Fundamental cardiac mechanics
Part I: Ode models of circulation and cell contraction

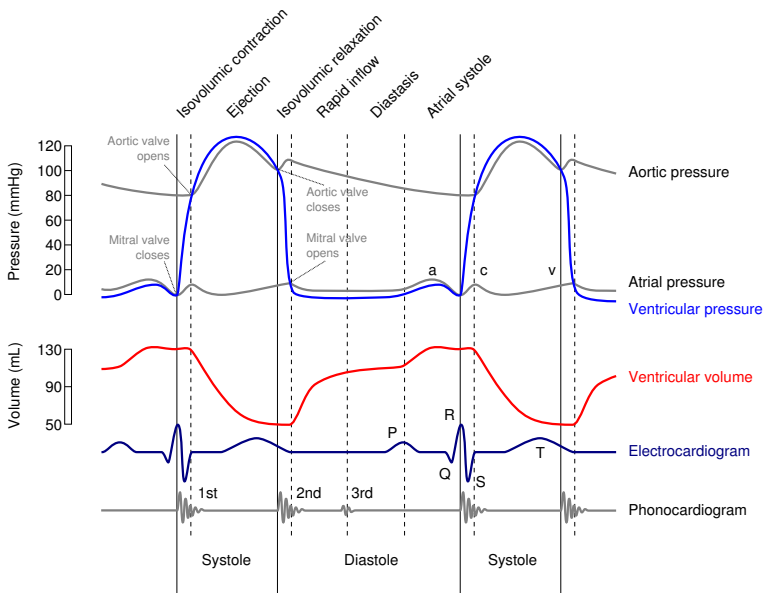
Joakim Sundnes

Jun 17, 2016

Outline

- The heart as a pump
  - The pressure volume loop
  - Phases of the cardiac cycle
  - Elastance models of the heart and circulation
- Introduction to sliding filament theory
  - Micro-structure of force development
  - Cross-bridge cycling
  - Regulation of force
  - Models of cell contraction

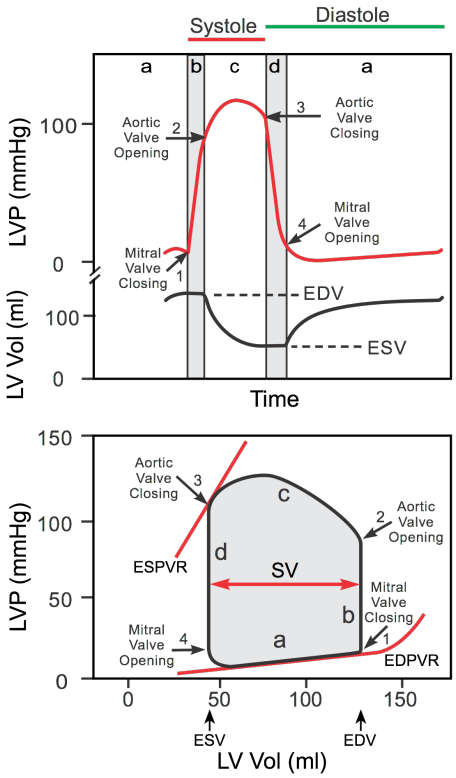
Overview of cardiac function (1)



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 decrases
- Isovolumic relaxation; the muscle is relaxing while all valves are closed. The volume remains constant while the pressure drops

The pressure-volume loop



Why model all this?

- Understand fundamental mechanisms
- Investigate pathologies and interventions:
  - What happens if ...?
- Linking cell level processes to overall heart function (advanced)

How can it be modeled?

