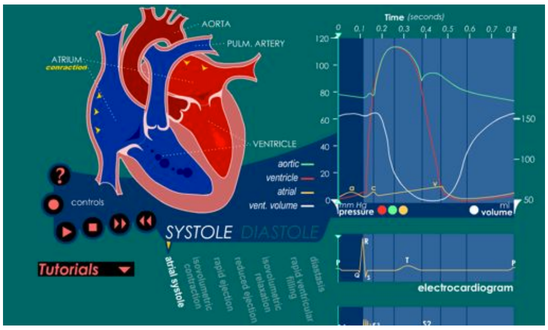
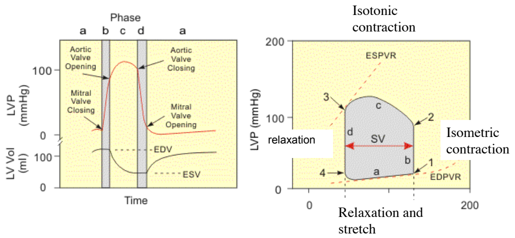
Mechanism of cardiac muscle contractility

Steven Marston 16/10/11



http://library.med.utah.edu/kw/pharm/hyper_heart1.html

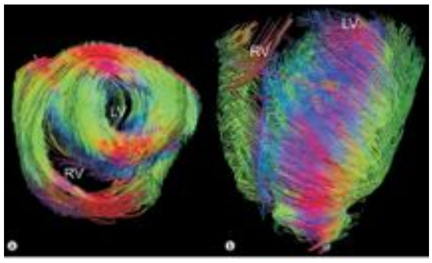
Relationship of contractile cycle to the cardiac cycle



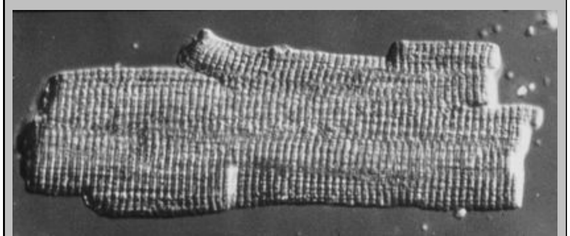
Length ≡ volume tension or force ≡ pressure

Muscle is a linear motor

Linear motion is converted to changes in heart chamber volume by the spiral arrangement of muscle fibres (wringer-like action)

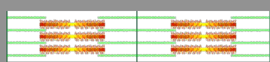


Schmid et al., Eur J Cardiol 2005
doi:10.1016/j.ejcts.2004.11.036



Myocyte

Myofibril

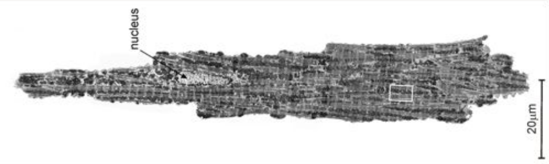


Sarcomere

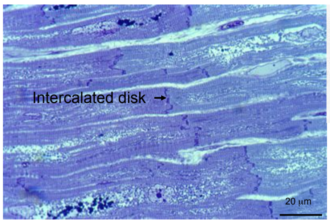
Actomyosin

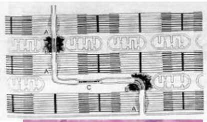
Isolated cardiomyocytes

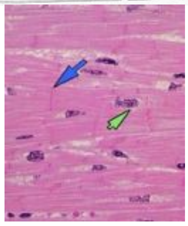
Prof N Severs



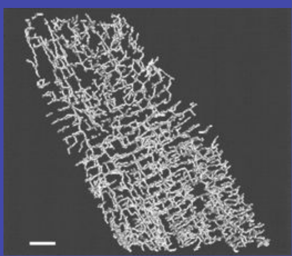
Intercalated disks, in longitudinal sections







