Mathematical modeling of ischemia and infarction

Mostly based on Cimponeriu, Starmer and Bezerianos:
A theoretical analysis of acute ischemia and infarction using ECG reconstruction on a 2-D model of myocardium

Outline

- Definitions.
- Clinical effects.
- Cellular changes during ischemia.
- Mathematical models on cell and tissue level.
- Results.

Definitions

- A part of the heart which lacks sufficient blood supply is called ischemic. The condition is normally caused by an obstruction of one or more of the coronary arteries. (Angina pectoris)
- If the obstruction of blood flow is sufficiently severe, the cells in the affected region start to die. This is called an infarction.

Clinical effects

- Heart failure is the number one cause of death in the western world.
- The majority of heart failures are caused by obstruction of the coronary arteries supplying blood to the heart.
- The pumping function of the heart muscle is impaired by insufficient oxygen supply, but the most dangerous effect of ischemia and infarction is that it causes arrhythmias.

Effects on cellular level

The blood flow to the heart serves two main purposes:

- To provide oxygen and energy for the hard work performed by the heart muscle.
- To remove waste products from the tissue.

When blood supply is lost, the cells stop contracting almost immediately to save energy, and waste products start piling up in the tissue.

Three important effects of acute ischemia are

- Reduced ATP-concentration and increased ADP concentration, caused by insufficient oxygen supply.
- Reduced intracellular and increased extracellular potassium concentration. This is caused by reduced activity of potassium pumps, as well as opening of ATP-sensitive potassium channels.
- Reduced intra- and extracellular pH, caused by insufficient removal of waste products.

Effects on tissue level

- Ischemia decouples gap junctions, probably as an effect of reduced pH. This reduces the overall conductivity of the tissue.
- Necrotic tissue (infarction) has even lower conductivity, and may be regarded as non-conductive.

Modeling ischemic cells

The remainder of the slides present results from Cimponeriu et al: Theoretical analysis of acute ischemia and infarction.

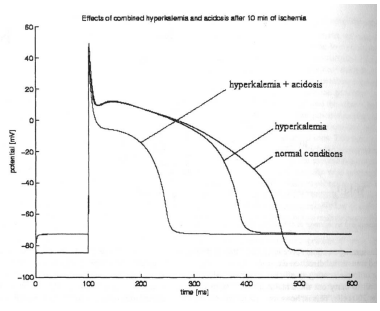
- The model for ischemic cells is based the Luo-Rudy I (LR I) cell model, which includes 5 ionic concentrations, 6 gate variables and 14 ionic currents.
- Extracellular potassium is a parameter in the model. The normal level is about 4.0 mM, and the ischemic condition is modeled by increasing this value to 9.0 mM.

- Reduced pH is known to reduce the conductance of a number of ion channels. The ischemic cell model includes this effect by reducing the conductance for sodium by 25 % and the conductance of calcium by 50 % .
- The effect of reduced ATP concentrations is not directly included in the model.

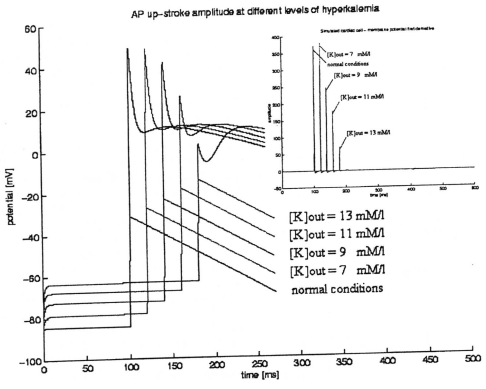
Experiments: The ischemic cell

- The cell model sketched above has been used to study the effects of ischemia on a single cell.
- Important in order to validate the mathematical model, and to be able to relate later tissue-scale observations to changes on the cellular level.

