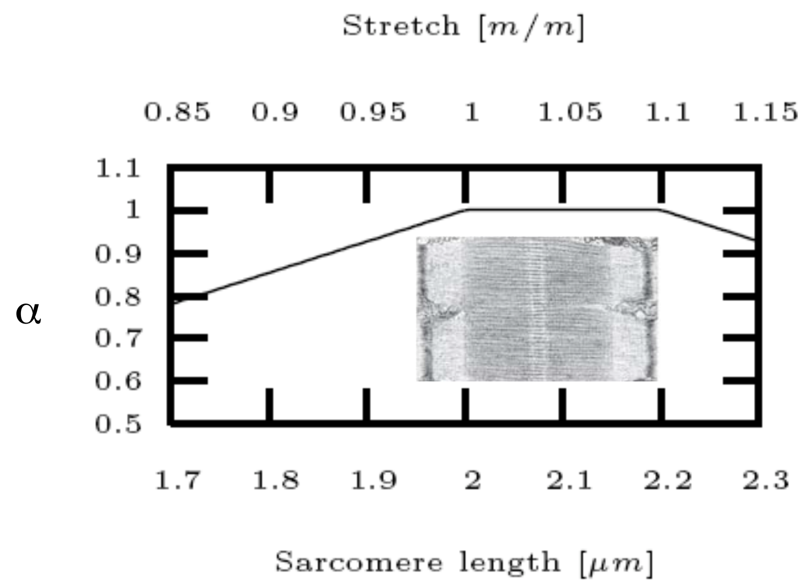
$$F = \alpha \frac{T1 + N1}{F_{max}}$$

F : Normalized force [N/N]

F_{max} : Maximal simulated force

α : Myofilament overlap function

Force is dependent on overlap of actin and myosin filaments.



Frank-Starling Mechanism

Force ~ initial length

Diastolic volume ~ cardiac output

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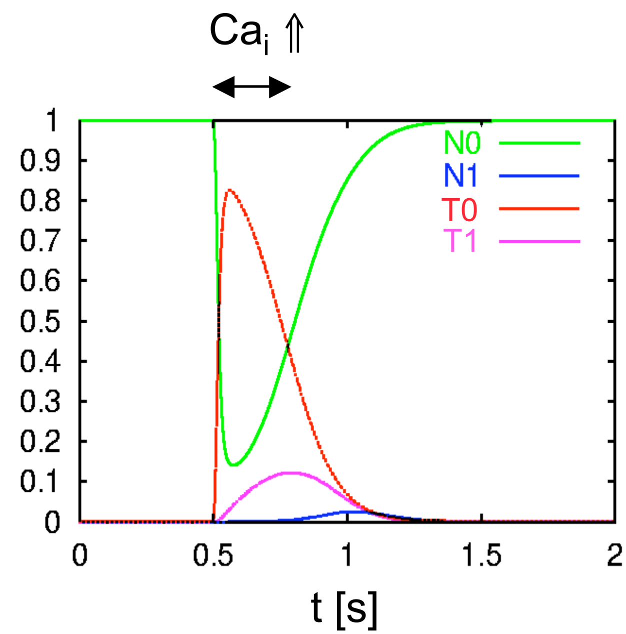
4-State Model of Force Development: Matrix Notation

$$\frac{\partial}{\partial t}\begin{pmatrix} N_0 \\ T_0 \\ T_1 \\ N_1 \end{pmatrix} = \begin{pmatrix} -K_l & k_l & 0 & g_0 + g_1 V \\ K_l & -f - k_l & g_0 + g_1 V & 0 \\ 0 & f & -g_0 - g_1 V - k_{-l} & K_l \\ 0 & 0 & k_{-l} & -g_0 - g_1 V - K_l \end{pmatrix}\begin{pmatrix} N_0 \\ T_0 \\ T_1 \\ N_1 \end{pmatrix}$$



Rate constants: $K_l, k_l, f, g_0, g_1, k_{-l}$ und V

States of Troponin	Calcium	Cross bridges
N_0	unbound	weak
T_0	bound	weak
T_1	bound	strong
N_1	unbound	strong

Numerical solution e.g. with Euler- and Runge-Kutta-methods

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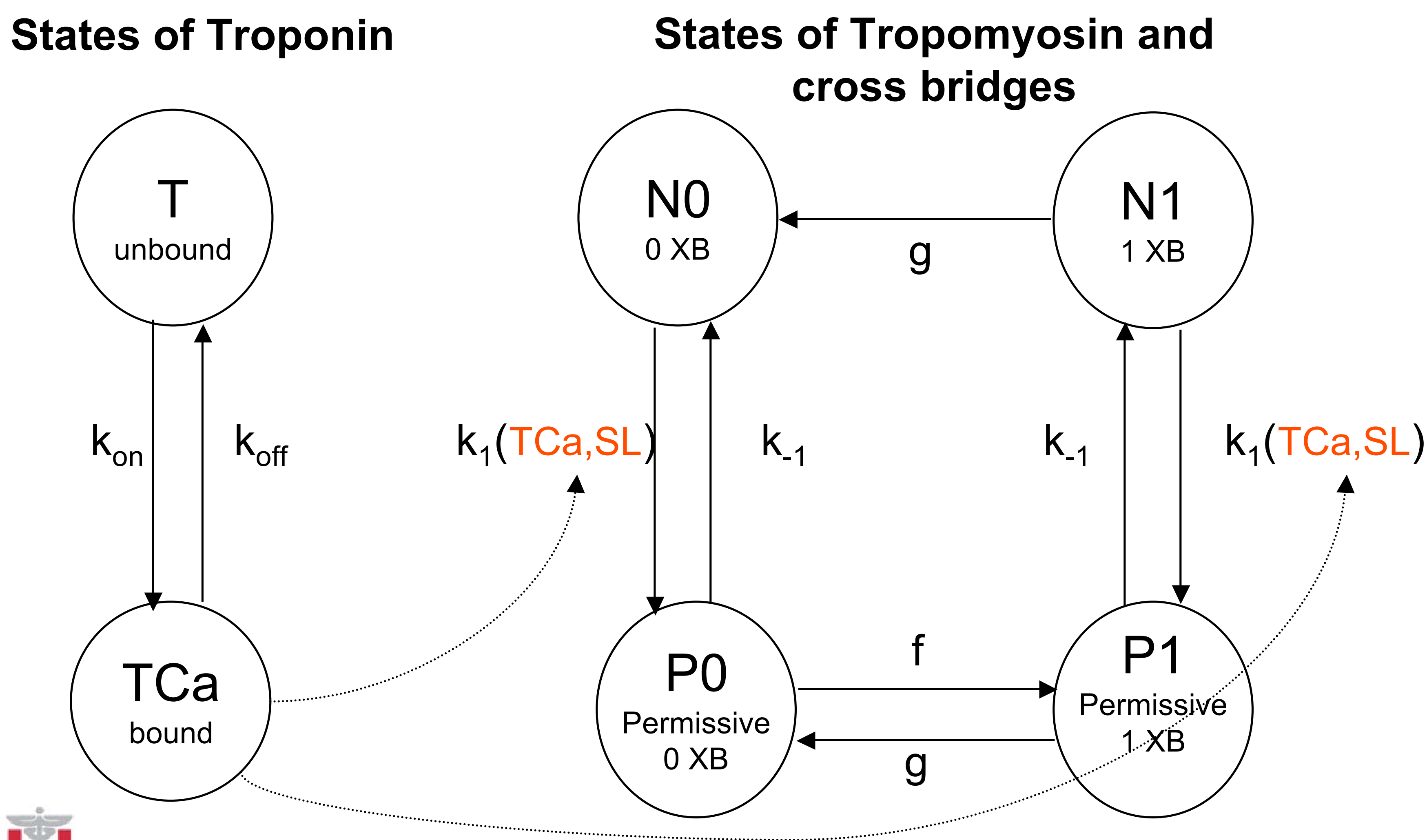
State Diagram of 3rd Model of Rice 1999 et al.