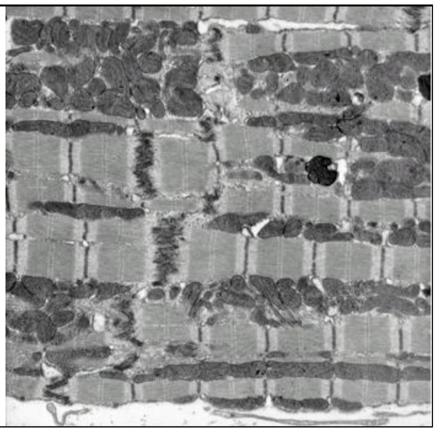
Three types of cell junction are present at the intercalated disk: gap junctions, fascia adherens junctions and desmosomes



The T-tubule system of an isolated rat cardiomyocyte

Mitochondria

Mitochondria occupy approximately 40% of the cytoplasm volume in cardiac cells because of the need for continuous aerobic metabolism in heart muscle. Skeletal muscle contains only about 2% of mitochondria



Prof N Severs

Contraction of a single human cardiac myocyte stimulated at 0.5 Hz

Mechanics and energetics of contractility

Thick and thin filaments and the sliding filament mechanism

The molecules of the contractile apparatus

Myosin, the motor protein and the crossbridge cycle

Ca^{2+} switching of contractility and troponin-tropomyosin

Modulation of Ca^{2+} switching by Length dependent activation and PKA dependent phosphorylation

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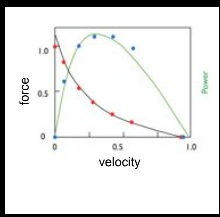
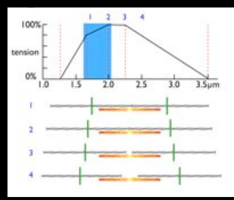
Force-velocity relationship



Maximum force is isometric
maximum speed is unloaded
maximum power is at an intermediate speed

Length-tension relationship



This relationship is due to the sliding filament mechanism of muscle contraction
Heart muscle contracts in the length range below optimum
The length-tension and force-velocity relationships are net result of the action of a large number of independent force generating molecules

Efficiency of energy conversion into work by intact papillary muscles from *ACTC* E99K and wild-type mouse

Steven Marston, Weihua Song, Nancy Curtin & Roger Woledge

National Heart & Lung Institute, Imperial College London

A → B + heat

Chemical reactions produce heat.
The amount of heat is proportional to the extent (mols) of reaction that occur.
When a reaction occurs in solution ALL of the energy is heat.

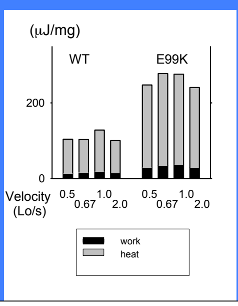
ATP → ADP + Pi + work + heat

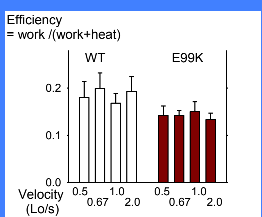
Muscle contraction is special because some of the energy from this reaction can be converted to WORK rather than heat. Work = integral of force & length change.

Note that other reactions occur too and are necessary for contraction (active transport of ions, resynthesis of ATP etc). All contribute to heat produced by muscle.

We detect heat as the increase in muscle temperature.

Transgenic muscle is less efficiency: smaller fraction of the total energy turnover is converted to work





Overall efficiency of conversion of the enrgy of ATP hydrolysis into work was 18%

The efficiency of the muscle motor is up to twice this vakue since some heat is produced by non-contractile events

- Work due to cycling crossbridges
- ATP used for active transport of ions (Ca^{2+}, Na^{+} & K^{+})
- Metabolic cost of ATP resynthesis by oxidative phosphorylation