Hyperkalemia and acidosis



AP upstroke amplitude



- The previous slide shows how the upstroke amplitude is affected by hyperkalemia. The upstroke is first unaffected or slightly increasing, because the resting potential is now closer to the threshold. At later stages (higher $[K_o]$), the inactivation of sodium channels causes the upstroke amplitude to be reduced.
- Inactivation of sodium channels is not modeled explcitly, but comes as a secondary effect of the changed equilibrium potential.

A 2D model of ischemic tissue

The work in the article is based on a monodomain model of cardiac tissue.

$$C\frac{\partial V}{\partial t} = -I_{\text{ion}} + \frac{1}{R_i}\left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}\right)$$

Here, R_i is described to as the cell-to-cell resistance. (In this PDE setting, it is more correctly referred to as the spatially averaged resistance.)

FD formulation

$$\begin{aligned} V_{ij}^{t+dt} &= -dtI_{\text{ion}} + qV_{i-1,j}^t \\ &\quad + qV_{i+1,j}^t + qV_{i,j-1}^t + qV_{i,j+1}^t + (1-4q)V_{i,j}^t \end{aligned}$$

$$q = \frac{1}{R_i}\frac{dt}{dx^2}$$

- $R_i = 200\Omega$cm in healthy tissue, $R_i = 2000\Omega$cm in the infarcted (dead) tissue and $R_i = 1000\Omega$cm in a borderzone of injured tissue. Hence, the tissue is modeled as isotropic.
- $dx = dy = 125\mu$m $= 1/8$mm.
- $dt = 0.625$ms. (Very large for an explicit scheme)

Experiments: Propagation

- What are the effects of ischemia and infarction on action potential propagation ?
- 2D simulations on a layer of 200×200 "cells".
- Propagation in normal conditions: A straight line depolarization wave (Figure 6).

Normal propagation

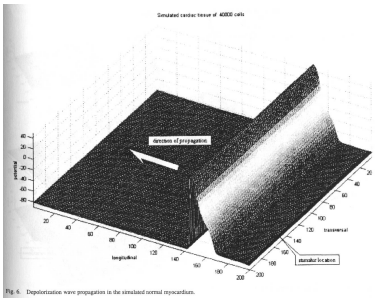
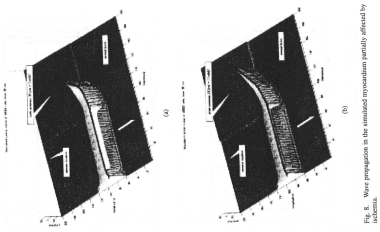


Fig. 6. Depolarization wave propagation in the simulated normal myocardium.

Propagation with ischemia

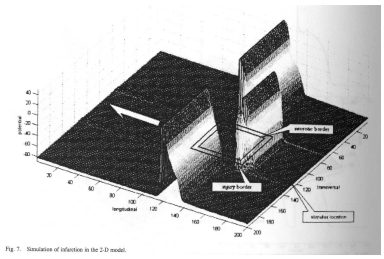
- An ischemic region, with hyperkalemia and acidosis, is defined as one quarter of the simulation domain.
- Demonstrates a visible tendency of re-entry, in particular in the early stages of ischemia.
- The re-entry tendency is linked to increased excitability and faster recovery of the ischemic cells.
- The phenomenon is still visible at later stages (higher $[K_o]$), but much less severe.
- Preliminary conclusion: The risk of arrythmias is largest in the early stages of ischemia. It is hence important to identify this condition in a clinical setting (ECG), and this motivates further experiments.



Propagation with an infarction

- An infarcted region (low conductivity, and hyperkalemia?) is defined as a square in the middle of the simulation domain.
- The infarct is surrounded by a transitional zone of injured tissue.
- Figure 7 shows the propagation obtained with this set-up. The depolarization wave breaks up because of the lower conductivity. This break-up of the signal may cause re-entry and arrythmias.

Propagation with infarcted region



Experiments: Reconstructed ECGs

- The findings of the previous experiments motivates further studies, more related to a clinical setting.
- In particular, it is of interest to study the changes on the ECG signal during the early phases of ischemia, when the risk of dangerous arrythmias was found to be particularly high.
- Computation of the ECG signal is difficult, because the model does not include neither the extracellular potential or a body surrounding the heart.