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Matrix representation of State Diagram

$$y = \begin{pmatrix} T \\ TCa \end{pmatrix}$$

States of Troponin

$$\dot{y} = \begin{pmatrix} -k_{on}[Ca] & k_{off} \\ k_{on}[Ca] & -k_{off} \end{pmatrix} y$$

Transitions

$$x = \begin{pmatrix} N_0 \\ P_0 \\ P_1 \\ N_1 \end{pmatrix}$$

States of Tropomyosin and cross bridges

$$\dot{x} = \begin{pmatrix} -k_1 & -k_{-1}(TCa, SL) & 0 & g \\ k_1 & k_{-1}(TCa, SL) - f & g & 0 \\ 0 & f & -g - k_{-1}(TCa, SL) & k_1 \\ 0 & 0 & k_{-1}(TCa, SL) & -g - k_1 \end{pmatrix} x$$

Transitions

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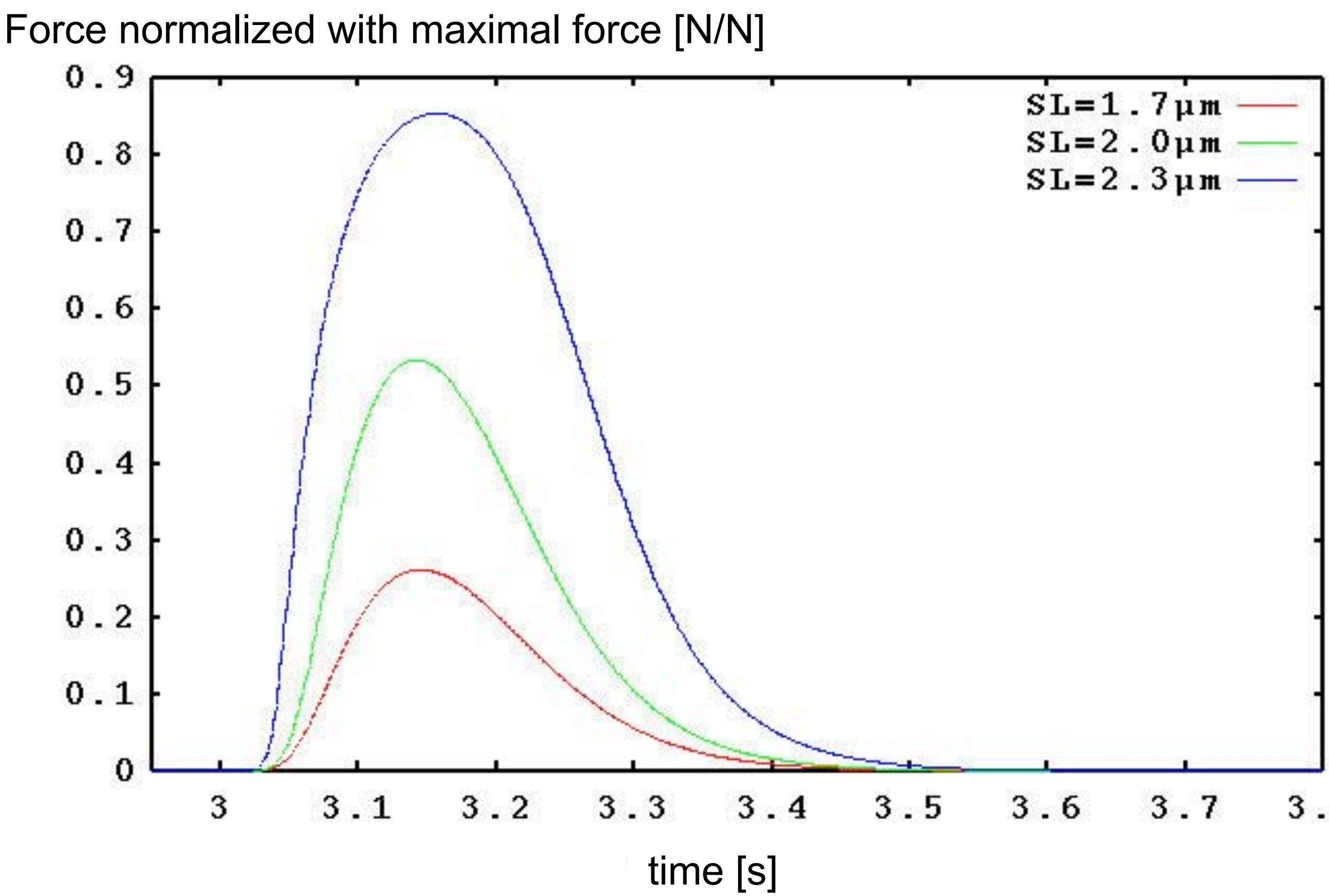
Model 3 from Rice et al., 1999

Force Development for Different Static Sarcomere Lengths (SL)



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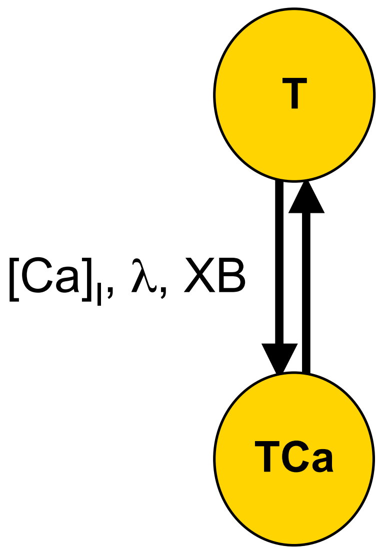
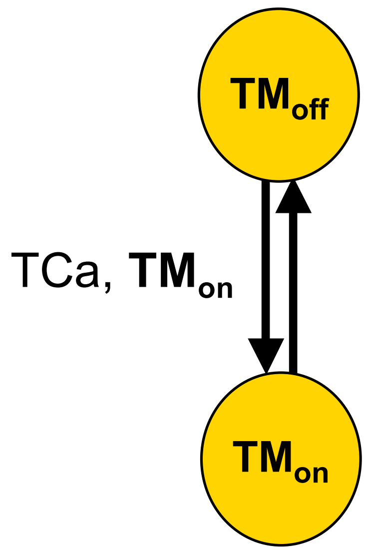
Model of Glänzel et al. 2002: Activation



