# Mechanical properties of the heart muscle

# Outline

- Crossbridge theory. How does a muscle contract?
- A mathematical model for heart muscle contraction.
- Coupling to electrophysiology

# 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

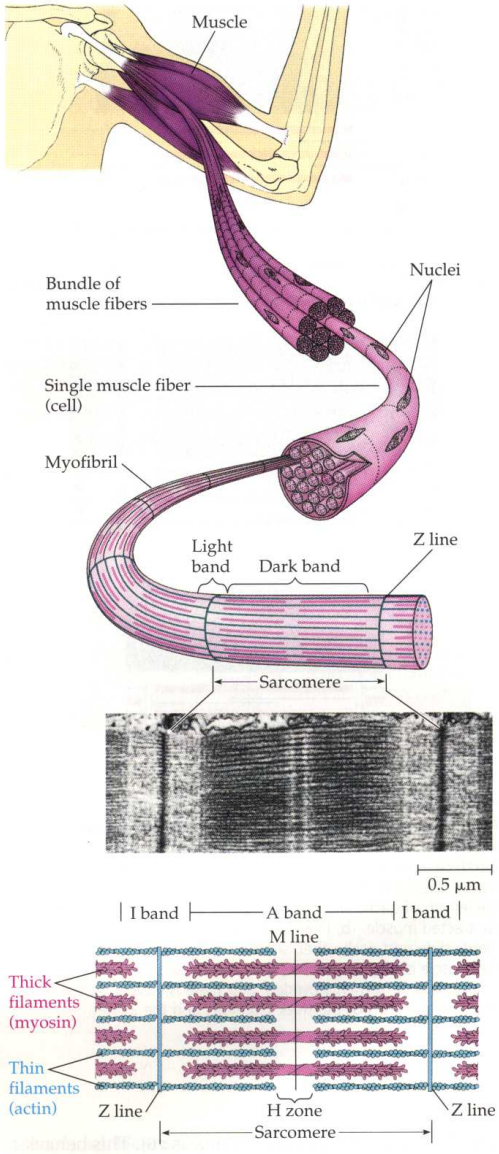
# Muscle cells

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

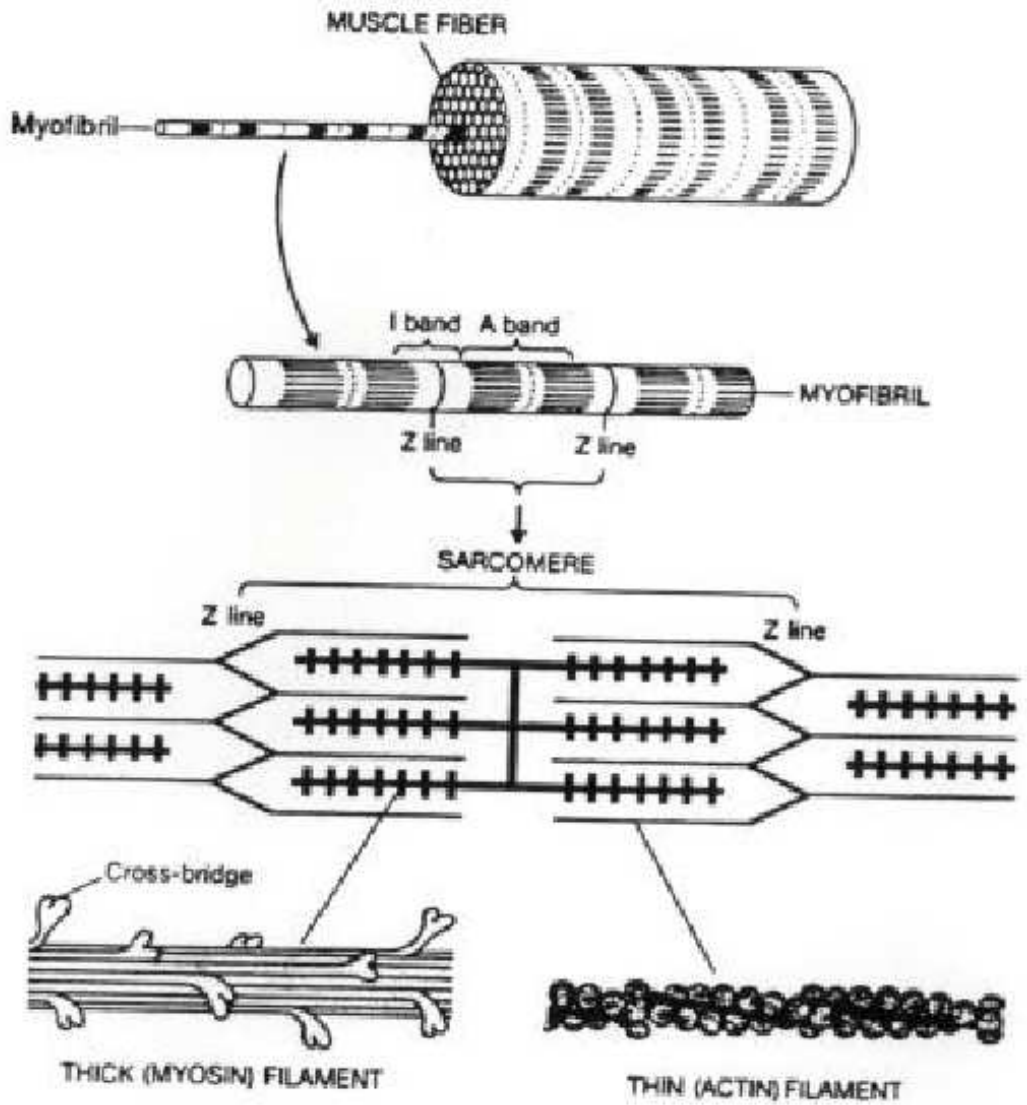
Most mathematical models have been developed for skeletal muscle.