The ECG signal is reconstructed based on volume-conductor theory. Given the membrane current

$$I_{\text{membrane}} = I_{\text{ion}} + C\frac{\partial V}{\partial t},$$

the potential at a distant point (x_p, y_p, z_p) is given by

$$e_p = \int\int_{\text{surface}} \frac{I_{\text{membrane}}}{\sqrt{(x-x_p)^2 + (y-y_p)^2 + z_p^2}} dxdy$$

- Based on the described formula, the electrical potential is computed in 3 different points P_1, P_2 and P_3.
- Three ECG leads are defined as the potential difference between these points.

Results: Normal ECG

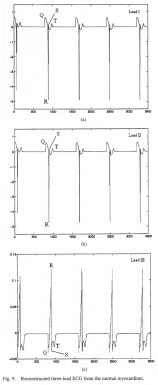


Fig. 9. Reconstructed three-lead ECG from the normal myocardium.

- Figure 9 shows the resulting three-lead ECG signals in normal conditions.
- Most of the important parts of a real ECG recording are present. One exception is the P-wave which results from the depolarization of the atria.
- The T-wave is inverted, because all the cells in the tissue model are of the same type.

Results: Early and acute ischemia

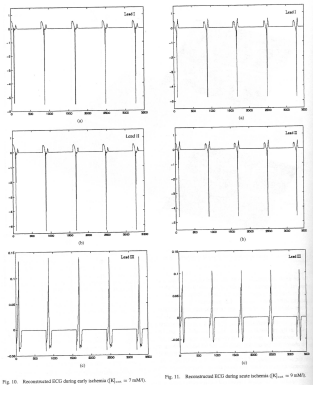


Fig. 10. Reconstructed ECG during early ischemia ($[K]_{out} = 7$ mM).

Fig. 11. Reconstructed ECG during acute ischemia ($[K]_{out} = 9$ mM).

- Figure 10 shows that the amplitude of the QRS complex increases in the early stage of ischemia, following the increased excitability of the cells.
- Figures 11 and 12 shows that the amplitude is reduced with increased hyperkalemia, following the reduced excitability caused by inactivation of sodium channels.
- Figure 12 shows that the QRS-complex becomes wider when $[K_o]$ is increased. This is caused by a reduced conduction velocity caused by the reduced excitability.

Results: Infarction

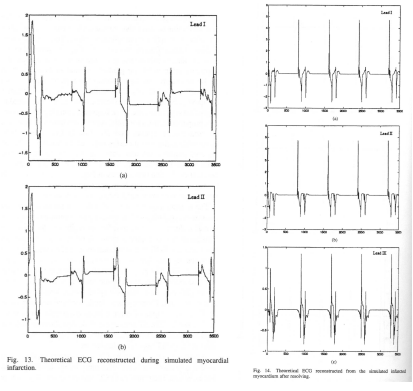


Fig. 13. Theoretical ECG reconstructed during simulated myocardial infarction.

Fig. 14. Theoretical ECG reconstructed from the simulated infarcted myocardium after remodeling.

- The nonuniform conductance and ionic concentrations ($[K_o]$) cause differences in the resting potential between the infarcted region and its surroundings. This leads to "injury currents".
- Comparing figures 13 and 14, we see that the most severe changes in the ECG signal are reversible, they are caused by the altered chemical concentrations. However, even after the chemical values have returned to normal, the ECG recordings are severely affected by the changed conductivity properties of the tissue.

Conclusions

- A fairly "simple" cardiac cell model was used to simulate normal and ischemic cells.
- An arrangement of 200×200 cells was used to study the effects of ischemia and infarction on signal propagation and ECG recordings.
- This simple experimental set-up was able to reproduce the qualitative characteristics of ECG signals.
- The ECG signal changed significantly during ischemia and infarction.
- Most important result: A simple mathematical model was sufficient to produce clinically interesting results.