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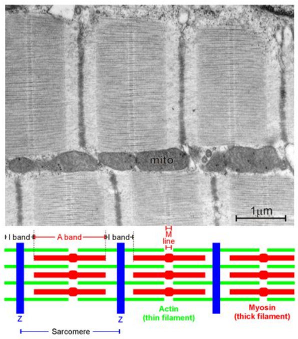
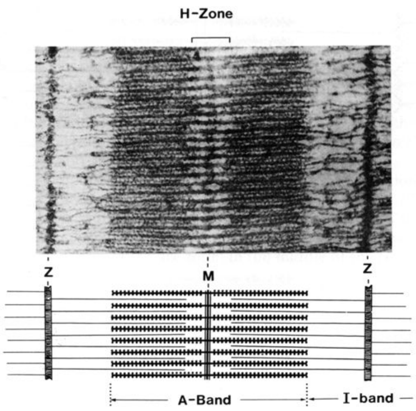
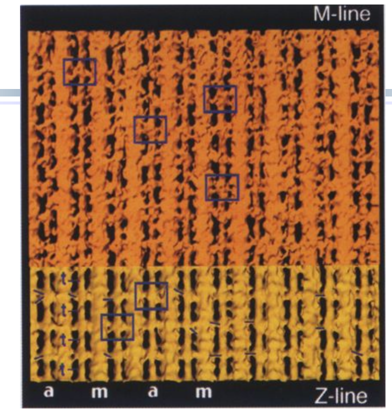
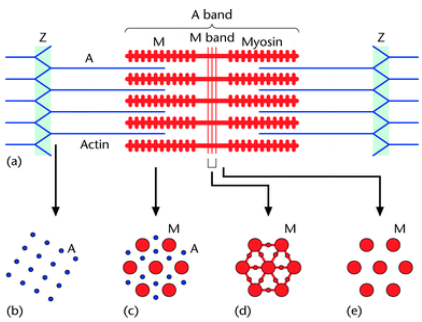








Various regions of the sarcomere (a) shown in transverse section:

(b) at the Z-line (Z-band), (c) in the overlap region of the A-band, (d) at the M-band and (e) in the non-overlap region of the A-band.

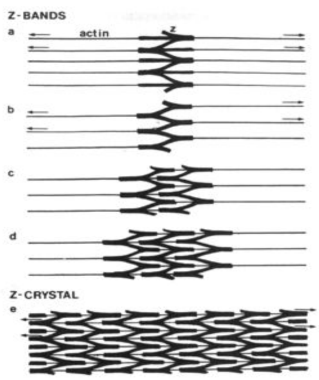
(A, M = actin, myosin filaments, mf = m-filaments)

The main structural protein of the Z-line is alpha-actinin

Some muscles or fibres have different levels of zig-zags -

slower muscles have thicker Z-bands

Some diseased muscles get very thick Z-bands; they are almost 'Z-crystals' (e.g. nemaline myopathy)



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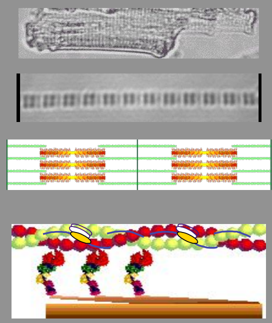
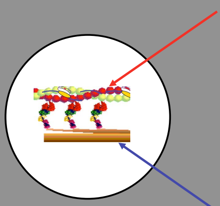


Myocyte

Myofibril

Sarcomere

Actomyosin

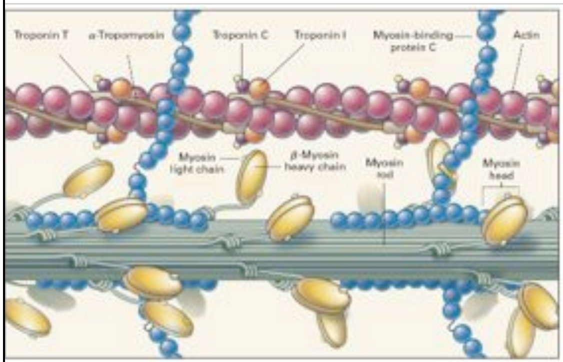


Thin filament

- Actin
- Tropomyosin
- Troponin I
- Troponin T
- Troponin C

Thick filament

- Myosin heavy chain
- Myosin light chain 1
- Myosin light chain 2
- Myosin binding protein C
- Titin



Expression of cardiac-specific muscle proteins

8 Heavy Chain (MyHC) genes, highly conserved:

Weiss, Schiaffino & Leinwand; *J. Mol. Biol.* 1999 **290**:61-75

•2 cardiac genes :