# Striated muscle cells

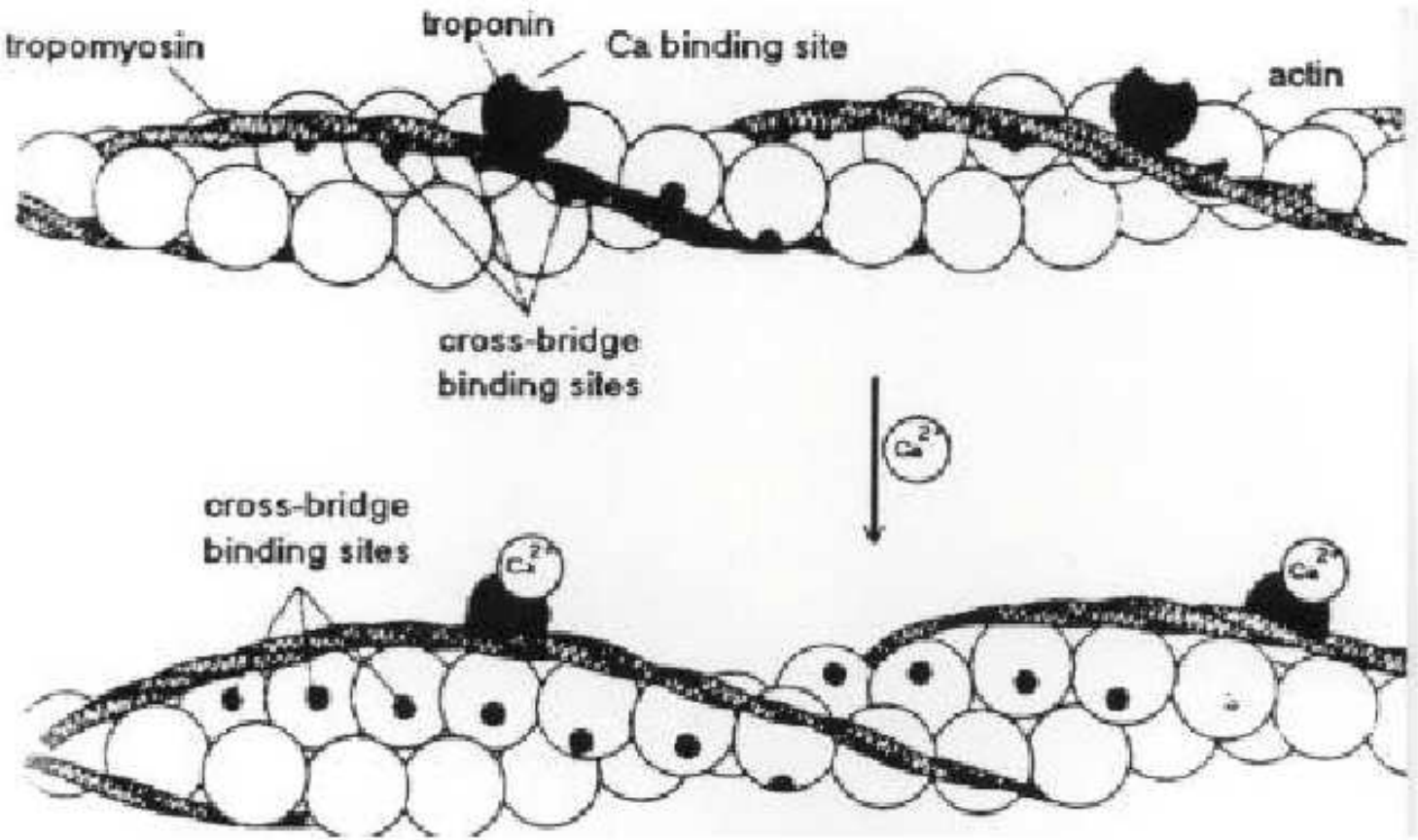
- Skeletal muscle cells and cardiac muscle cells have similar, but not identical, contractile mechanisms.
- A muscle cell (cardiac or skeletal) contains smaller units called myofibrils, which in turn are made up of sarcomeres.
- The sarcomere contains overlapping thin and thick filaments, which are responsible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