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

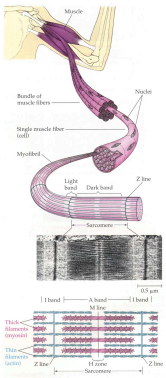
Muscle cells

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

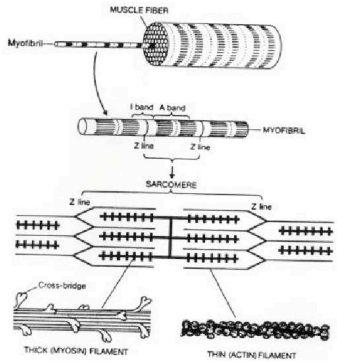
Most mathematical models have been developed for skeletal muscle.

Striated muscle cells

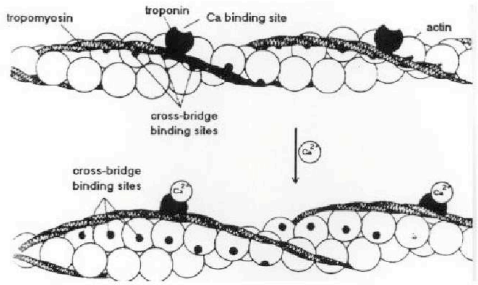
- Skeletal muscle cells and cardiac muscle cells have similar, but not identical, contractile mechanisms.
- A muscle cell (cardiac or skeletal) contains smaller units called myofibrils, which in turn are made up of sarcomeres.
- The sarcomere contains overlapping thin and thick filaments, which are responsible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



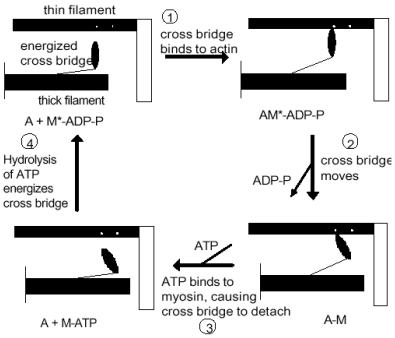
- In the base configuration, tropomyosin blocks the cross-bridge binding sites on the actin.
- Troponin contains binding sites for calcium, and binding of calcium causes the tropomyosin to move, exposing the actin binding sites for the cross-bridges to attach.



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 (λ): 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:

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

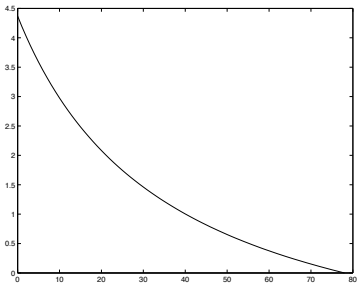
Inserting $T = 0$ in the Hill equation gives

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

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

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

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

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

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

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

Length dependence

- Isometric tension T_0 depends on length (λ) 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 :

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

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

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

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

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:

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

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 ΔL.
- The following relation is valid for small deformation in many construction materials:

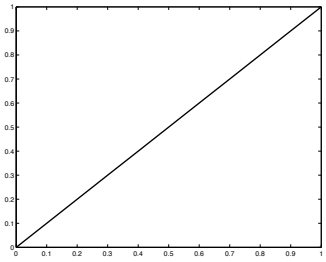
$$\frac{F}{A} = E\frac{\Delta L}{L}$$

- 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 compli-

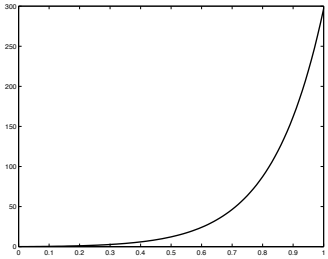
A linear elastic material

- 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 σ_p is computed from a stress-strain relation.
- Active stress σ_a is computed from a muscle model like the HMT model.
- The sum of the two stresses is inserted into the equibrium equation, which is then solved to determine the deformations

Complete model

The complete electrical and mechanical activity of one heart beat consists of the follwoing 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).