MyHC-α – chromosome 14

MyHC-β also called MyHC type I or β-slow, chromosome 17

93% identity, but <81% identity with other isoforms

•6 skeletal genes

MyHC-embryonic – chromosome 17

MyHC-perinatal – chromosome 17

MyHC-IIa – chromosome 17

MyHC-IIb – chromosome 17

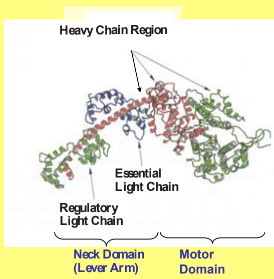
MyHC-IIx/d – chromosome 17

MyHC-extraocular – chromosome 14

Cardiac-specific troponin and regulatory light chain (phosphorylatable)

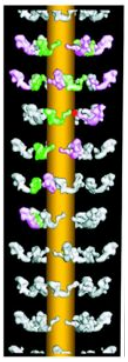
Myosin head S1 crystal structure

Rayment *et al.* (1993) Science, 261, 50-58

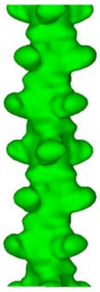


Shaft of the thick filament. Myosin molecules packed parallel 'crowns' of three myosin heads every 14.5 nm

Hind Al-Khayat



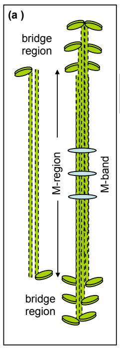
Model based on X-ray diffraction



Structure computed from em images

Centre of the thick filament. Myosin molecules packed antiparallel leaving a bare zone with M-line in the centre

Hind Al-Khayat



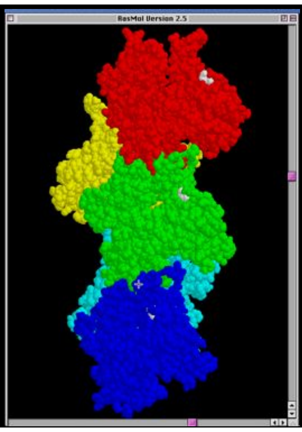
Polymerisation: Nucleation and elongation.

interaction with four other actins*.

Z-line and sarcomere formation

interaction with

α-actinin,
tropomyosin*
nebulin*
titin
tropomodulin



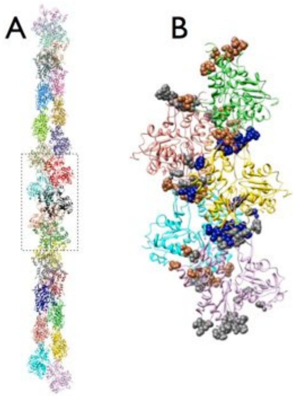
Contractility

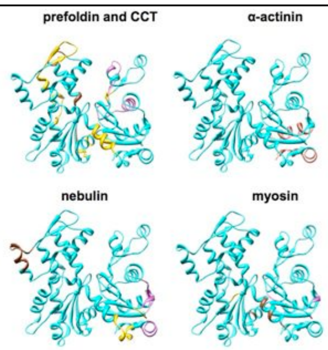
Interaction with myosin* in weak and strong complexes

Regulation

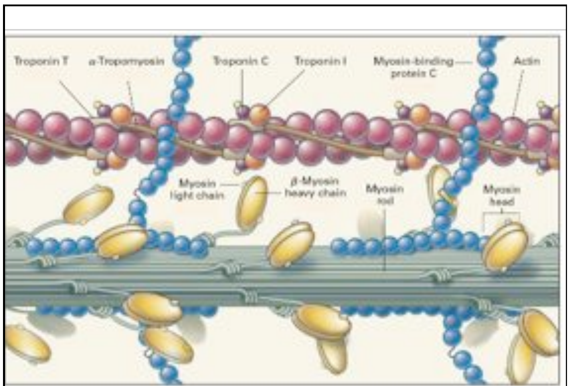
Interaction with tropomyosin* and troponin* (mainly TnI)

Actin filaments formed by polymerisation of actin monomers





Actin monomer interacts with many proteins



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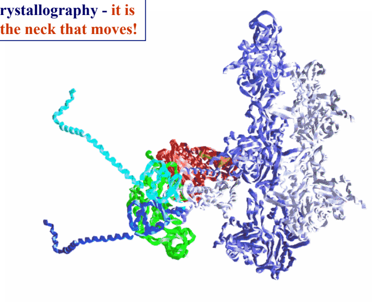
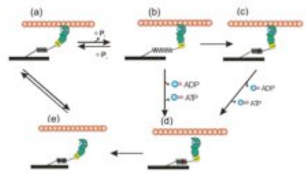
Force and movement: myosin motor interaction with actin