MUSCLE FIBER
Myofibril
I band
A band
MYOFIBRIL
Z line
Z line
SARCOMERE
Z line
Z line
Cross-bridge
THICK (MYOSIN) FILAMENT
THIN (ACTIN) FILAMENT

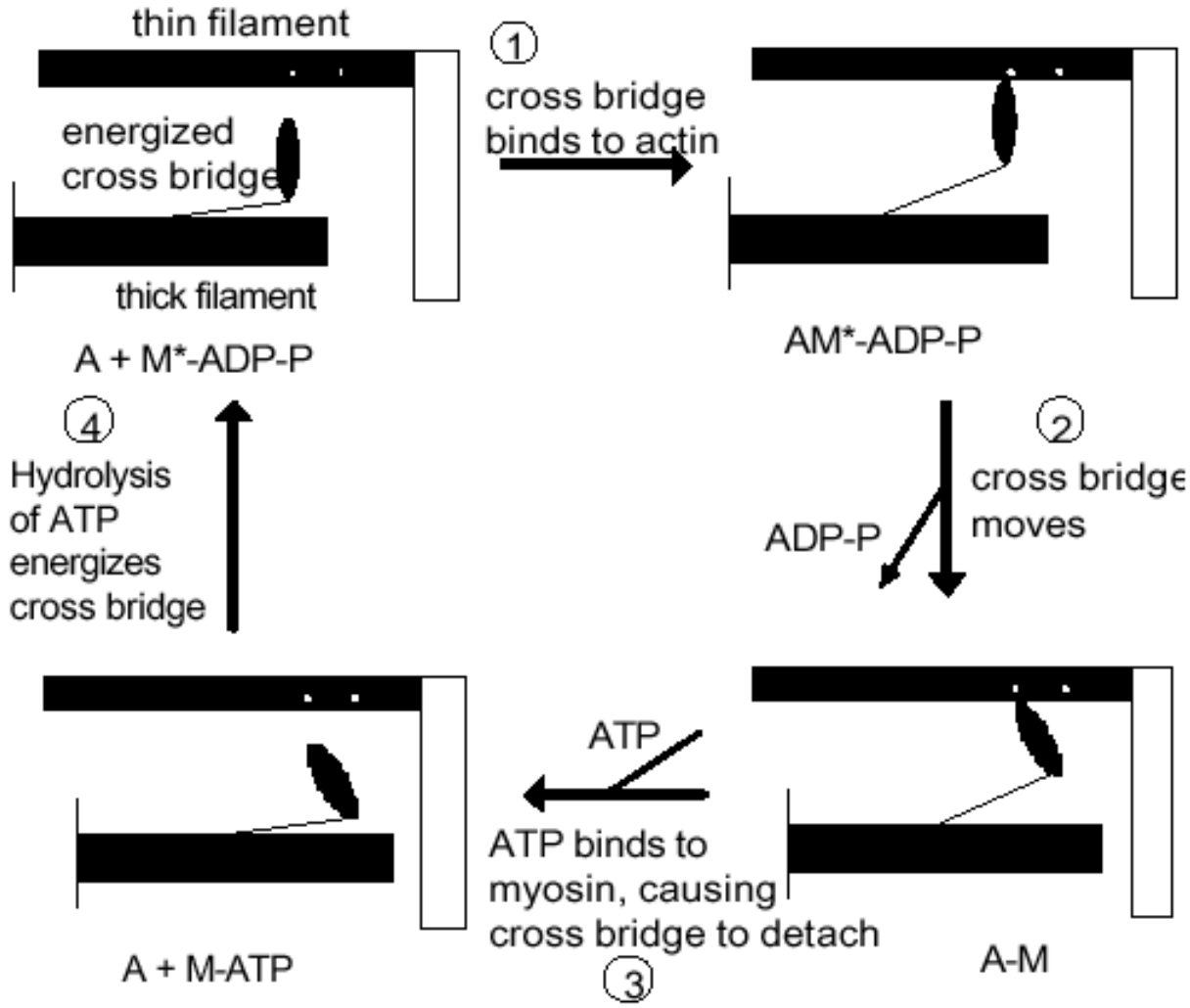
- In the base configuration, tropomyosin blocks the cross-bridge binding sites on the actin.
- Troponin contains binding sites for calcium, and binding of calcium causes the tropomyosin to move, exposing the actin binding sites for the cross-bridges to attach.