Ca-binding to Troponin C



Shifting of Tropomyosin

T	Troponin
TCa	Troponin with bound calcium
TM_{off}	Tropomyosin in non-permissive state
TM_{on}	Tropomyosin in permissive state
λ	Stretch
XB	Cross-bridges
$[Ca]_i$	Free calcium in intra-cellular fluid

Cooperativity mechanisms

XB-TN
TM-TM

(Glänzel, Diploma Thesis, IBT, Universität Karlsruhe (TH), 2002,
Sachse et al, IJBC, 2003,
Sachse et al, LNCS 2674, 2003)

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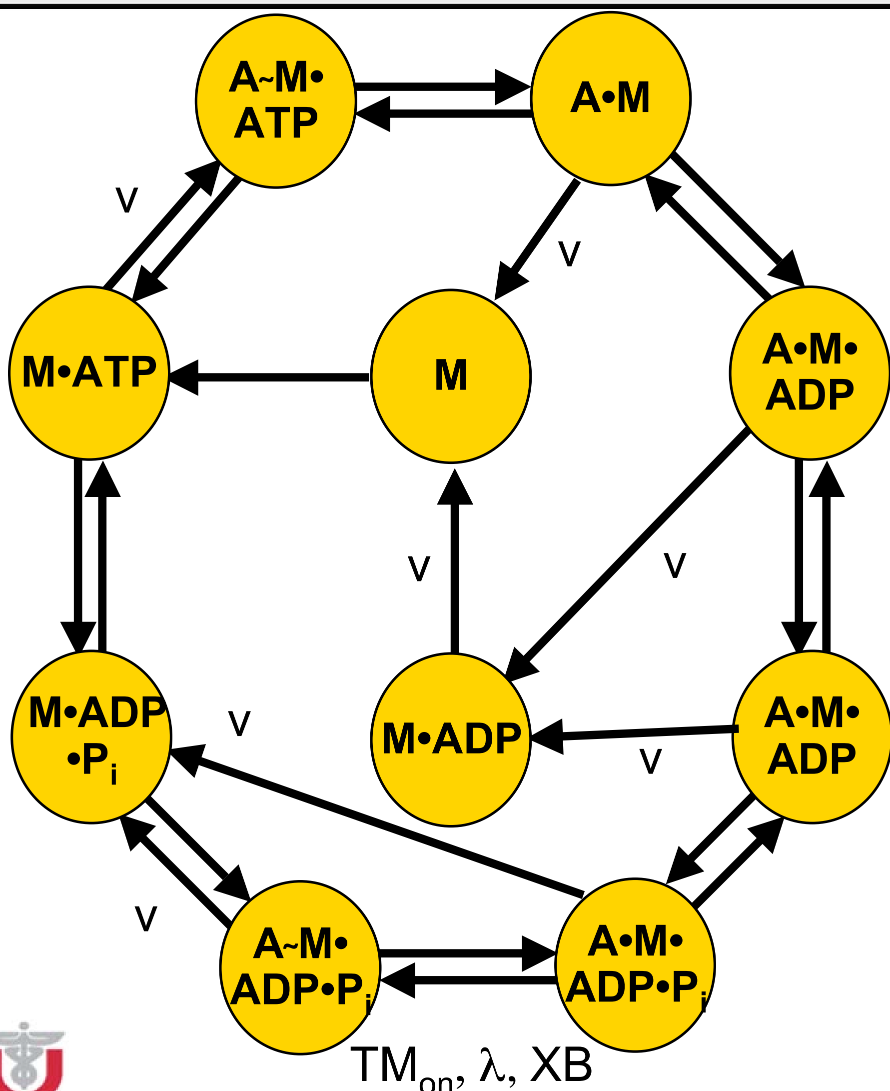
Model of Glänzel et al. 2002: Crossbridge Cycling



A	Actin
M	Myosin
ATP	Adenosine triphospate
ADP	Adenosine diphosphate
P_i	Phosphate
λ	Stretch
v	Velocity of filaments
XB	Cross-bridges
~	weakly coupled
•	**strong binding**

Cooperativity mechanism

XB-XB

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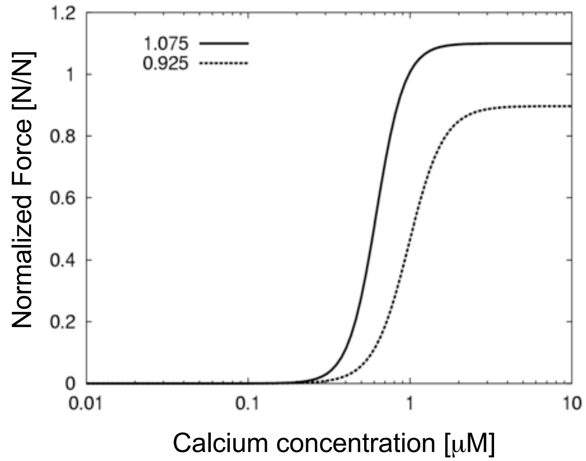
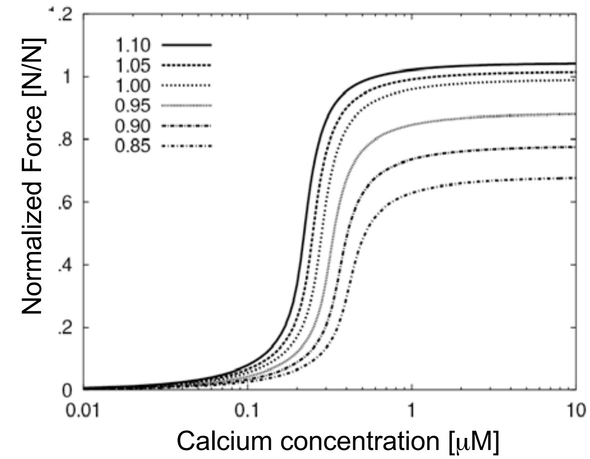
Reconstruction of Static Measurements

Study
- Species: rat
- Ventricular myocytes
- Resting length ~ 2μm

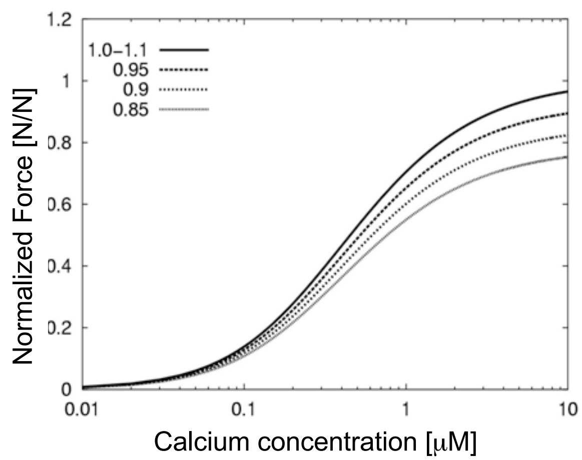
Protocol
- Calcium concentration constant
- Stretch constant



