

# Mechanical properties of the heart muscle

# Outline

- Crossbridge theory. How does a muscle contract?
- A mathematical model for heart muscle contraction.
- Coupling to electrophysiology
- (Notes on passive mechanics and full-scale heart mechanics models)

# What will not be covered?

- Non-linear solid mechanics
- Constitutive laws for passive properties of heart tissue

# Possible (advanced) reading

- Cell contraction: Hunter PJ, McCulloch AD, ter Keurs HE. Modelling the mechanical properties of cardiac muscle. Prog Biophys Mol Biol. 1998;69(2-3):289-331.
- Basic continuum mechanics: George E. Mase, Continuum mechanics
- Non-linear mechanics: Gerhard Holzapfel, Non-linear solid mechanics, a continuum approach for engineering

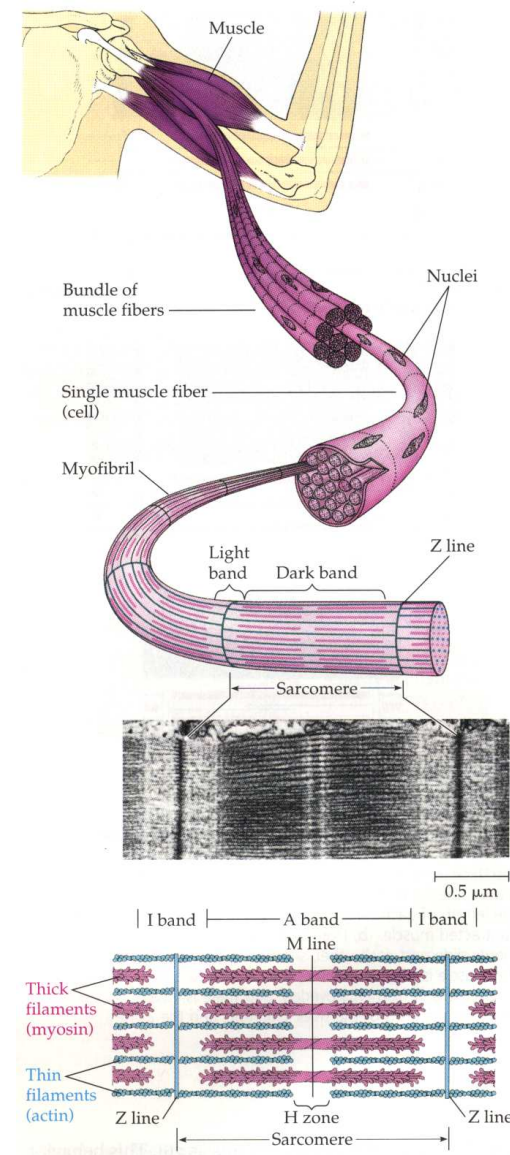
# Muscle cells

- Smooth muscle
- Striated muscle
  - Cardiac muscle
  - Skeletal muscle

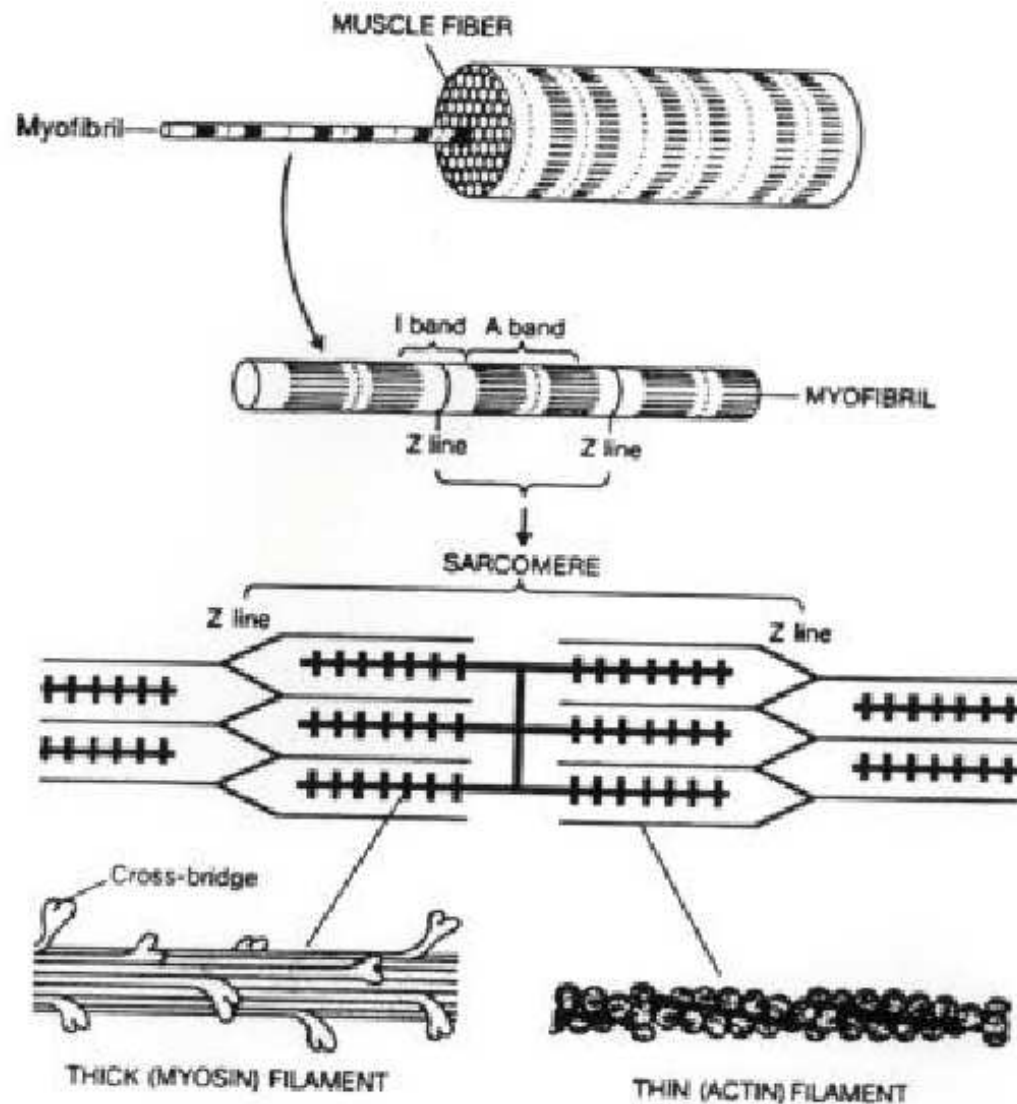
Most mathematical models have been developed for skeletal muscle.