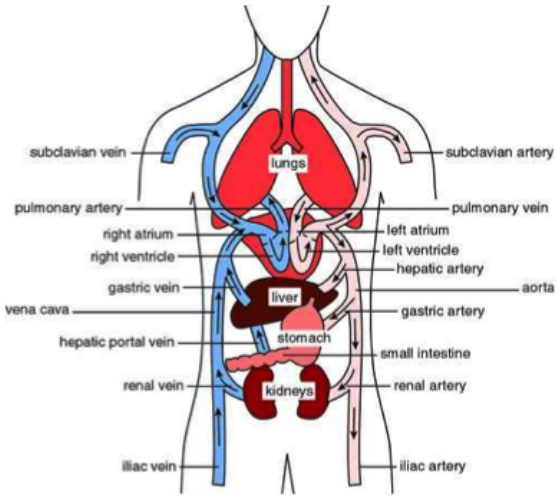
- Top-down (Today (June 17), morning lecture):
  - Derive relations for macroscopic function of the heart and other parts of the circulatory system
- Bottom-up/multiscale (Late morning/afternoon):
  - Model the biophysics of cell contraction

– Integrate into tissue/organ models
– Couple to models of circulation

Modeling the heart and circulation

- Overview of the circulatory system
- Important quantities
- Resistance and compliance vessels
- Models for the circulatory system
- Examples and extensions

The circulatory system



Important quantities (1)

- Heart rate, measured in beats per minute.
- Cardiac output: The rate of blood flow through the circulatory system, measured in liters/minute.
- Stroke volume: the difference between the end-diastolic volume and the end-systolic volume, i.e. the volume of blood ejected from the heart during a heart beat, measured in liters.

Important quantities (2)

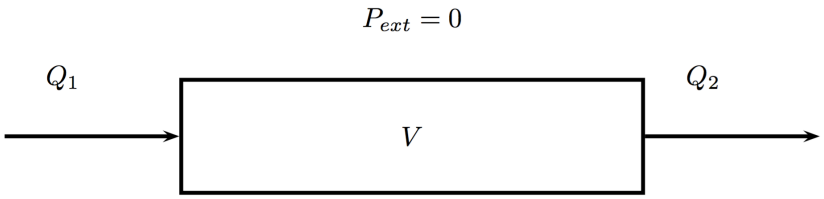
The cardiac ouput Q is given by

$$Q = FV_{stroke}$$

Typical values:

- $F = 80$ beats/minute.
- $V_{stroke} = 70\text{cm}^3/\text{beat} = 0.070$ liters/beat.
- $Q = 5.6$ liters/minute.

Resistance and compliance vessels



- V = vessel volume,
- P_{ext} = external pressure,
- P_1 = upstream pressure,
- P_2 = downstream pressure,
- Q_1 = inflow,
- Q_2 = outflow.

Resistance vessels

Assume that the vessel is rigid, so that V is constant. Then we have

$$Q_1 = Q_2 = Q_*.$$

The flow through the vessel will depend on the pressure drop through the vessel. The simplest assumption is that Q_* is a linear function of the pressure difference $P_1 - P_2$:

$$Q_* = \frac{P_1 - P_2}{R},$$

where R is the resistance of the vessel.

Compliance vessels

Assume that the resistance over the vessel is negligible. This gives

$$P_1 = P_2 = P_*$$

Assume further that the volume depends on the pressure P_*. We assume the simple linear relation

$$V = V_d + CP_*,$$

where C is the compliance of the vessel and V_d is the "dead volume", the volume at $P_* = 0$.

Vessels in the circulation

- All blood vessels can be viewed as either resistance vessels or compliance vessels. (This is a reasonable assumption, although all vessels have both compliance and resistance.)
- Large arteries and veins; negligible resistance, significant compliance.
- Arterioles and capillaries; negligible compliance, significant resistance.

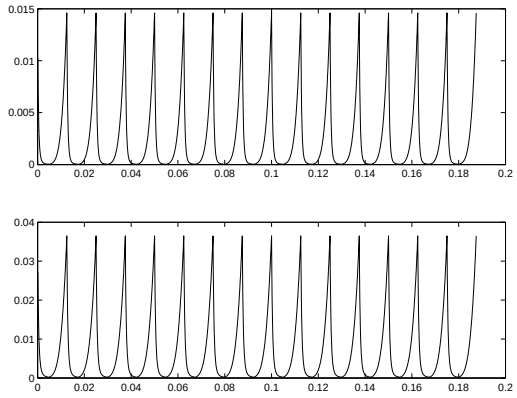
The heart as a compliance vessel (1)

The heart may be viewed as a pair of compliance vessels, where the compliance changes with time,

$$V(t) = V_d + C(t)P.$$

The function $V(t)$ should be specified so that it takes on a large value $C_{diastole}$ when the heart is relaxed, and a small value $C_{systole}$ when the heart contracts.