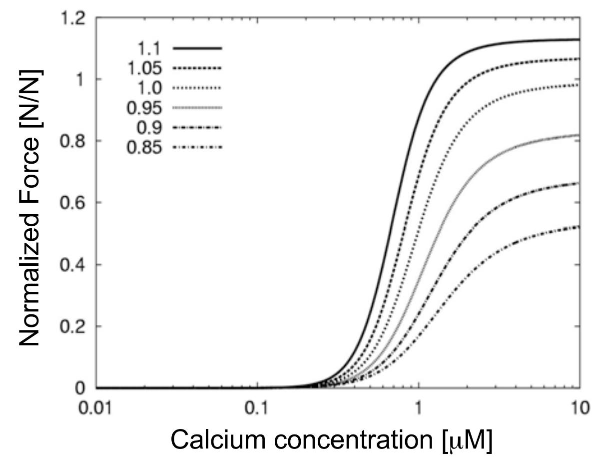
Measurement ter Keurs et al. 00



Model of Glänzel et al. 02



Model Peterson et al. 91



3rd model Rice et al. 99

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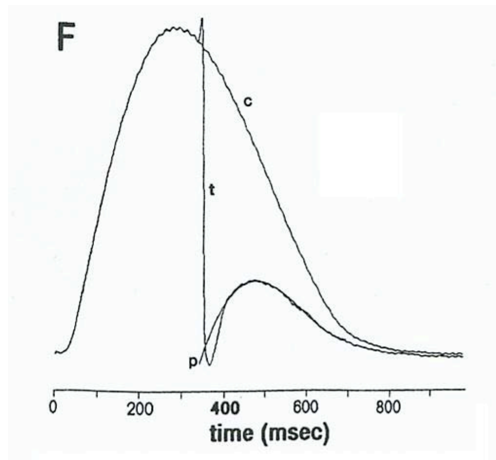
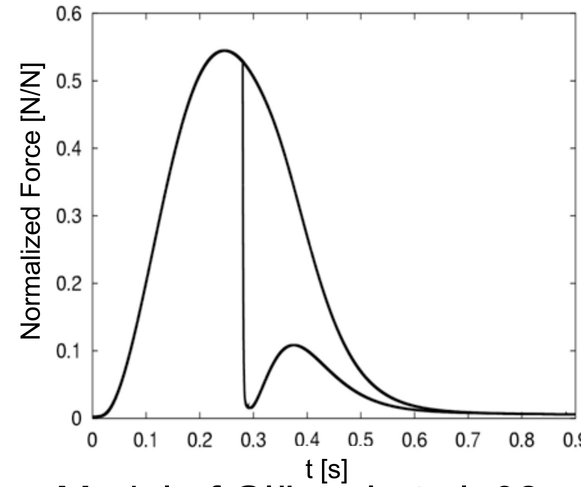
Reconstruction of Length Switch Experiments

Study
- Species: rabbit
- Ventricular myocytes

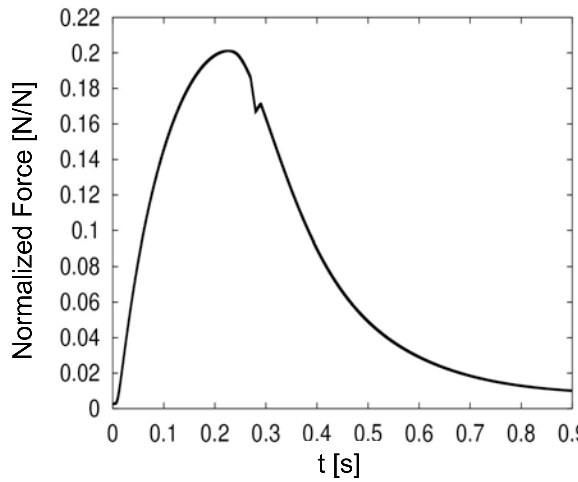
Length Switch Experiment
- Stretch of 4.6% in 10 ms
- Return to original configuration in 10 ms