# Striated muscle cells

- Skeletal muscle cells and cardiac muscle cells have similar, but not identical, contractile mechanisms.
- A muscle cell (cardiac or skeletal) contains smaller units called myofibrils, which in turn are made up of sarcomeres.
- The sarcomere contains overlapping thin and thick filaments, which are responsible for the force development in the muscle cells.

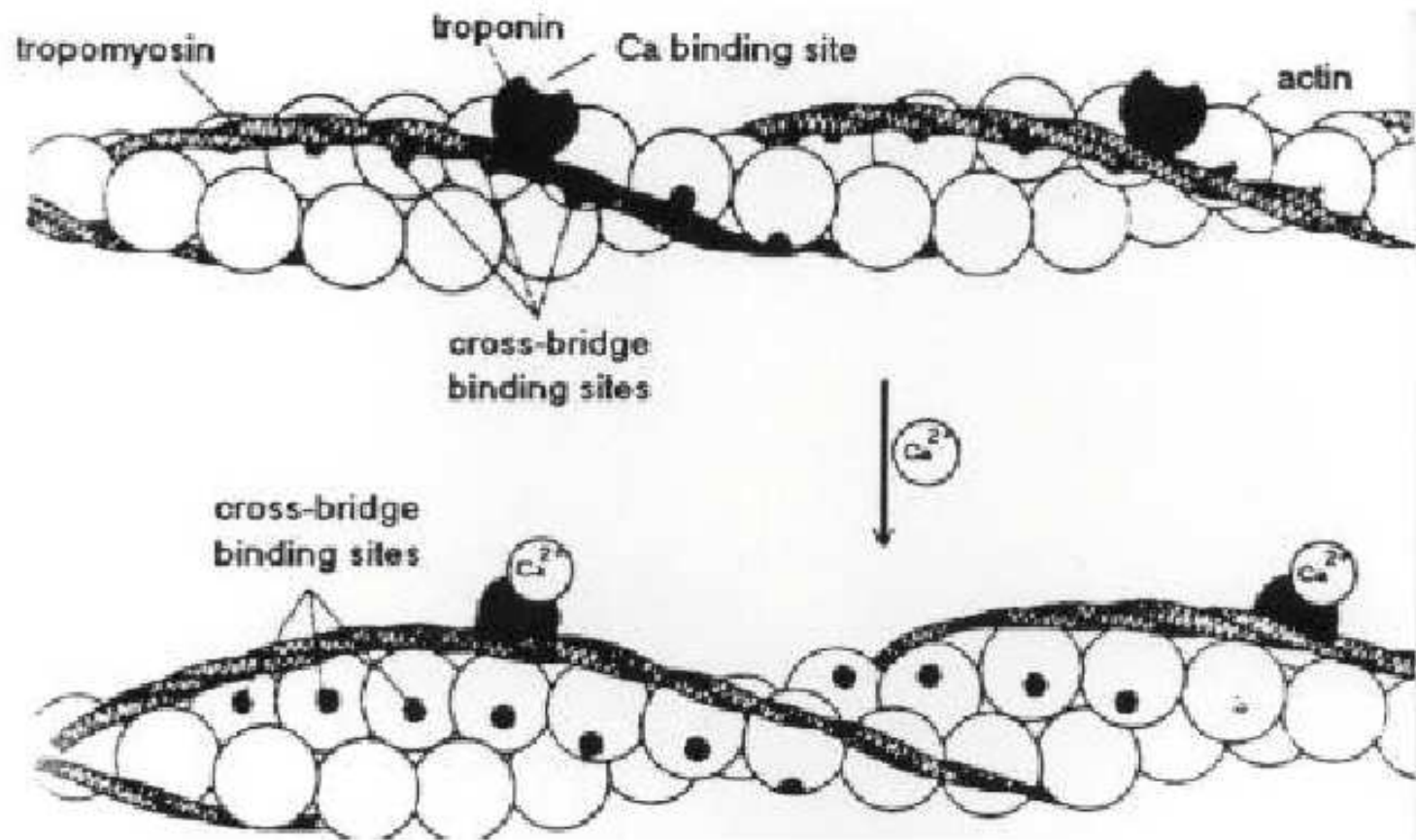


- Thick filaments are made up of the protein myosin. The myosin molecules have heads which form *cross-bridges* that interact with the thin filaments to generate force.