The heart as a compliance vessel (2)



From Hoppensteadt & Peskin, Modeling and Simulation in Medicine and the Life Sciences, Springer 2002.

Modeling the heart valves (1)

Characteristic properties of a heart valve:

- Low resistance for flow in the "forward" direction.
- High resistance for flow in the "backward" direction.

Modeling the heart valves (2)

The operation of the valve can be seen as a switching function that depends on the pressure difference across the valve. The switching function can be expressed as

$$S = \begin{cases} 1 & \text{if} P_1 > P_2 \\ 0 & \text{if} P_1 < P_2 \end{cases}$$

Modeling the heart valves (3)

The flow through the valve can be modeled as flow through a resistance vessel multiplied by the switching function. We have

$$Q_* = \frac{(P_1 - P_2)S}{R},$$

where R will typically be very low for a healthy valve.

Circulation dynamics (1)

For a compliance vessel that is not in steady state, we have

$$\frac{dV}{dt} = Q_1 - Q_2.$$

If we assume the vessel is connected to resistance vessels, the flows are given by

$$Q_j = \frac{P^{in} - P^{out}}{R_j}.$$

Circulation dynamics (2)

The flows Q_j depend on the pressures, which can be computed from the linear pressure-volume relation:

$$P_i = (V_i - V_{d,i})/C_i,$$

where $V_{d,i}, C_i$ are the unloaded volume and the compliance for vessel i. These are assumed constant for arteries and veins, and time dependent for the heart.

Another common formulation is to use the elastance instead of the compliance, $E_i = 1/C_i$, which gives

$$P_i = E_i(V_i - V_{d,i}),$$

Circulation dynamics (3)

The circulatory system can now be viewed as a set of compliance vessels connected by valves and resistance vessels. For each compliance vessel we have

$$\frac{V_i}{dt} = Q_i^{in} - Q_i^{out},$$

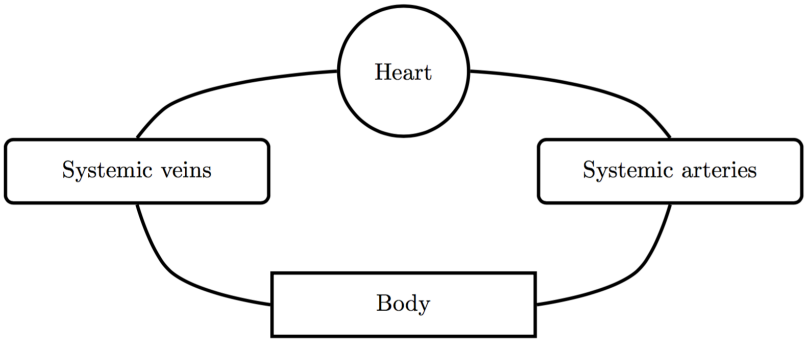
with flows given by

$$Q_i^{in} = \frac{P_{i-1} - P_i}{R_{i-1,i}} = \frac{E_{i-1}(V_{i-1} - V_{d,i-1}) - E_i(V_i - V_{d,i})}{R_{i-1,i}}$$
$$Q_i^{out} = \frac{P_i - P_{i+1}}{R_{i,i+1}} = \frac{E_i(V_i - V_{d,i}) - E_{i+1}(V_{i+1} - V_{d,i+1})}{R_{i,i+1}}$$

where we have introduced $R_{i,i+1}$ to denote the resistance between vessel i and vessel $i + 1$.