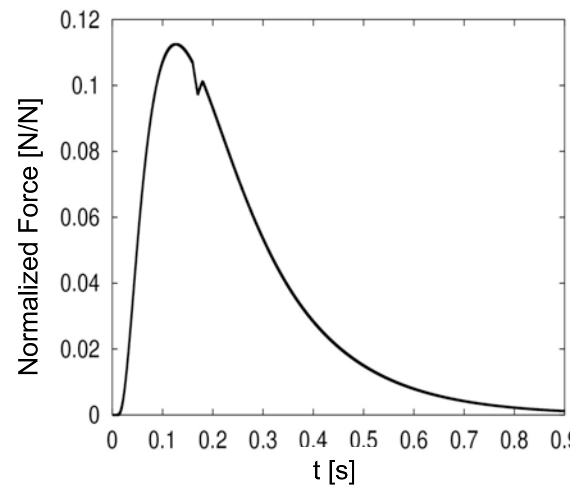
Measurement Peterson et al. 91



Model of Glänzel et al. 02



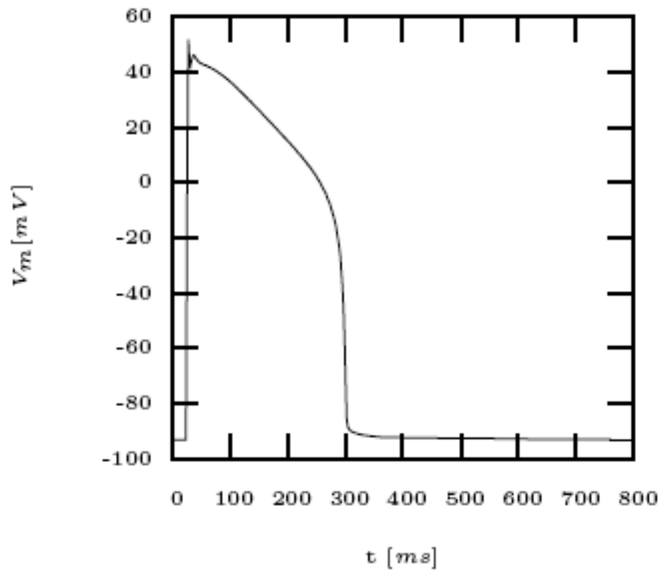
Model Peterson et al. 91

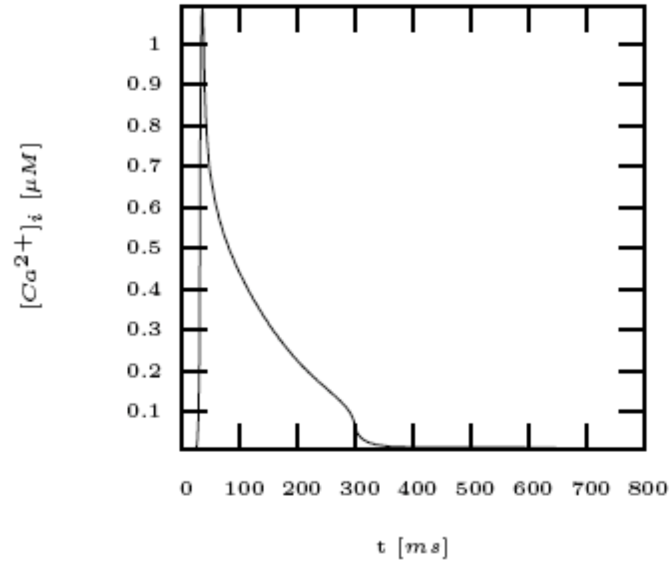


3rd model Rice et al. 99

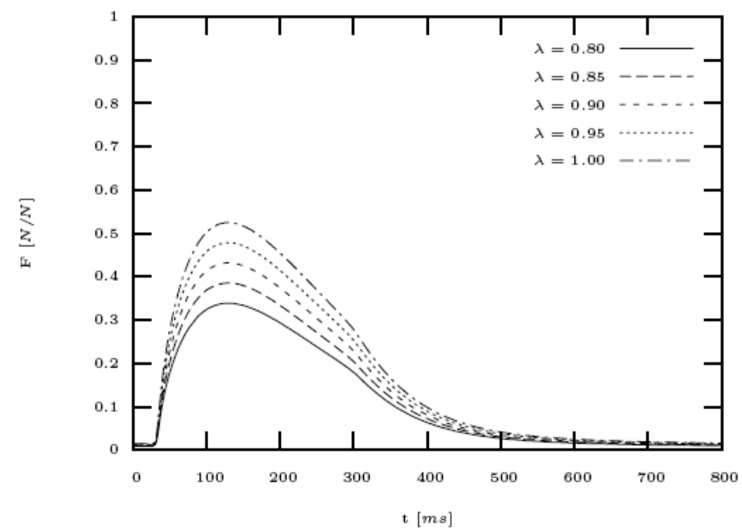
CVRTI

Coupling of Force with Electrophysiological Models: Basics



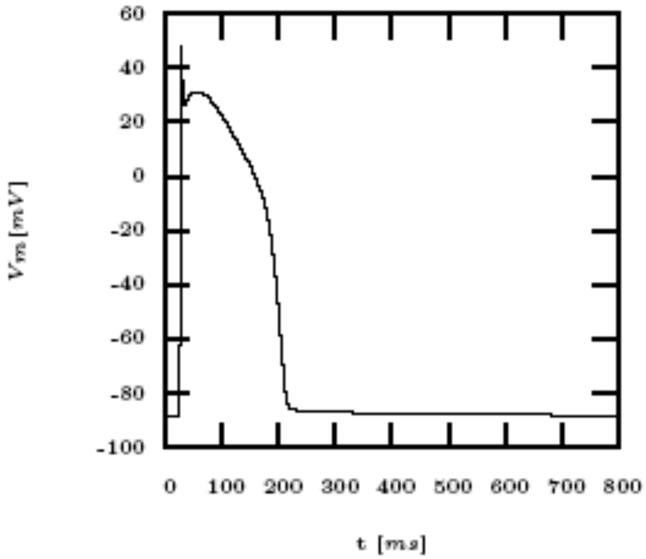


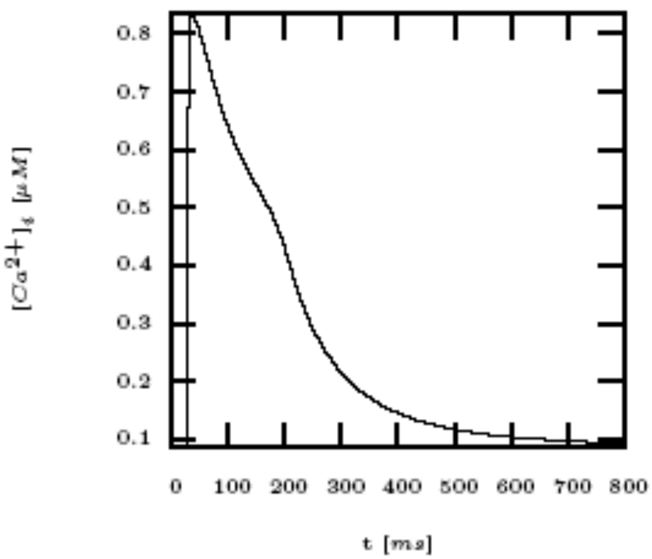
- Noble-Varghese-Kohl-Noble model
- Rice-Winslow-Hunter model 1st
- Stimulus at t=35 ms
- Sarcomere stretch λ



CVRTI

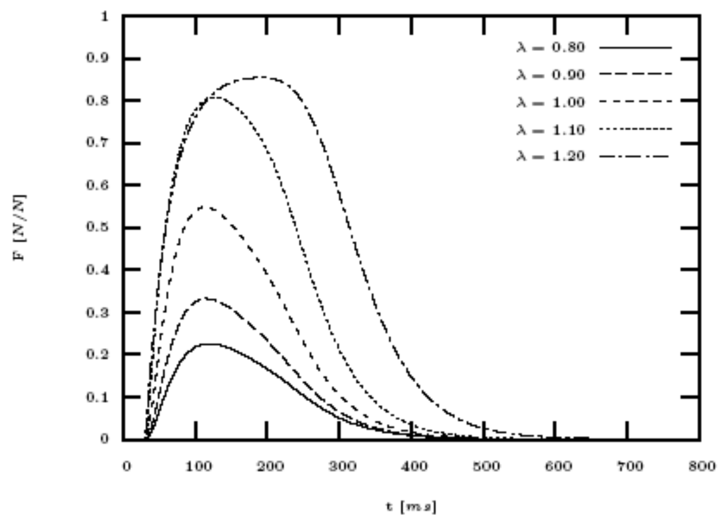
Coupling of Force with Electrophysiological Models





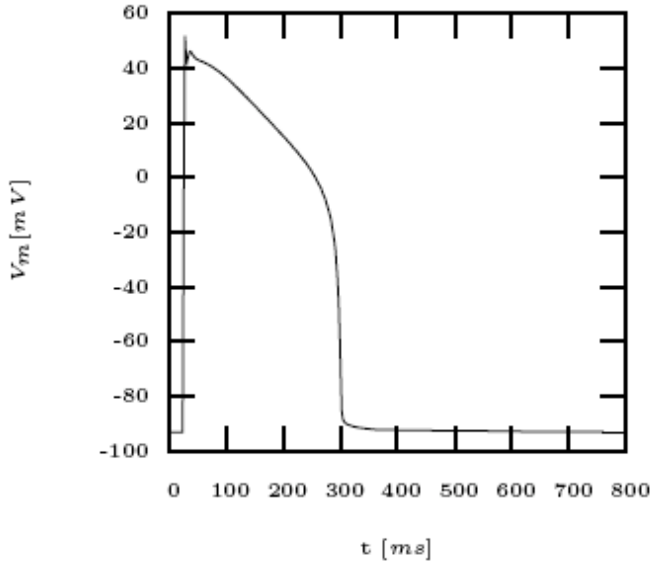
- Luo-Rudy model (Guinea pig ventricular)
- Rice-Winslow-Hunter model 3rd (rabbit ventricular)
- Stimulus at t=35 ms
- Sarcomere stretch λ