- Thin filaments contain the three proteins actin, tropomyosin and troponin.
- The actin forms a double helix around a backbone formed by tropomyosin.





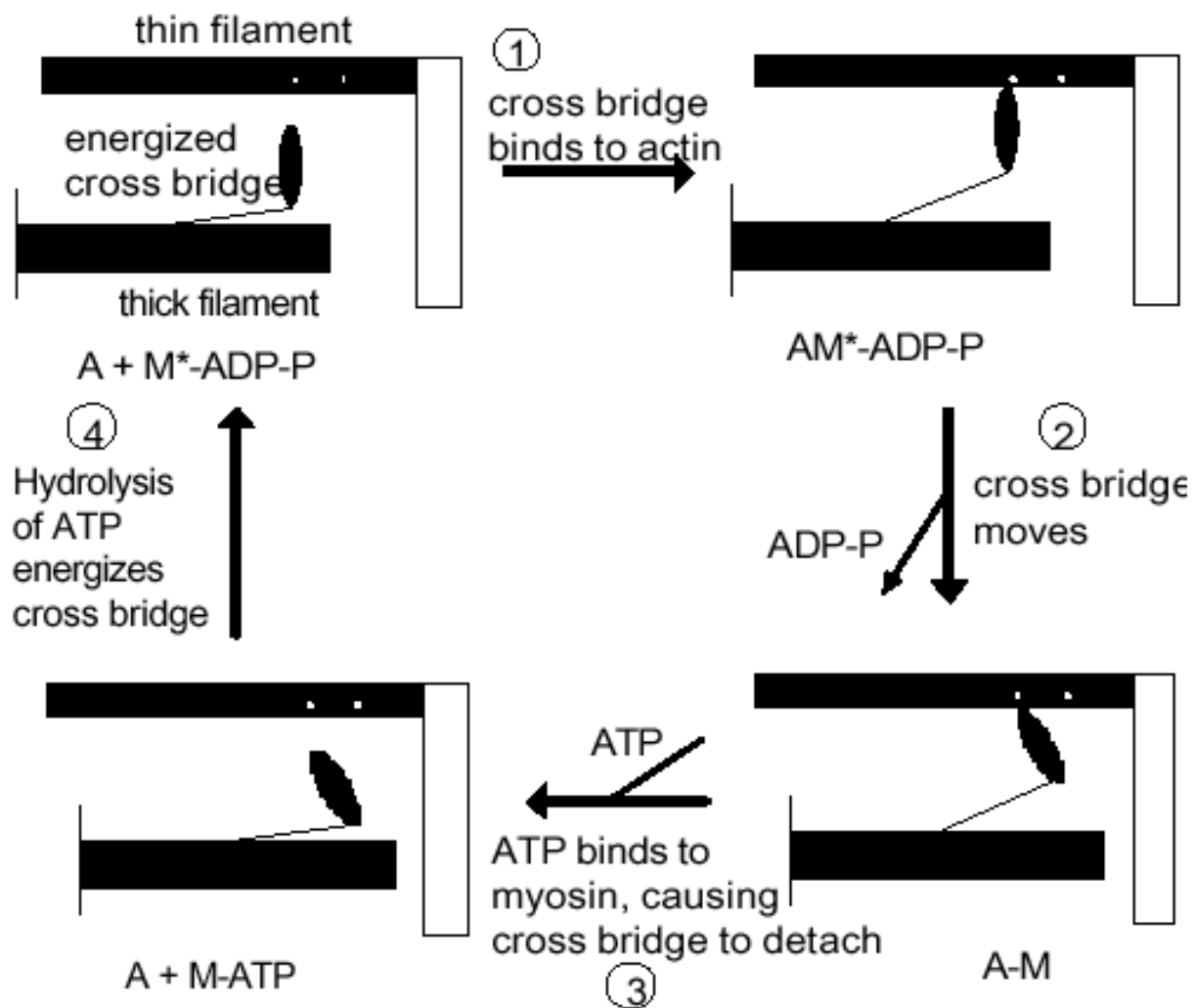
- In the base configuration, tropomyosin blocks the cross-bridge binding sites on the actin.
- Troponin contains binding sites for calcium, and binding of calcium causes the tropomyosin to move, exposing the actin binding sites for the cross-bridges to attach.