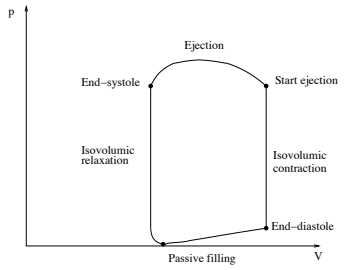
Note on boundary conditions

- 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 decrases
- 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.

Models for the circulatory system

Outline

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

The circulatory system

Figure from Hoppensteadt og Peskin: Modeling and simulation in medicine and the life sciences.

Important quantities

- 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.

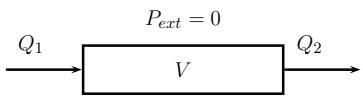
The cardiac ouput Q is given by

$$Q = FV_{stroke}$$

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

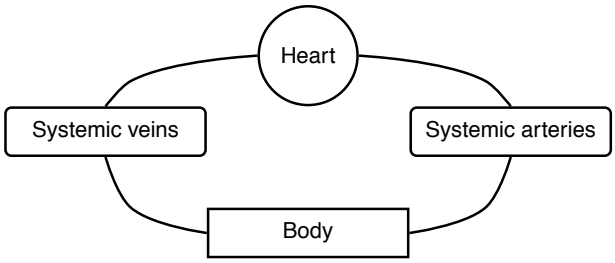
$$P_1 = P_2 = P_*$$

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 $P_* = 0$.

- 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.

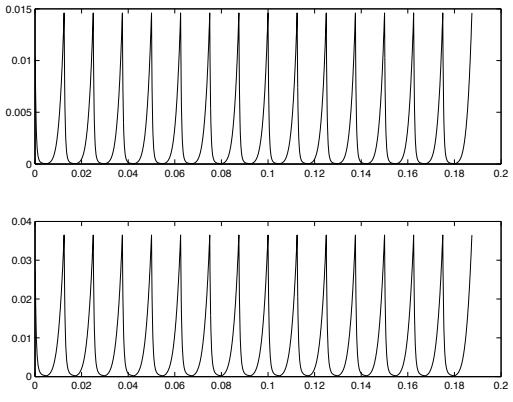


The heart as a compliance vessel

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.



Modeling the heart valves

Characteristic properties of a heart valve:

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

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

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

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.

Dynamics of the arterial pulse

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

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

From the pressure-volume relation for a compliance vessel we get

$$\frac{d(CP)}{dt} = Q_1 - Q_2.$$

When C is constant (which it is for every vessel except for the heart muscle itself) we have

$$C\frac{dP}{dt} = Q_1 - Q_2.$$

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

$$\frac{d(C_i P_i)}{dt} = Q_i^{in} - Q_i^{out},$$

while the flows in the resistance vessels follow the relation

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

A simple model for the circulatory system

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. For the left ventricle we have

$$\frac{d(C(t)P_{lv})}{dt} = Q^{in} - Q^{out},$$

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

$$Q_{in} = \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}}, \quad (5)$$

$$Q_{out} = \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}}. \quad (6)$$

We get

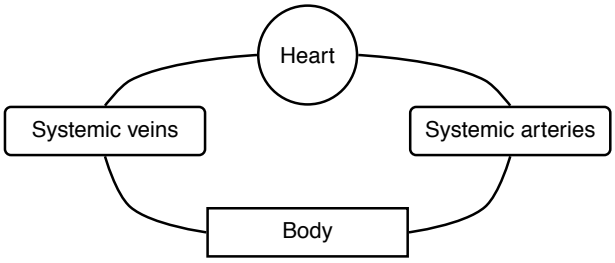
$$\frac{d(C(t)P_{lv})}{dt} = \frac{P_{sv} - P_{lv}}{S_{mi}R_{mi}} - \frac{P_{lv} - P_{sa}}{S_{ao}R_{ao}},$$