A simple model (1)

Consider first a simple model consisting of three compliance vessels; the left ventricle, the systemic arteries, and the systemic veins. These are connected by two valves, and a resistance vessel describing the flow through the systemic tissues.



A simple model (2)

For the left ventricle we have

$$\frac{dV_{lv}}{dt} = Q^{in} - Q^{out},$$

with Q^{in} and Q^{out} given by

$$Q_{in} = \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}},$$
$$Q_{out} = \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}}.$$

We get

$$\frac{dV_{lv}}{dt} = \frac{P_{sv} - P_{lv}}{S_{mi}R_{mi}} - \frac{P_{lv} - P_{sa}}{S_{ao}R_{ao}},$$

A simple model (3)

Similar calculations for the two other compliance vessels gives the system

$$\frac{dV_{lv}}{dt} = \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}} - \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}},$$
$$\frac{dV_{sa}}{dt} = \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}} - \frac{P_{sa} - P_{sv}}{R_{sys}},$$
$$\frac{dV_{sv}}{dt} = \frac{P_{sa} - P_{sv}}{R_{sys}} - \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}}.$$

With the pressures given by relations $P_i = E_i(V_i - Vd, i)$ To have a solvable system we need to specify parameters $R_{mi}, R_{ao}, R_{sys}, C_{sa}, C_{sv}$ and the function $C_{lv}(t)$.

A more realistic model (1)

The model can easily be improved to a more realistic model describing six compliance vessels:

- The left ventricle, $V_{lv}, E_{lv}(t)$,
- the right ventricle, $V_{rv}, E_{rv}(t)$,
- the systemic arteries, V_{sa}, E_{sa},
- the systemic veins, V_{sv}, E_{sv},
- the pulmonary arteries, and V_{pa}, E_{pa}, and
- the pulmonary veins, V_{pv}, E_{pv}.

A more realistic model (2)

The flows are governed by two resistance vessels and four valves:

- Systemic circulation, R_{sys},
- pulmonary circulation, R_{pu},
- aortic valve (left ventricle to systemic arteries), R_{ao}, S_{ao},
- tricuspid valve (systemic veins to right ventricle), R_{tri}, S_{tri},
- pulmonary valve (right ventricle to pulmonary arteries), R_{puv}, S_{puv},
- mitral valve (pulmonary veins to left ventricle) ,R_{mi}, S_{mi}.

A more realistic model (3)

This gives the ODE system

$$\begin{aligned}
\frac{V_{lv}}{dt} &= \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}} - \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}}, \\
\frac{dV_{sa}}{dt} &= \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}} - \frac{P_{sa} - P_{sv}}{R_{sys}}, \\
\frac{dV_{sv}}{dt} &= \frac{P_{sa} - P_{sv}}{R_{sys}} - \frac{S_{tri}(P_{sv} - P_{rv})}{R_{tri}}, \\
\frac{dV_{rv}}{dt} &= \frac{S_{tri}(P_{sv} - P_{rv})}{R_{tri}} - \frac{S_{puv}(P_{rv} - P_{pa})}{R_{puv}}, \\
\frac{dV_{pa}}{dt} &= \frac{S_{puv}(P_{rv} - P_{pa})}{R_{puv}} - \frac{P_{pa} - P_{pv}}{R_{pu}}, \\
\frac{dV_{pv}}{dt} &= \frac{P_{pa} - P_{pv}}{R_{pu}} - \frac{S_{mi}(P_{pv} - P_{lv})}{R_{mi}}.
\end{aligned}$$

with pressures given by the formulas above.

Exercise/tutorial

- Python/matlab code in repo: *SUURPh-summer-school/L14/circ_models*
- Three models:
  - Systemic (simple three-compartment model)
  - circ_no_atria (full circulation, six compartments)
  - circ_full (full circulation with atria, eight compartments)
- Run two test cases:
  - Aortic stenosis: Increase aortic resistance from 0.5 to 50
  - Physical exercise: Reduce systemic resistance from 246.9382 to 50
- What happens in the two cases?
- Is the model response realistic?