After calcium has bound to the troponin to expose the binding sites, the force development in the muscle happens in four stages:

1. An energized cross-bridge binds to actin.
2. The cross-bridge moves to its energetically preferred position, pulling the thin filament.
3. ATP binds to the myosin, causing the cross-bridge to detach.
4. Hydrolysis of ATP energizes the cross-bridge.

During muscle contraction, each cross-bridge goes through this cycle repeatedly.



# Cardiac muscle

- The ability of a muscle to produce tension depends on the overlap between thick and thin filaments.
  - Skeletal muscle; always close to optimal overlap
  - Not the case for cardiac muscle; force dependent on length

- Cross bridge binding and detachment depends on tension. The rate of detachment is higher at lower tension
- Experiments show that attachment and detachment of cross-bridges depends not only on the current state of the muscle, but also on the history of length changes.

# Important quantities

- Isometric tension ( $T_0$ ): the tension generated by a muscle contracting at a fixed length. The maximum isometric tension (for a maximally activated muscle) is approximately constant for skeletal muscle, but for cardiac muscle it is dependent on length.
- Tension ( $T$ ): Actively developed tension. Normally a function of isometric tension and the rate of shortening:

$$T = T_0 f(V),$$

where  $V$  is the rate of shortening and  $f(V)$  is some *force-velocity relation*.

- Fibre extension ratio ( $\lambda$ ): Current sarcomere length divided by the slack length.

# Force-velocity relations

- The classical equation of Hill (1938) describes the relation between velocity and tension in a muscle that contracts against a constant load (*isotonic* contraction).

$$(T + a)V = b(T_0 - T)$$

- $T_0$  is the isometric tension and  $V$  is the velocity.  $a$  and  $b$  are parameters which are fitted to experimental data.
- Recall that  $T_0$  is constant for skeletal muscle cells, dependent on length in cardiac cells



Velocity as function of force:

$$V = b \frac{T_0 - T}{T + a}$$

Force as function of velocity:

$$T = \frac{bT_0 - aV}{b + V}$$

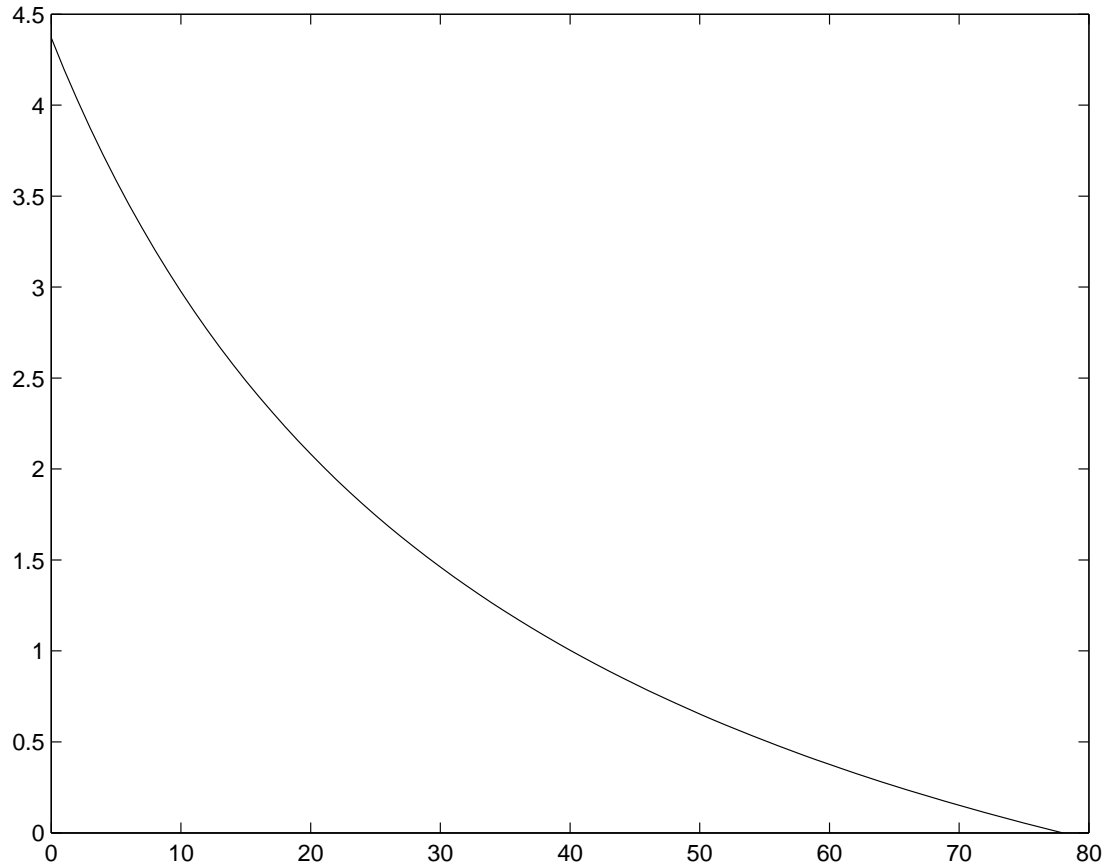
Inserting  $T = 0$  in the Hill equation gives