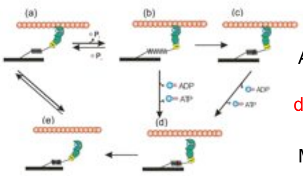
Here are two different head shapes on actin based on X-ray crystallography - it is mainly the neck that moves!



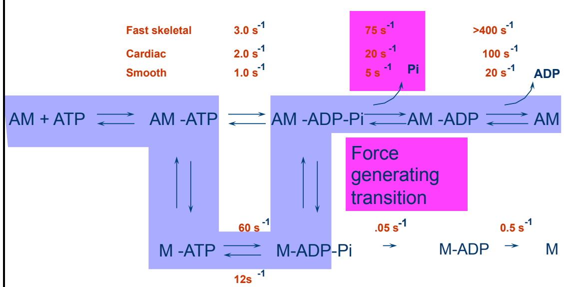
The crossbridge cycle

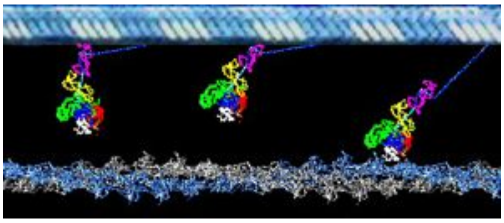


The crossbridge cycle



A COMPARISON OF THE ATP HYDROLYSIS MECHANISM FOR DIFFERENT TYPES OF MUSCLE





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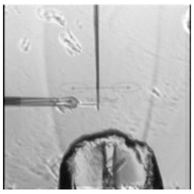
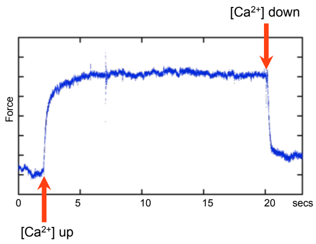
Ca^{2+} control of contraction and relaxation: troponin and tropomyosin





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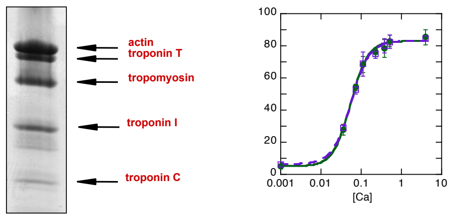
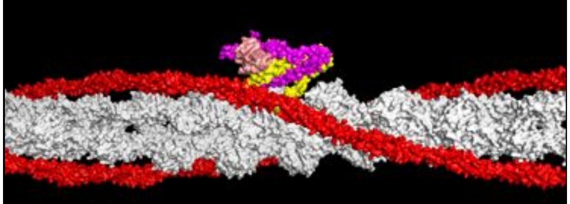
Ca^{2+} controls muscle contractility via troponin and tropomyosin

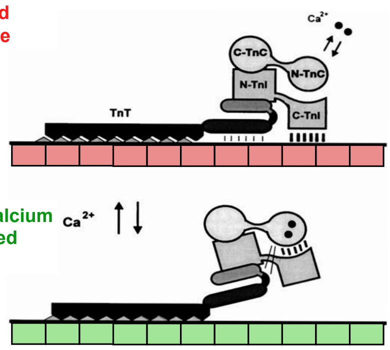


Reconstituted thin filament

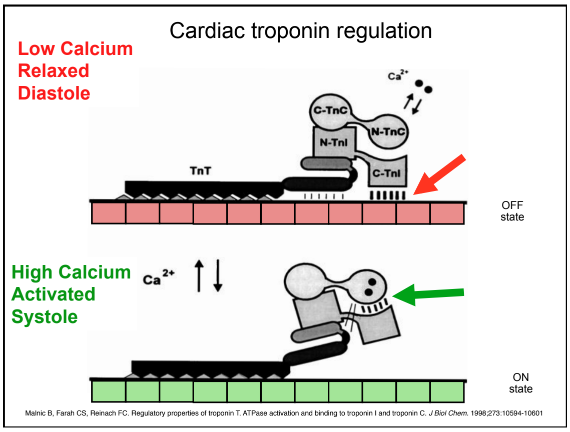


Pirani A, Vinogradova MV, Curmi PM et al. An Atomic Model of the Thin Filament in the Relaxed and Ca(2+)-Activated States. J Mol Biol. 2006