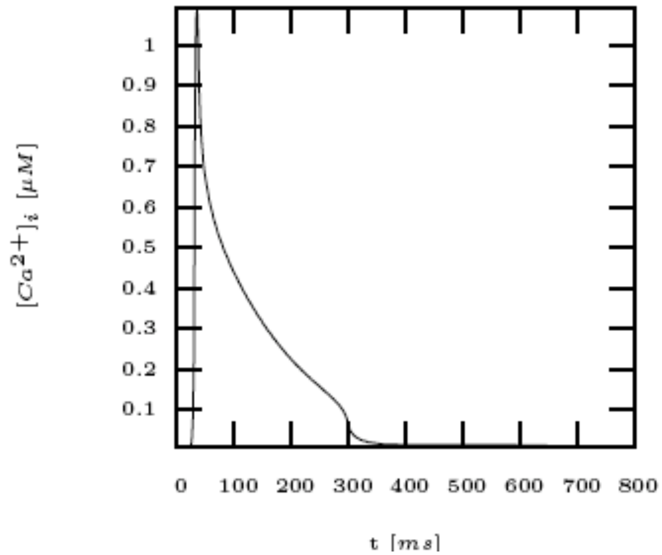
Species don't fit



CVRTI

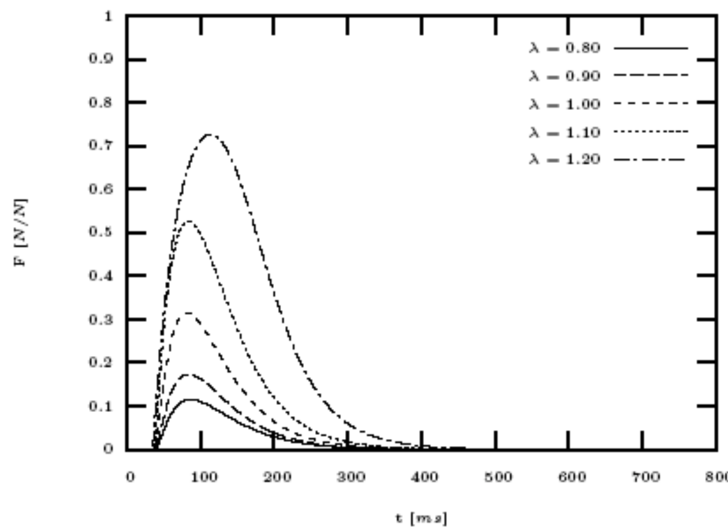
Coupling of Force with Electrophysiological Models





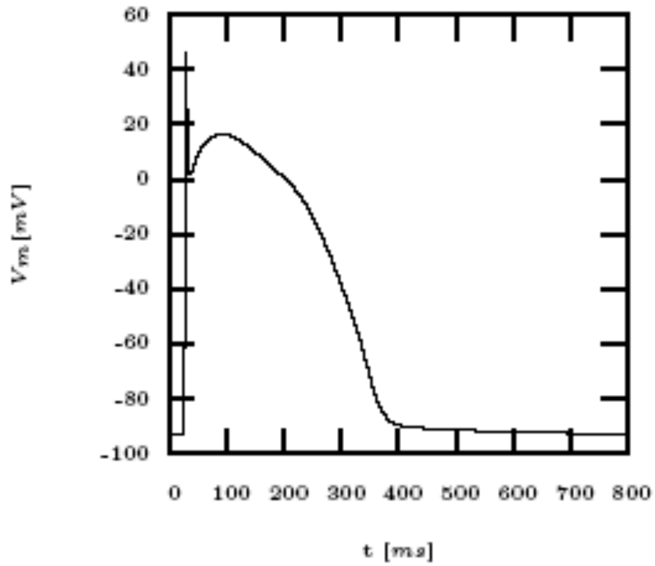
- Noble-Varghese-Kohl-Noble model (Guinea pig ventricular)
- Rice-Winslow-Hunter model 3rd (rabbit ventricular)
- Stimulus at t=35 ms
- Sarcomere stretch λ

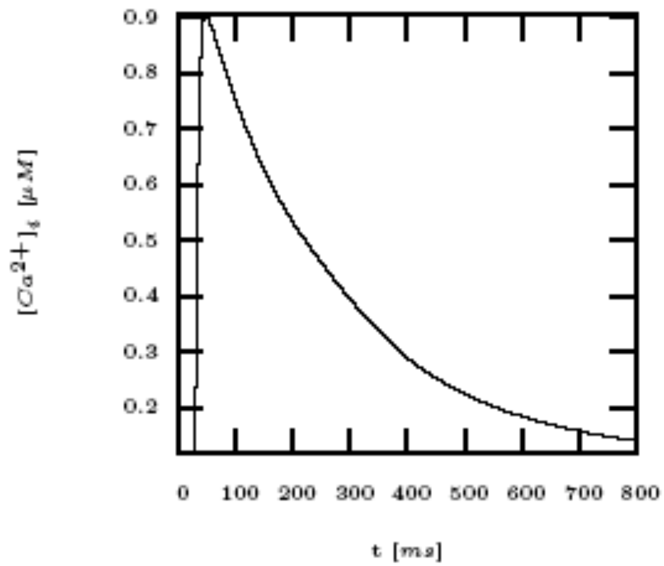
Differences in force development due to differences of Ca transient



CVRTI

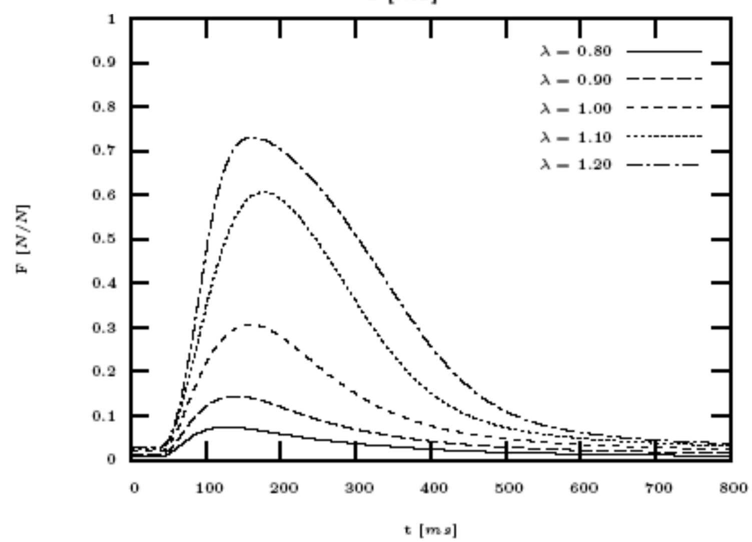
Coupling of Force with Electrophysiological Model: Human