Summary

- The entire circulation can be described using simple the building blocks of compliance and resistance vessels
- Simple models fail to describe correct physiological response, but are easily extended with baroreflex and more compartments, for remarkably realistic pressure- and flow profiles (See for instance *http://www.physiome.org/Models/*)

- Even with 50+ compartments, the heart is described as a time varying elastance:
  - Hard to relate changes on cell level to overall contractility and stiffness (elastance)
  - What about regional injuries such as an infarct?
- Multiscale models offer another dimension of modeling, integrating from the cell level to tissue and the complete organ

Multiscale mechanical models

- Describe how the electrical signal triggers contraction of a single cell
- Connect cells, embed in tissue
- Couple with circulation models for flows and pressures (boundary conditions)

Modeling cardiac cell contraction

- Crossbridge theory. How do muscles contract?
- A model for muscle contraction.
- Coupling to electrophysilogy (excitation-contraction coupling)

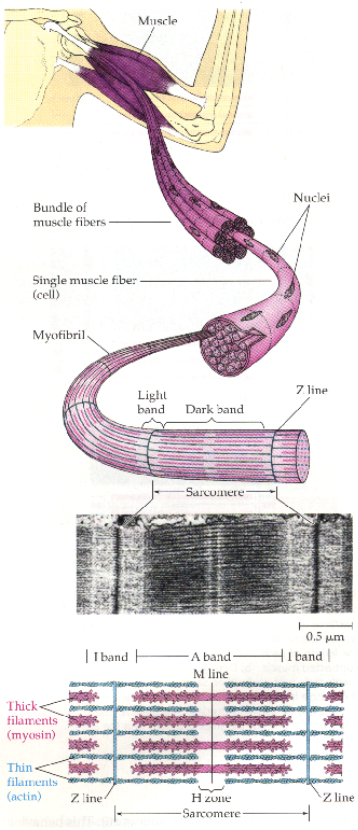
Three main groups of muscle cells

- Smooth muscle
- Cardiac muscle
- Skeletal muscle

Cardiac muscle cells are so-called striated muscles, and have very similar contractile mechanisms. Skeletal muscle has been most extensively studied and modeled.

Striated muscle cells

- 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.



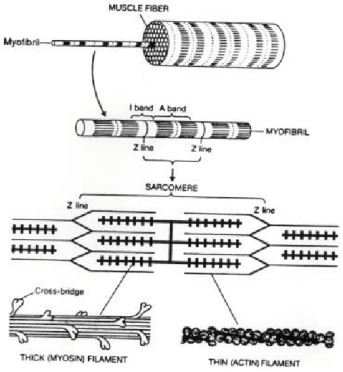
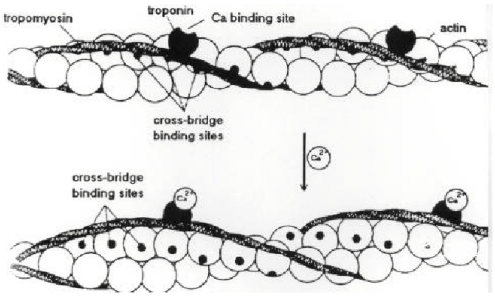


Figure 1: * Thick filaments are made up of the protein myosin. The myosin molecules have heads which form cross-bridges that interact with the thin filaments to generate force. * Thin filaments contain the three proteins actin, tropomyosin and troponin. * The actin forms a double helix around a backbone formed by tropomyosin.

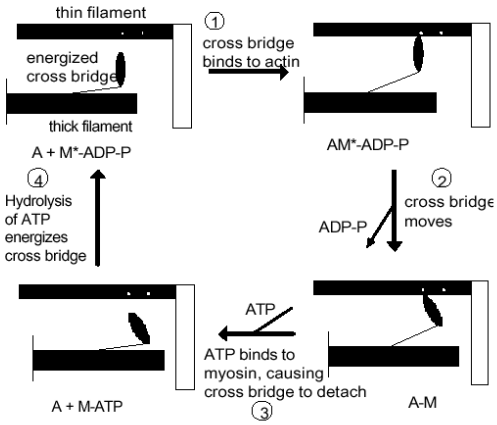
Overlapping thin and thick filaments

Force regulation



- 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.