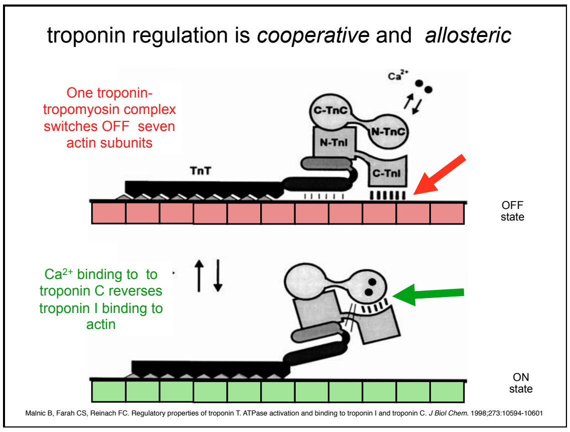
Cardiac troponin regulation



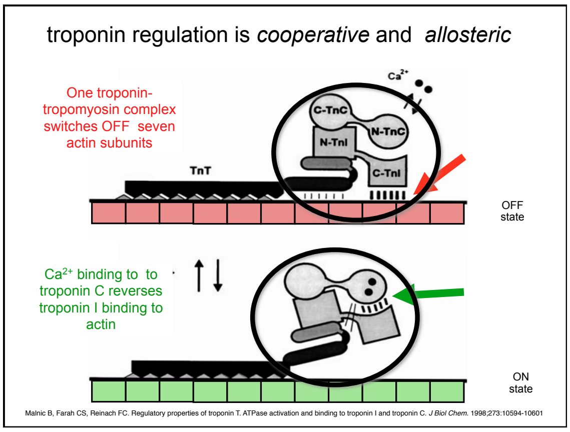
Malnic B, Farah CS, Reinach FC. Regulatory properties of troponin T. ATPase activation and binding to troponin I and troponin C. *J Biol Chem.* 1998;273:10594-10601



Cardiac troponin regulation
Low Calcium
Relaxed
Diastole
Ca2+
C-TnC
N-TnC
N-TnI
C-TnI
TnT
OFF
state
High Calcium
Activated
Systole
Ca2+
ON
state
Malnic B, Farah CS, Reinach FC. Regulatory properties of troponin T. ATPase activation and binding to troponin I and troponin C. J Biol Chem. 1998;273:10594-10601



troponin regulation is cooperative and allosteric
One troponin-tropomyosin complex switches OFF seven actin subunits
Ca2+
C-TnC
N-TnC
N-TnI
C-TnI
TnT
OFF
state
Ca2+ binding to to troponin C reverses troponin I binding to actin
ON
state
Malnic B, Farah CS, Reinach FC. Regulatory properties of troponin T. ATPase activation and binding to troponin I and troponin C. J Biol Chem. 1998;273:10594-10601