$$V_0 = \frac{bT_0}{a},$$

which is the maximum contraction velocity of the muscle. The maximum velocity  $V_0$  is sometimes regarded as a parameter in the model, and used to eliminate  $b$ .

$$-\frac{V}{V_0} = \frac{T/T_0 - 1}{T + a}$$

# A typical Hill-curve



●  $x$ -axis; force (g/cm<sup>2</sup>)

●  $y$ -axis; velocity (cm/s)

To summarize, the force development in muscle fibers depends on the rate of cross-bridges binding and detaching to the the actin sites. This in turn depends on

- Sarcomere length
- Shortening velocity
- (History of length changes.)
- The proportion of actin sites available, which depends on the amount of calcium bound to Troponin C (which in turn depends on the intracellular calcium concentration and tension).

# A model for the contracting muscle

A detailed mathematical model for the actively contracting muscle fiber should include the following:

- The intracellular calcium concentration,  $[Ca^{2+}]_i$ .
- The concentration of calcium bound to Troponin C,  $[Ca^{2+}]_b$ . This depends on  $[Ca^{2+}]_i$  and the tension  $T$ .
- The proportion of actin sites available for cross-bridge binding. Depends on  $[Ca^{2+}]_b$ .
- The length-tension dependence.
- Force-velocity relation.

# An example model: HMT

- The Hunter-McCulloch-terKeurs (HMT) model was published in 1998
- Includes all features presented on the previous slides
- System of ODEs coupled with algebraic relations
- Original paper contains detailed description of experiments and parameter fitting

# Ca<sup>2+</sup> binding

- We regard  $[Ca_i^{2+}]$  as an input parameter (obtained from cell electrophysiology models)
- Calcium binding is described with an ODE

$$\frac{d[Ca^{2+}]_b}{dt} = \rho_0 [Ca^{2+}]_i ([Ca^{2+}]_{bmax} - [Ca^{2+}]_b) - \rho_1 \left(1 - \frac{T}{\gamma T_0}\right) [Ca^{2+}]_b$$

- Attachment rate increases with increased  $[Ca^{2+}]_i$  and decreases with increasing  $[Ca^{2+}]_b$
- Detachment rate decreases with increasing tension  $T$ , and increases with increasing  $[Ca^{2+}]_b$

# Binding site kinetics

- The process from calcium binding to exposure of binding sites is not instant, but subject to a time delay
- A parameter  $z \in [0, 1]$  represents the proportion of actin sites available for cross-bridge binding.
- Dynamics described by an ODE

$$\frac{dz}{dt} = \alpha_0 \left[ \left( \frac{[\text{Ca}^{2+}]_b}{C_{50}} \right)^n (1 - z) - z \right]$$



# Length dependence

- Isometric tension  $T_0$  depends on length ( $\lambda$ ) and number of available binding sites ( $z$ )
- The tension is given by an algebraic relation

$$T_0 = T_{ref}(1 + \beta_0(\lambda - 1))z,$$

where  $z$  is given by the previous equation.