Similar calculations for the two other compliance vessels gives the system

$$\frac{d(C(t)P_{lv})}{dt} = \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}} - \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}}, \quad (7)$$

$$C_{sa}\frac{dP_{sa}}{dt} = \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}} - \frac{P_{sa} - P_{sv}}{R_{sys}}, \quad (8)$$

$$C_{sv}\frac{dP_{sv}}{dt} = \frac{P_{sa} - P_{sv}}{R_{sys}} - \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}}. \quad (9)$$



With a specification of the parameters $R_{mi}, R_{ao}, R_{sys}, C_{sa}, C_{sv}$ and the function $C_{lv}(t)$, this is a system of ordinary differential equations that can be solved for the unknown pressures P_{lv}, P_{sa}, and P_{sv}. When the pressures are determined they can be used to compute volumes and flows in the system.

A more realistic model

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

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

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}.

This gives the ODE system

$$\frac{d(C_{lv}(t)P_{lv})}{dt} = \frac{S_{mi}(P_{sv} - P_{lv})}{R_{mi}} - \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}}, \quad (10)$$

$$\frac{dC_{sa}P_{sa}}{dt} = \frac{S_{ao}(P_{lv} - P_{sa})}{R_{ao}} - \frac{P_{sa} - P_{sv}}{R_{sys}}, \quad (11)$$

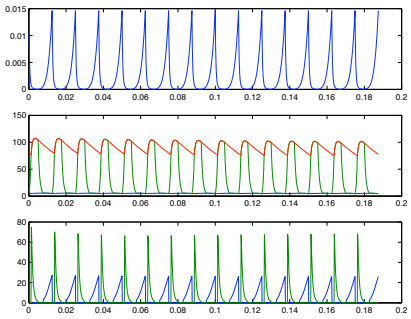
$$\frac{dC_{sv}P_{sv}}{dt} = \frac{P_{sa} - P_{sv}}{R_{sys}} - \frac{S_{tri}(P_{sv} - P_{rv})}{R_{tri}}, \quad (12)$$

$$\frac{d(C_{rv}(t)P_{rv})}{dt} = \frac{S_{tri}(P_{sv} - P_{rv})}{R_{tri}} - \frac{S_{puv}(P_{rv} - P_{pa})}{R_{puv}}, \quad (13)$$

$$\frac{dC_{pa}P_{pa}}{dt} = \frac{S_{puv}(P_{rv} - P_{pa})}{R_{puv}} - \frac{P_{pa} - P_{pv}}{R_{pu}}, \quad (14)$$

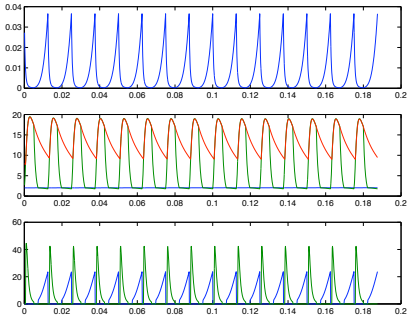
$$\frac{dC_{pv}P_{pv}}{dt} = \frac{P_{pa} - P_{pv}}{R_{pu}} - \frac{S_{mi}(P_{pv} - P_{lv})}{R_{mi}}. \quad (15)$$

LV compliance, pressures and flows



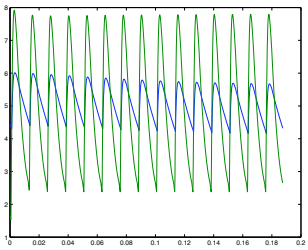
Top: C_lv, Middle: P_{pv} (blue), P_{lv} (green), P_{sa} (red), Bottom: Q_{mi}, Q_{ao}.

RV compliance, pressures and flows



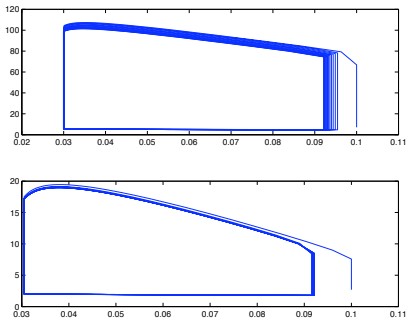
Top: C_rv, Middle: P_{sv} (blue), P_{rv} (green), P_{pa} (red), Bottom: Q_{tri}, Q_{puv}.