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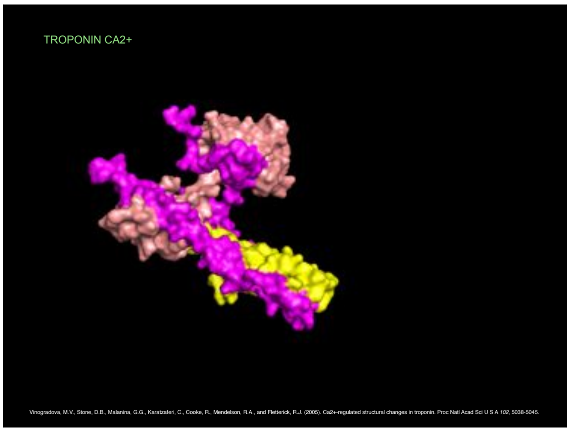
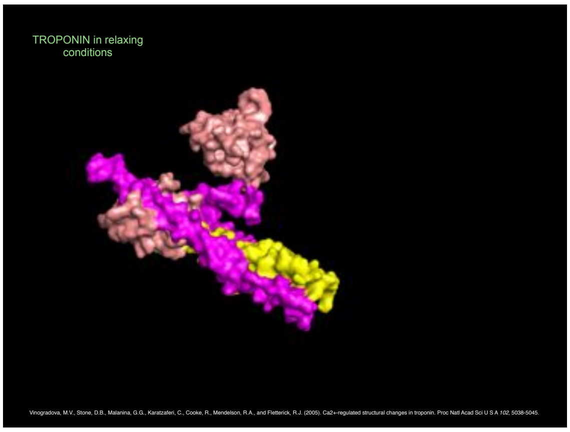
C-TnC
N-TnC
N-TnI
C-TnI
TnT
OFF
state
Ca2+ binding to to troponin C reverses troponin I binding to actin
ON
state
Malnic B, Farah CS, Reinach FC. Regulatory properties of troponin T. ATPase activation and binding to troponin I and troponin C. J Biol Chem. 1998;273:10594-10601



TROPONIN CA2+
Vinogradova, M.V., Stone, D.B., Malanina, G.G., Karatzaferi, C., Cooke, R., Mendelson, R.A., and Fletterick, R.J. (2005). Ca2+-regulated structural changes in troponin. Proc Natl Acad Sci U S A 102, 5038-5045.



TROPONIN in relaxing
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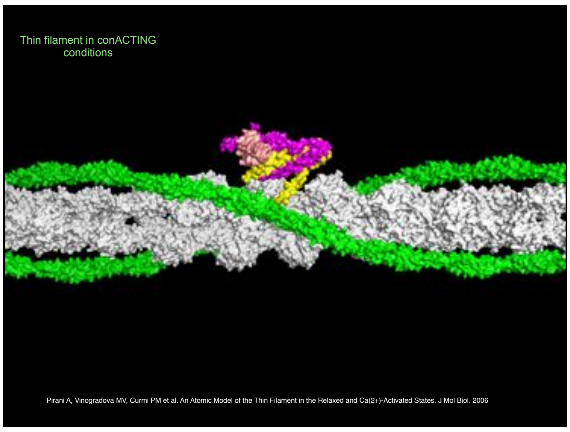

Thin filament in conACTING
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Thin filament in relaxing conditions

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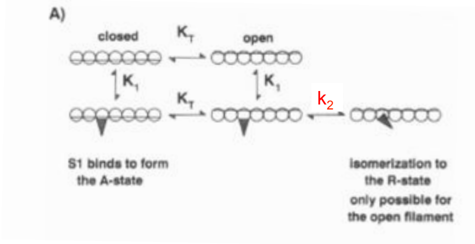
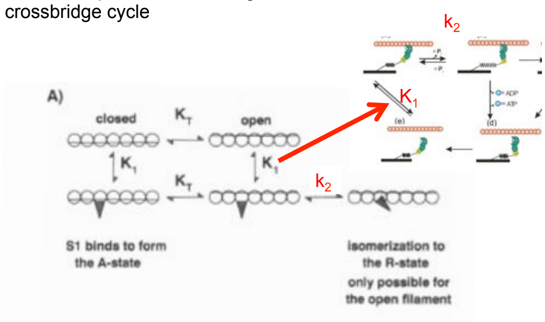
The two state model of Ca^{2+}-switching proposes that Ca^{2+} controls the equilibrium between open and closed states



Relationship of Ca^{2+}-switching to the crossbridge cycle



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Ca^{2+} switching of contractility and troponin-tropomyosin

Modulation of Ca^{2+} switching by Length dependent activation and PKA dependent phosphorylation

Ca2+ switching of troponin is coordinated with excitation-contraction coupling and is modulated by sarcomere length and β-adrenergic stimulation