- Priebe-Beuckelmann model (human ventricular)
- Glänzel-Sachse-Seemann model (human ventricular)
- Stimulus at t=35 ms with frequency
- Sarcomere stretch λ

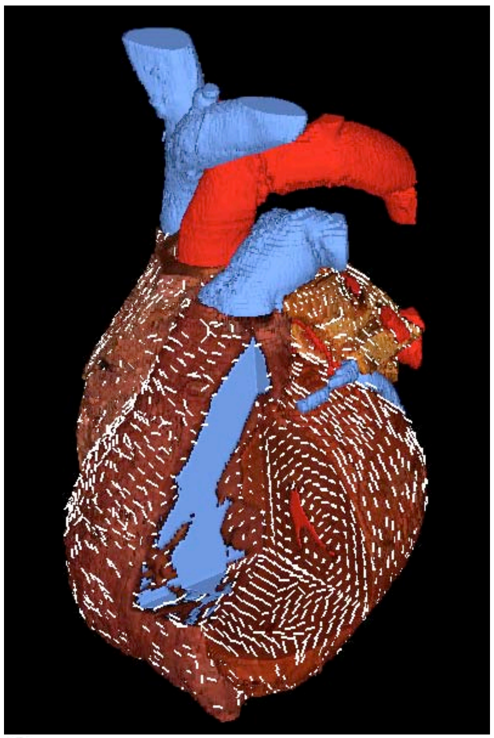
Validation with measured data necessary!



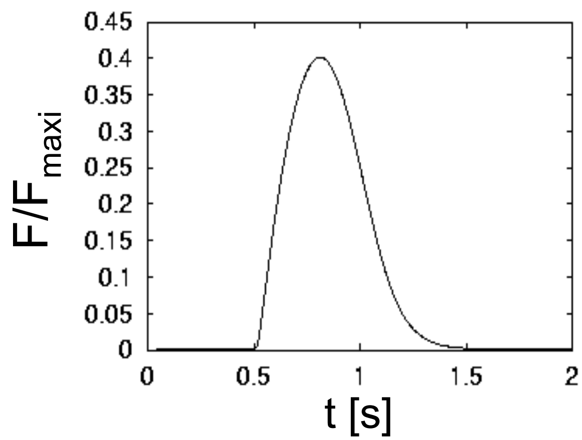
CVRTI

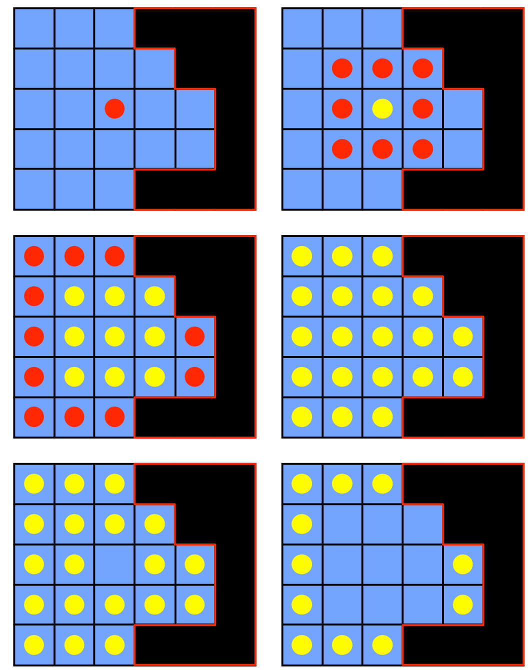
Modeling Force Development with Cellular Automaton

Anatomical Model	Physiological Parameters	Cellular Automaton



- **Force**
- Transmembrane voltage
- Calcium concentration

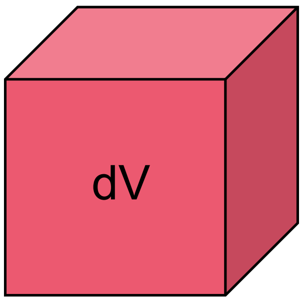




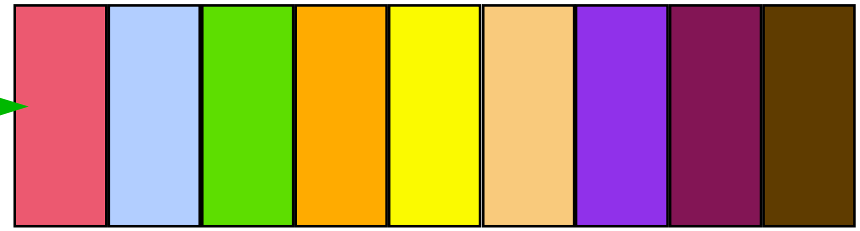
CVRTI

Parameters for Simulation: Lookup Tables

Known per
volume element dV
and for time t



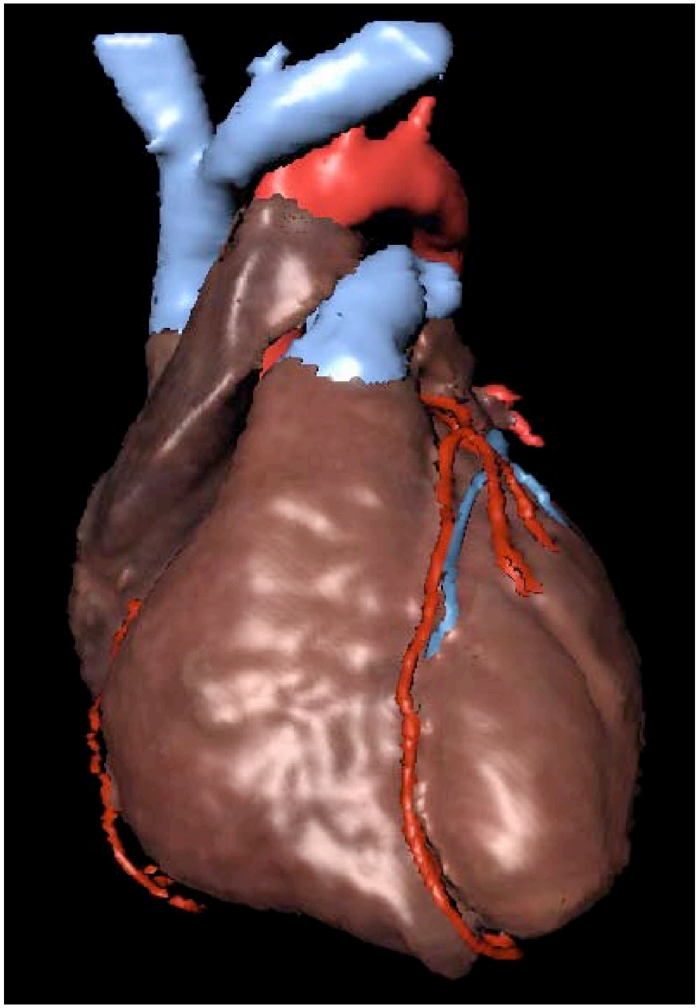
- Stimulus
- Time since activation t_S
- Stimulus frequency f
- Tissue type