The cross-bridge cycle (1)



The cross-bridge cycle (2)

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

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

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

Many factors affect force development

- Effective overlap of thick and thin filaments; overlap and force increase when cell is stretched, up to a limit
- Velocity of contraction; cross-bridge cycle cannot "keep up" with high contraction rates, reducing developed tension
- Cooperativity; a formed cross bridge increases the likelyhood of nearby cross-bridges to form

Important quantities

- Isometric tension (T_0): the tension generated by a muscle contracting at a fixed length. Depends on the activation level (i.e. Ca concentration) and length (stretch) of the muscle cell
- Tension (T): Tension developed during active shortening. In phenomenological models, this is often obtained by a scaling of the isometric tension: $T = T_0 f(V)$, where V is the rate of shortening and $f(V) < 1$ is some *force-velocity relation*.

Force-velocity relations (1)

- 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

Force-velocity relations (2)

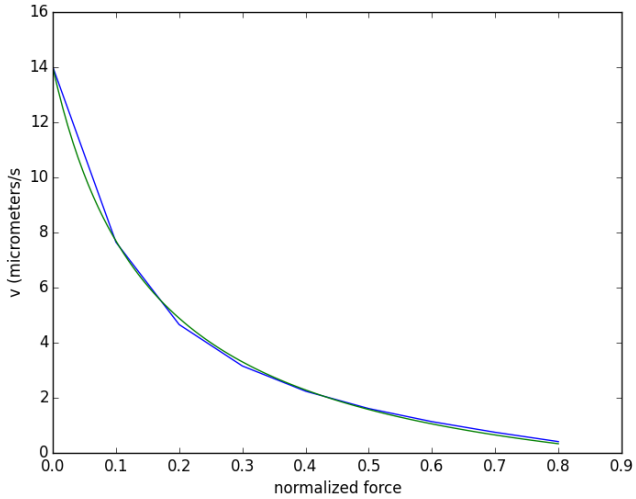
Velocity as function of force:

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

Force as function of velocity:

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

A typical Hill-curve



Force-velocity relation for the model by Rice et al (2008).

Summary of model requirements

A model of cell contraction must include the following:

- Calcium binding to Troponin C
- Exposure of cross bridge binding sites on the actin
- Cycling of cross-bridges to develop force
- Force-dependence on filament overlap and contraction velocity
  - Often phenomenological (Hunter et al (1998), Niederer et al (2006))
  - Recent models are more mechanistic (Rice et al (2008), Campbell et al (2009))

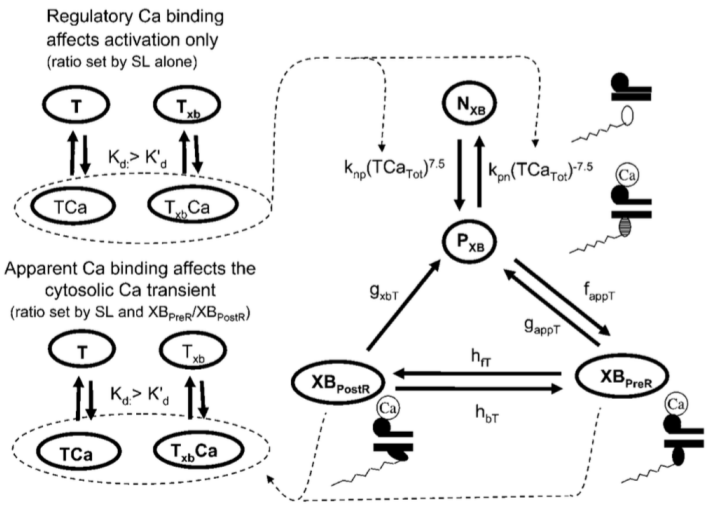
An example model; Rice et al (2008)