# Force-velocity relation

- Active tension development depends on isometric tension and rate of shortening
- Force-velocity relation given by a Hill function

$$(T + a)V = b(T_0 - T)$$

# (More advanced T-V relation)

- Experimental data shows that the binding and detachment of cross-bridges depends not only on the present state of the muscle fiber, but also on the history of length changes
- The Hill function only includes the current velocity, so it is not able to describe this behavior
- The HMT model uses a standard Hill function, but with velocity  $V$  replaced by a so-called fading memory model, which contains information on the history of length changes
- For simplicity we here assume a classical Hill-type relation

- Active tension from Hill model

$$T = T_0 \frac{1 - aV}{1 + V},$$

- $a$  is a parameter describing the steepness of the force-velocity curve (fitted to experimental data)

# HMT model summary

Tension  $T$  is computed from two ODEs and two algebraic relations :

$$\frac{d[\text{Ca}^{2+}]_b}{dt} = f_1([\text{Ca}^{2+}]_i, [\text{Ca}^{2+}]_b, T_{\text{active}}, T_0) \quad (1)$$

$$\frac{dz}{dt} = f_2(z, \lambda, [\text{Ca}^{2+}]_b) \quad (2)$$

$$T_0 = f_3(\lambda, z) \quad (3)$$

$$T_{\text{active}} = f_4(T_0, \lambda, t) \quad (4)$$

# Coupling to electrophysiology

- Coupling of the HMT model to an electrophysiology model is straight-forward.
- To increase the realism of the coupled model the cell model should include stretch-activated channels. This allows a two-way coupling between the electrophysiology and the mechanics of the muscle, *excitation-contraction coupling* and *mechano-electric feedback*.

# Summary (1)

- The force-development in muscles is caused by the binding of cross-bridges to actin sites on the thin filaments.
- The cross-bridge binding depends on the intracellular calcium concentration, providing the link between electrical activation and contraction (excitation-contraction coupling).
- Accurate models should include stretch-activated channels in the ionic current models (mechano-electric feedback).
- Heart muscle is more complicated to model than skeletal muscle, because the force development is length-dependent.

# Summary (2)

- The model for cross-bridge binding and force development is expressed as a system of ordinary differential equations and algebraic expressions
- The models can easily be coupled to ODE systems for cell electrophysiology, because of the dependence on intracellular calcium



# Modeling the complete muscle (1)

- The HMT model only gives the force development in a single muscle fibre.
- The deformation of the muscle is the result of active force developed in the cells, and passive forces developed by the elastic properties of the tissue.
- Modeling the deformation of the muscle requires advanced continuum mechanics
- Detailed description beyond the scope of this course, simple overview provided for completeness

# Modeling the complete muscle (2)

- The key variables in solid mechanics problems are *stresses* and *strains*
- Stress = force per area, strain = relative deformation
- Stress tensor:

$$\sigma_{ij} = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_{22} & \sigma_{23} \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix}$$

- Strain tensor:

$$\epsilon_{ij} = \begin{bmatrix} \epsilon_{11} & \epsilon_{12} & \epsilon_{13} \\ \epsilon_{21} & \epsilon_{22} & \epsilon_{23} \\ \epsilon_{31} & \epsilon_{32} & \epsilon_{33} \end{bmatrix}$$

# Modeling the complete muscle (3)

- The equilibrium equation relevant for the heart reads

$$\nabla \cdot \sigma = \mathbf{0}$$

(The divergence of the stress tensor is zero)

- Vector equation = 3 scalar equations, symmetric stress tensor = 6 scalar unknowns
- Equation is valid for any material, need to be complemented with information on material behavior
- Material described by *constitutive laws*, typically a *stress-strain relation*

# Simple stress-strain relation

- Say we pull a rod with length  $L$  and cross-sectional area  $A$  using a force  $F$ . This results in a length increase  $\Delta L$ .
- The following relation is valid for small deformation in many construction materials:

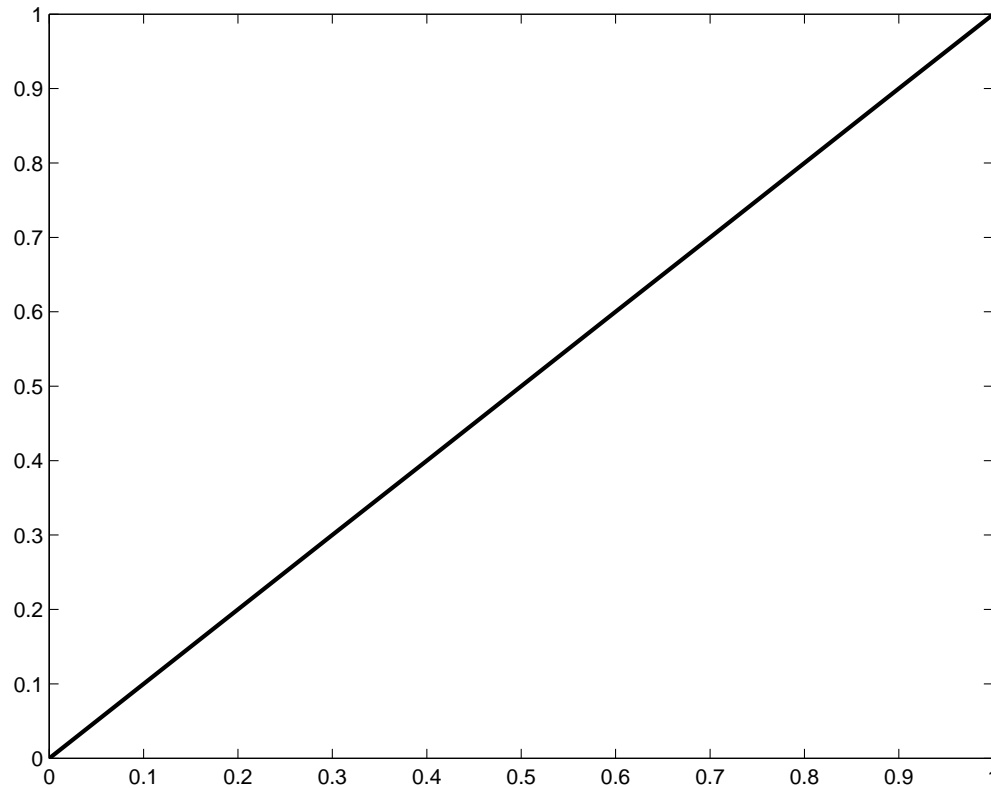
$$\frac{F}{A} = E \frac{\Delta L}{L}$$

- The quantity  $\Delta L/L$  is called the *strain*,  $F/A$  is the *stress*, and  $E$  is a parameter characterizing the stiffness of the material (Young's modulus).
- This relation is called a stress-strain relation. This linear relation is known as Hooke's law.

Stress-strain relations in the heart are much more complicated, but the principle is exactly the same.

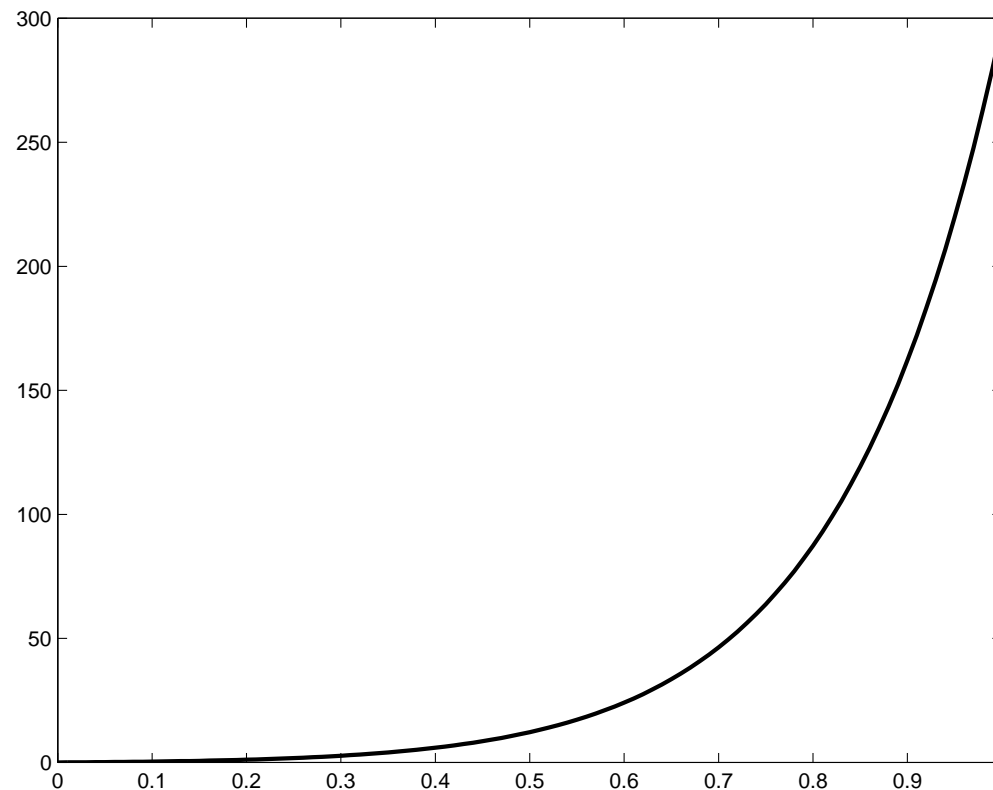
# A linear elastic material

- Hooke's law
- Normally applicable only for small deformations



# Non-linear (hyper)elastic materials

- For materials undergoing large elastic deformations, the stress-strain relation is normally non-linear



- For the heart, the tissue is also anisotropic, with different material characteristics in different directions

# Coupling active and passive stresses

To model both the active contraction and the passive material properties of the heart, we introduce a stress that consists of two parts.

$$T = \sigma_p + \sigma_a.$$

- Passive stress  $\sigma_p$  is computed from a stress-strain relation.
- Active stress  $\sigma_a$  is computed from a muscle model like the HMT model.
- The sum of the two stresses is inserted into the equilibrium equation, which is then solved to determine the deformations

# Complete model

The complete electrical and mechanical activity of one heart beat consists of the following components:

- Cell model describing electrical activation.
- Cell model describing contraction (for instance HMT). Receives calcium concentration from el-phys model and gives tension as output.
- Elasticity equation describing the passive material properties. Takes the tension from the HMT model as input, returns the deformation of the muscle.
- Equation describing the propagation of the electrical signal through the tissue (bidomain model).