Systemic and pulmonary flows



Q_{sys} (blue) and Q_{pu} (green). Note the higher maximum flow in the pulmonary system despite the lower pressure. This is caused by the low resistance in the pulmonaries.

Pressure volume loops

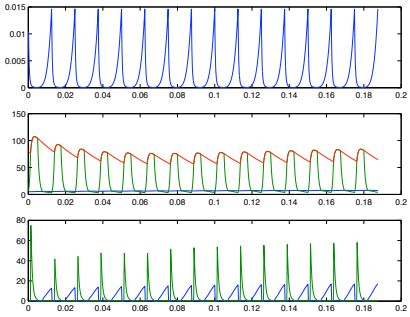


Top: left ventricle, bottom: right ventricle.

Mitral valve stenosis

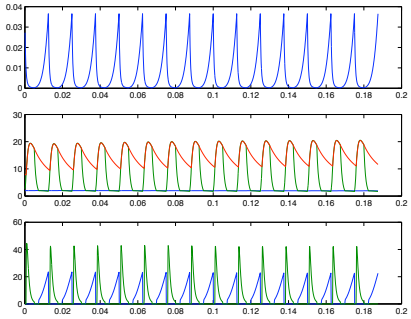
- R_{mi} changes from 0.01 to 0.2.

LV compliance, pressures and flows



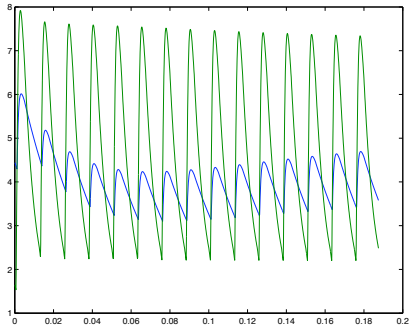
Reduced in-flow to the LV causes reduced filling and thereby reduced LV pressure and arterial pressure.

RV compliance, pressures and flows



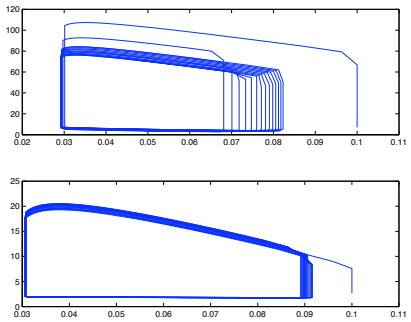
The RV pressure increases because blood is shifted from the systemic circulation to the pulmonary circulation.

Systemic and pulmonary flows



Blood is shifted from the systemic circulation to the pulmonary circulation.

Pressure volume loops

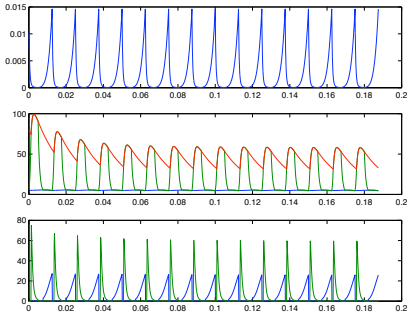


Reduced filling of the LV, slightly higher pressure in the RV.

Reduced systemic resistance

- R_{sys} reduced from 17.5 to 8.5.
- This can be the result of for instance physical activity, when smooth muscle in the circulatory system reduce the resistance to increase blood flow to certain muscles.

LV compliance, pressures and flows



The arterial pressure drops dramatically. This is not consistent with what happens during physical activity.

Summary

- Models for the circulatory system can be constructed from very simple components.
- The models are remarkably realistic, but the simple model presented here has some important limitations.
- The models may be extended to include feedback loops through the nervous system.
- The simple components of the model can be replaced by more advanced models. For instance, the varying compliance model for the heart may be replaced by a bidomain and mechanics solver that relates pressures and volumes.