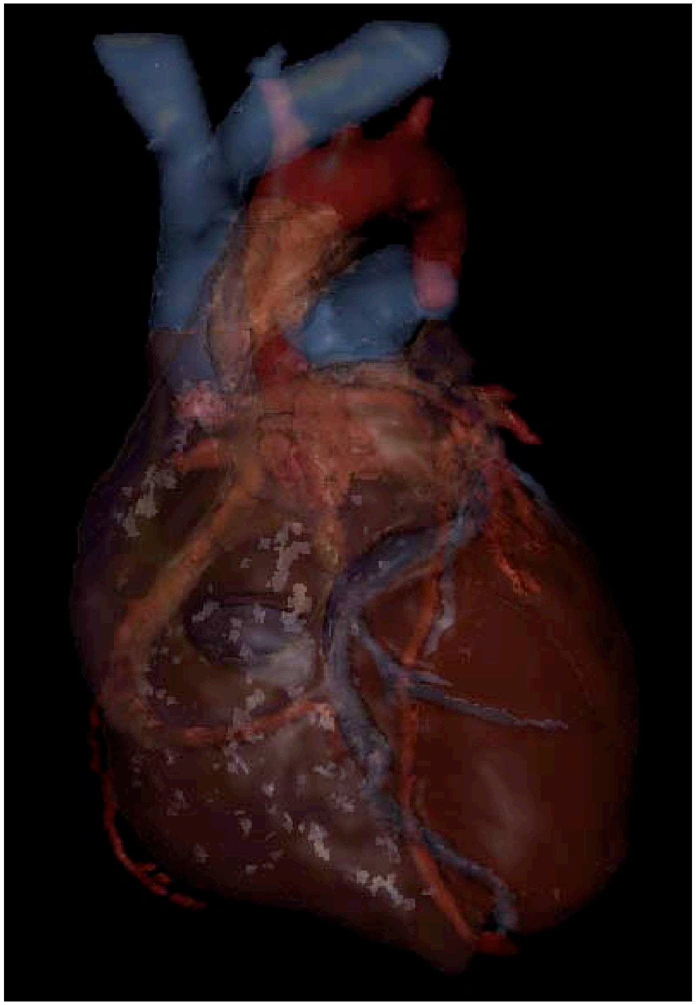


- Force (t_S) (instead of transmembrane voltage)
- Refractory period (t_S)
- Autorhythmicity (t_S)
- Conduction velocity (f)
- Excitable neighborhood (constant)

CVRTI

Modeling of Force Development: Sinus Rhythm

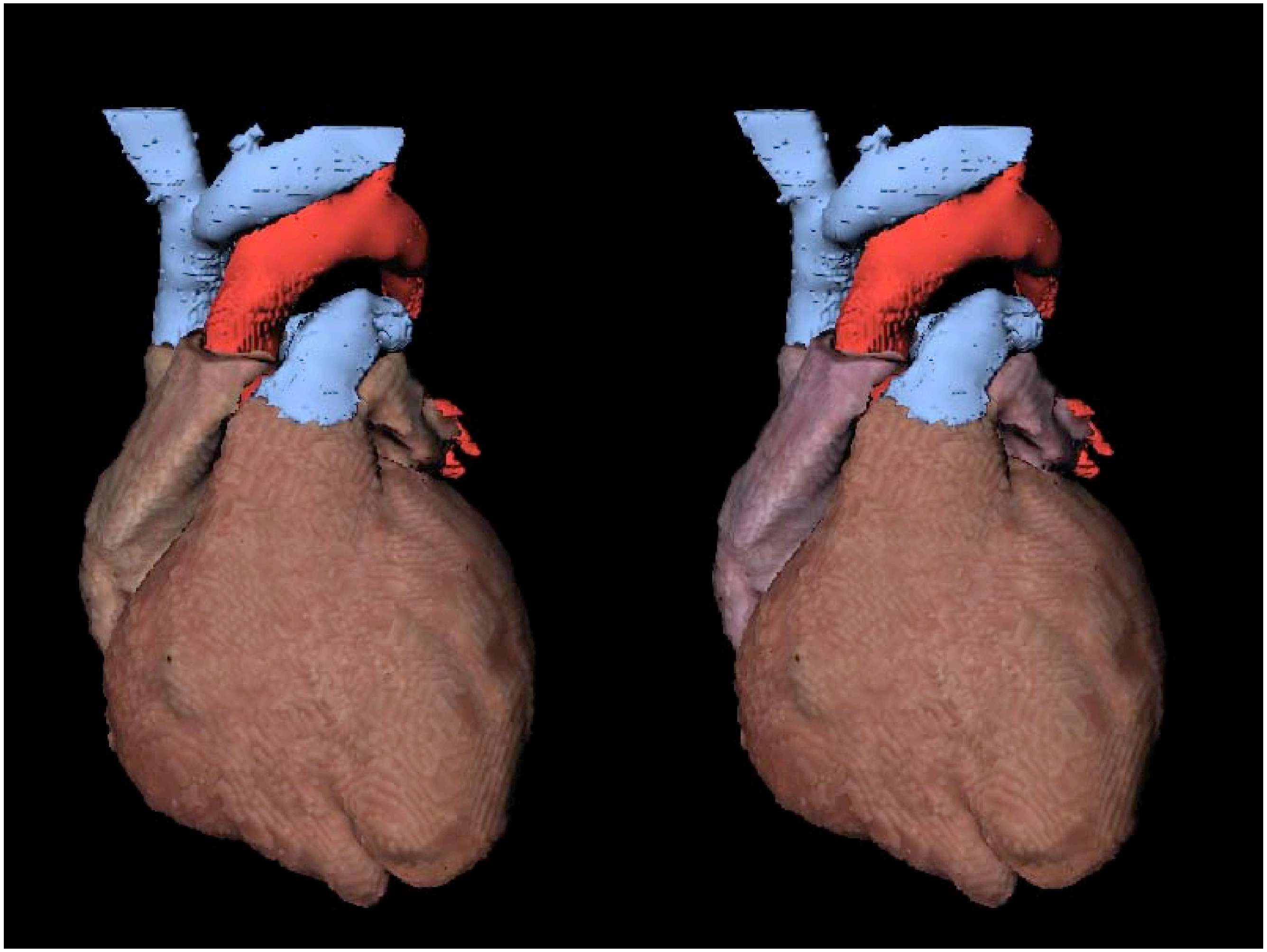




CVRTI

Modeling of Force Development: Coupling

Transmembrane Voltage



Normalized Force

CVRTI

Group Work

Discuss the application of cellular automata for simulation of electrophysiology and force development.

Which simulations are more realistic?

CVRTI