- Rice, Wang, Bers, de Tombe: *Approximate Model of Cooperative Activation and Crossbridge Cycling in Cardiac Muscle Using Ordinary Differential Equations*, Biophysical journal, 2008.
- A hybrid model;
  - Some model components described in great detail and biophysical rigour

  - Some components deliberately simplified and phenomenological, to keep complexity at a reasonable level

- Conceptually simple (but the devil is in the details)

The model has eight main state variables



+ 3 mechanical (Sarcomere length and crossbridge distortions). Calcium is considered an input variable.

Two ODEs describe calcium binding and detachment

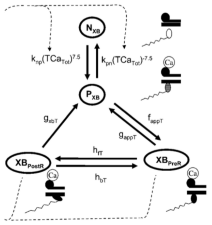
The model treats Ca binding sites with nearby cross-bridges separately from those without nearby cross-bridges:

$$\frac{dTRPN_{CaL}}{dt} = k_{onT}Ca_i(1 - TRPN_{CaL}) - k_{offLT}TRPN_{CaL}$$
$$\frac{dTRPN_{CaH}}{dt} = k_{onT}Ca_i(1 - TRPNCaH) - k_{offHT}TRPN_{CaH}$$

The sites with bound cross-bridges have a higher Ca affinitiy, represented by a lower detachment rate: $k_{offHT} < k_{offLT}$.

Six ODEs describe cross-bridge (XB) cycling

$$\frac{dN_{NoXB}}{dt} = k_{pnT}P_{NoXB} - k_{npT}N_{NoXB}$$
$$\frac{dP_{NoXB}}{dt} = k_{npT}N_{NoXB} - k_{pnT}P_{NoXB}$$
$$\frac{dN}{dt} = k_{pn}P - k_{npT}N$$
$$\frac{dP}{dt} = k_{npT}N - k_{pn}P - f_{appT}P + g_{appT}XB_{prer} + g_{xbT}) * XB_{postr}$$
$$\frac{dXB_{prer}}{dt} = f_{appT}P + h_{bT}XB_{postr} - (g_{appT} + h_{fT})XB_{prer}$$
$$\frac{dXB_{postr}}{dt} = h_{fT}XB_{prer} - (h_{bT}XB_{postr} + g_{xbT}) * XB_{postr}$$



Only strongly-bound XBs develop force

Force is proportional to the number of strongly bound XBs

$$F \sim (XB_{prer} + XB_{postr})$$

The Rice model describes the XBs as linear springs. The force developed by a cross bridge is equal to a spring constant multiplied with its distortion (strain):

$$F \sim k_{XB}(XB_{prer}xXB_{prer} + XB_{postr}xXB_{postr})$$

Concept originally presented by Razumova et al (1999).

Cross bridge distortion comes from two sources

- Lengthening or shortening a muscle will change the distortion of all strongly bound XBs. In the model the XB distortions depend on dSL/dt, with SL being sarcomere length.
- Cross-bridges going from pre- to post-rotation state (and back) will induce a distortion (x_0)

$$\frac{dxXB_{prer}}{dt} \sim \frac{dSL}{dt} + (-f_{appT}xXB_{prer} + hbT * (xXB_{postr} - (x_0 + xXB_{prer})))$$
$$\frac{dxXB_{postr}}{dt} \sim \frac{dSL}{dt} + h_{fT}(xXBprer + x_0 - xXBpostr)$$

Warning: The published model includes much more complex expressions. The important part is the overall concept.

Demo of classical cell mechanics experiments

From Rice et al (2008).

Coupling to electrophysiology

- Coupling of the Rice model to an electrophysiology (EP) model is straightforward; just take Ca from EP model as input to Rice model.
- Often some overlap, since most EP models describe binding of Ca to Troponin; we need to adjust the models slightly to get the right Ca dynamics.
- Can be extended with more mechanisms of mechano-electric feedback (MEF), such as stretch-activated channels.