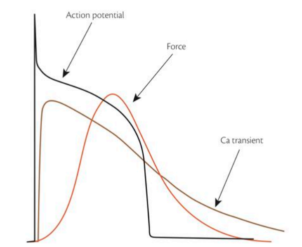
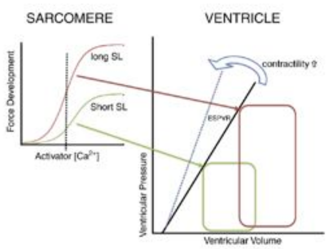


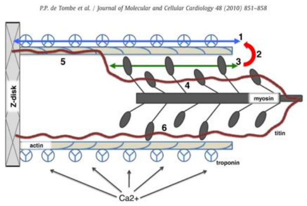
Fig. 16.1.2.14 The relationship between the action potential, the Ca^{2+}-transient and the generation of force. The peak of force production is not achieved until near the end of the plateau phase of the action potential and lags behind the peak of the Ca^{2+}-transient. This reflects the time required for Ca^{2+}-induced Ca^{2+}-release and cross-bridge cycling.

The Frank–Starling mechanism and myofilament length dependent activation



The Frank–Starling mechanism and myofilament length dependent activation. The Frank–Starling Law of the Heart describes a fundamental property of the heart (figure on the right). That is, for a given contractile state there is a unique relationship between end-systolic pressure reached in the heart and end-systolic pressure (ESPVR); increased contractility results in an increased slope of the ESPVR (cf. blue arrow). Increased ventricular filling (pre-load; red PV loop) leads to an increase in ventricular pressure development at end-systole which allows for (i) increased stroke volume for a given systolic pressure (after-load) and (ii) sustained stroke volume at elevated systolic pressure.

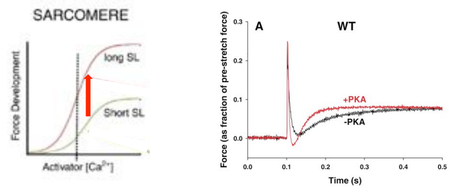
The Frank–Starling mechanism and myofilament length dependent activation



Myofilament length dependent activation could be the result of:
(i)modulation of pathways involving thin filament activation by troponin, either by directly modulating troponin-troponin cooperative interaction or via a titin-actin interaction modulating the level of thin filament activation, either directly or by altered troponin Ca2+ binding affinity.
(ii) Alterations in the cooperative interaction between force generating cross-bridges because the number of attached cross-bridges varies with sarcomere length.
(iii)MyBP-C interaction with myosin in the A-band may alter the arrangement of the S-2 domain of myosin heads that are interacting with actin in a length dependent manner.

The Frank–Starling mechanism and myofilament length dependent activation

Stretch-activation



When cardiac muscle is stretched during filling it initiates a delayed tension response which plays a role in FS mechanism by synchronising contraction in the following systole. The rate of this is controlled via PKA phosphorylation of MyBP-C

Modulation of contractility in the coordinated response of the heart to exercise

	Rest	*Hard exercise*	
Oxygen consumption (litres/min)	0.25	3.0	
Cardiac output (litres/min)	4.8	21.6	↑5x
Heart rate (beats/min)	60.0	180.0	↑3x
Stroke volume (ml)	80.0	120.0	↑1.5x
End-diastolic volume (ml)	120.0	140.0	
Residual volume (end-systolic)	40.0	20.0	
Ejection fraction	0.67	0.86	
Cycle time (s)	1.0	0.33	↓1/3
Duration of systole (s)	0.35	0.2	
Duration of diastole (s)	0.65	0.13	↓1/5

(After Rerych, S. K., Scholz, P. M., Newman, G. E. *et al.* (1978) *Annals of Surgery*, **187**, 449–458)

Modulation of contractility in the coordinated response of the heart to exercise

β-adrenergic receptor activation leads to the release of cyclic AMP and activation of protein kinase A

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Troponin and inotropy

- The troponin I subunit is a substrate for protein kinase A which is actvated by cAMP.
- Phosphorylation of troponin I decreases Ca^{2+} sensitivity and increases crossbridge turnover rate
- This change contributes to the lusitropic and inotropic response

MyBP-C and inotropy

- MyBP-C is phosphorylated at three sites by PKA
- Phosphorylation increases the rate of stretch activation
- This accelerates the kinetics of force development, contributing to the inotropic response


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