tropomyosin
troponin
Ca binding site
actin
cross-bridge
binding sites
$Ca^{2+}$
cross-bridge
binding sites
$Ca^{2+}$
$Ca^{2+}$

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.


thin filament
energized cross bridge
thick filament
A + M*-ADP-P
1
cross bridge binds to actin
AM*-ADP-P
2
cross bridge moves
ADP-P
3
ATP binds to myosin, causing cross bridge to detach
ATP
A-M
A + M-ATP
4
Hydrolysis of ATP energizes cross bridge

# 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:

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

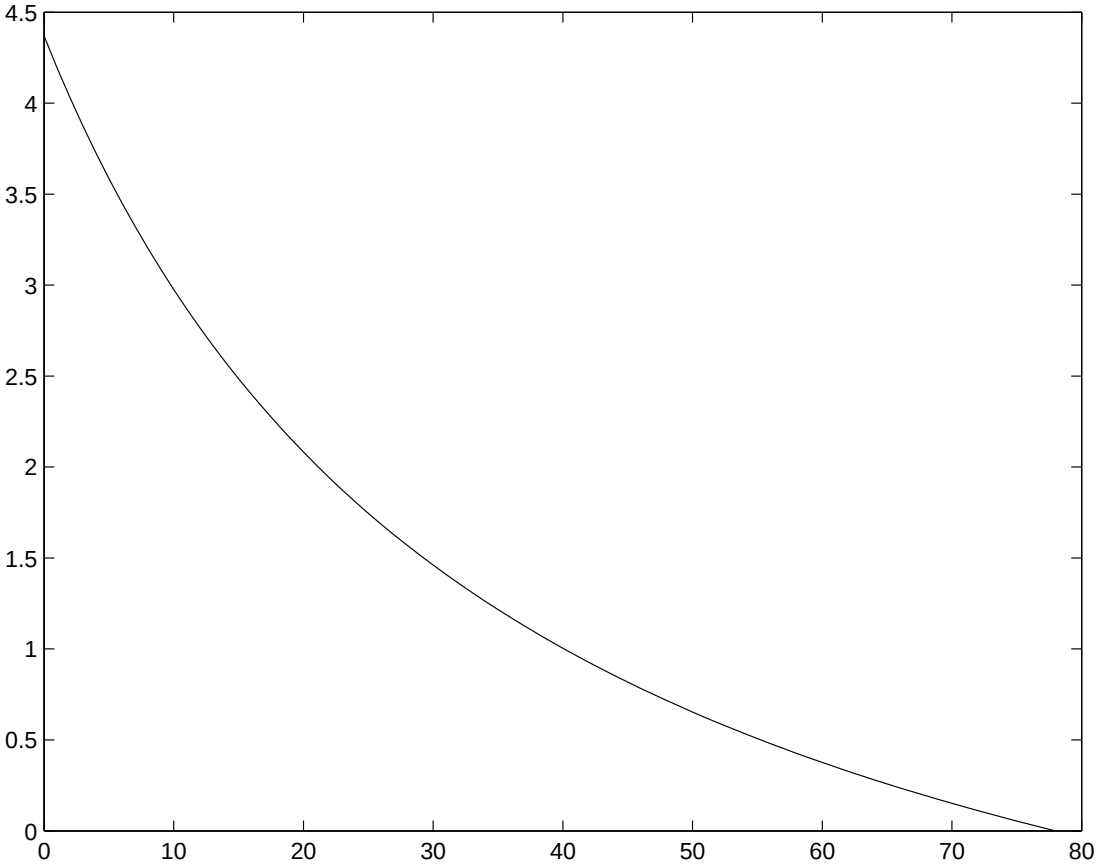
Inserting $T = 0$ in the Hill equation gives

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

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$^2$)
- $y$-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, $[\mathrm{Ca}^{2+}]_i$.
- The concentration of calcium bound to Troponin C, $[\mathrm{Ca}^{2+}]_b$. This depends on $[\mathrm{Ca}^{2+}]_i$ and the tension $T$.
- The proportion of actin sites available for cross-bridge binding. Depends on $[\mathrm{Ca}^{2+}]_b$.
- 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

# $\mathrm{Ca}^{2+}$ binding

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

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

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

# 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

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

# 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 :

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

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

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

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

# 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