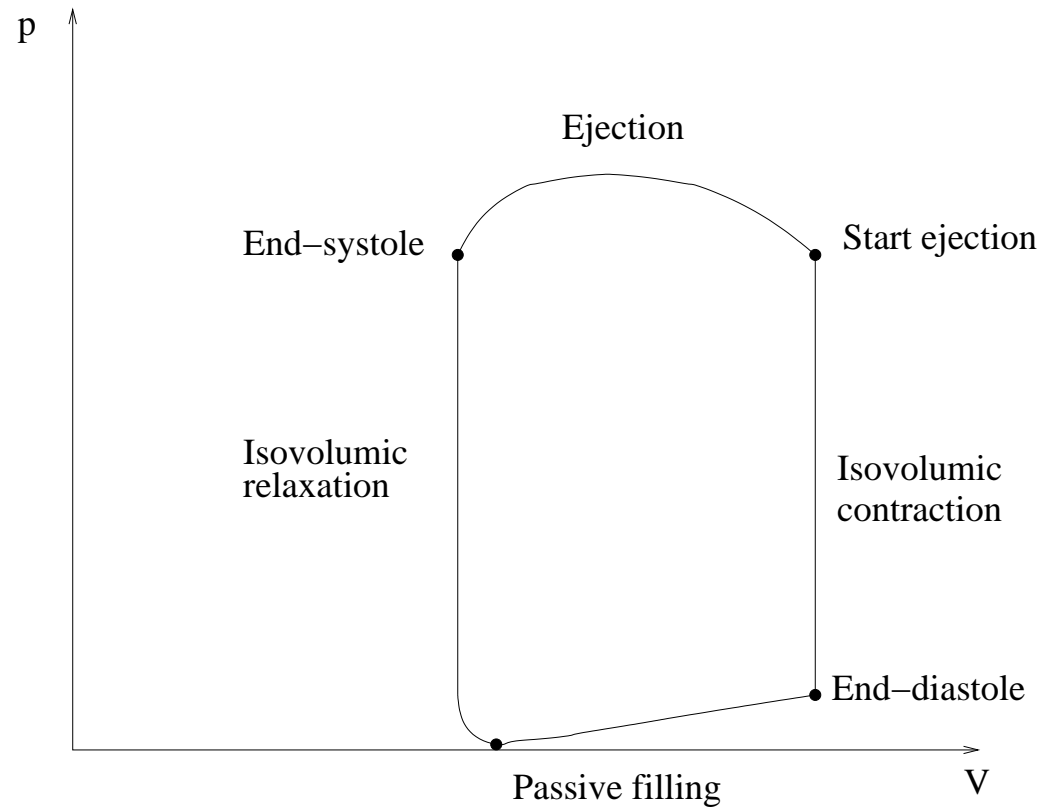
# Note on boundary conditions

- Normal to assume a combination of displacement and pressure boundary conditions
- Zero displacement at the base, zero pressure at the epicardial (outer) surface (really an approximation, since this varies with breathing etc)
- Pressure boundary conditions on endocardial (inner) surface varies through the heart cycle
- Additional difficulty; endocardial pressure is developed by the contracting muscle, and also depends whether the heart valves are open or closed

# The four phases of the heart cycle

- Passive filling; the muscle is relaxed and is filled with blood from the venous system (and the atria). Increase of pressure (small) and volume (large)
- Isovolumic contraction; the heart muscle contracts while all valves are closed. The cavity pressure increases while the volume stays constant
- Ejection; the valves open to allow blood to be ejected into the arteries. Pressure increases at first, then drops. Volume decreases
- Isovolumic relaxation; the muscle is relaxing while all valves are closed. The volume remains constant while the pressure drops

# The pressure-volume loop



# Summary

- The force-development in muscles is caused by the binding of cross-bridges to actin sites on the thin filaments.
- The cross-bridge binding depends on the intracellular calcium concentration, providing the link between electrical activation and contraction (excitation-contraction coupling).
- Accurate models should include stretch-activated channels in the ionic current models (mechano-electric feedback).

- Heart muscle is more complicated to model than skeletal muscle, because the force development is length-dependent.
- The complete heart muscle may be modeled as an elastic medium where the stress tensor has one active and one passive part.