Multiscale model of the human cardiovascular system: healthy and pathological behaviours

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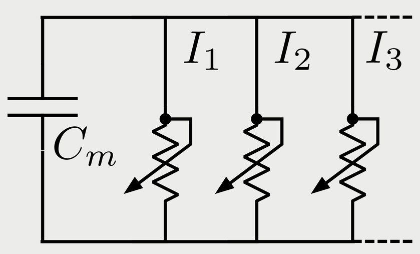
Many cardiovascular system (CVS) models describe the heart contraction with phenomenological models (like the varying elastance model). In this work, a more realistic model of the CVS is presented, where the heart contraction is described instead at the cellular scale.

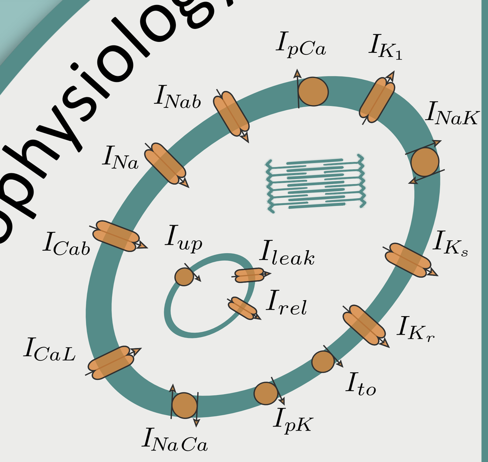
Electrophysiology

Membrane potential V is described with the following equation:

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} + \sum_i I_i + I_{stim} = 0$$



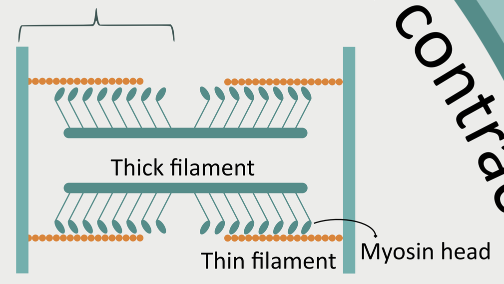
where an expression for each ionic current and the stimulus current is needed.
Ionic concentrations are also described by this model. Intracellular calcium allows for the connexion between the electrophysiology and the mechanical contraction.



Ventricular myocyte = cardiac cell, excitable and contractile

Ref: Ten Tusscher, K.H.W.J. & Panfilov, A. V, 2006. Alternans and spiral breakup in a human ventricular tissue model. American Journal of Physiology-Heart and Circulatory Physiology, 291(3), pp.H1088–H1100.

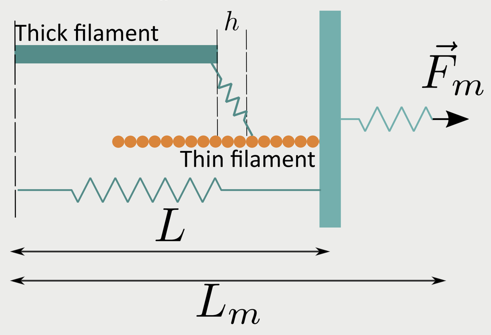
Mechanical contraction



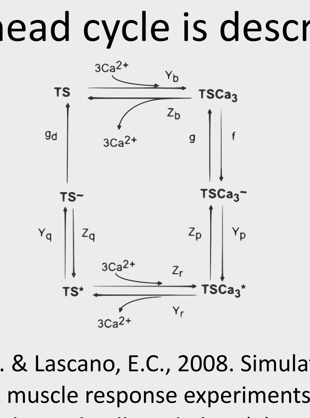
Sarcomere = basic contractile unit of the myocyte

The contraction of a half-sarcomere of length L is described as follow:

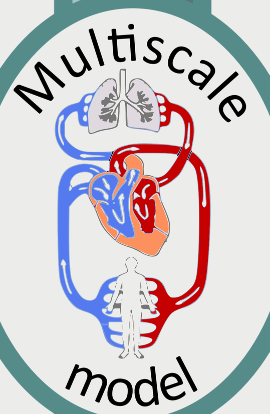
$$L = X + h$$
$$\frac{\mathrm{d}X}{\mathrm{d}t} = B(h - h_c)$$



The myosin head cycle is described by a 6-state model:



Ref: Negroni, J.A. & Lascano, E.C., 2008. Simulation of steady state and transient cardiac muscle response experiments with a Huxley-based contraction model. J Mol Cell Cardiol, 45(2), pp.300–312.



Hemodynamics

Passive chambers: pressure and volume are linked with the elastance of the chamber:

$$P = EV$$

Blood flow is related to the pressure at the entrance and at the exit of a chamber and to the resistance of the blood vessels:

$$Q = \frac{P_i - P_o}{R}$$

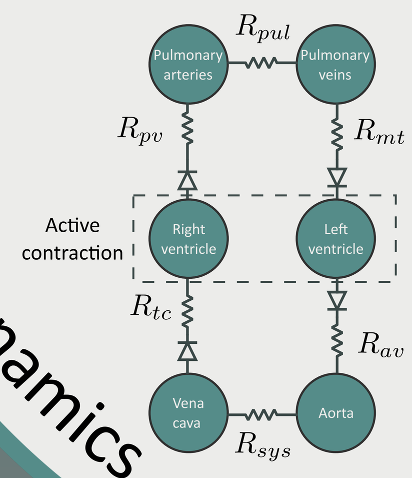
Volume of a chamber varies according to

$$\frac{\mathrm{d}V}{\mathrm{d}t} = Q_{in} - Q_{out}$$

The four cardiac valves act as diods to allow for the unidirectionanality of the flow.

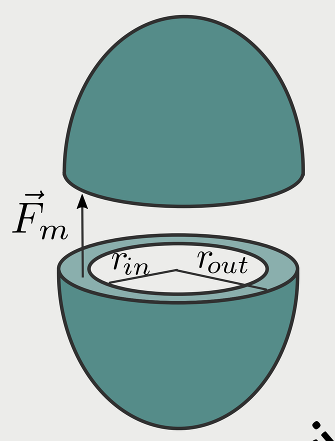
Ref: Burkhoff, D. & Tyberg, J. V., 1993. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol Heart Circ Physiol*, 265(5), pp.H1819–1828

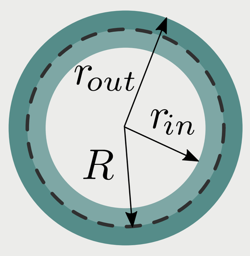
Cardiovascular system (CVS) = 6-chamber model: 4 passive chambers and 2 active chambers



Spherical ventricles

Ventricles = thick spheres with an incompressible wall volume





N half-sarcomeres of length L_m are aligned along a circle of radius R:

$$L_m = \frac{2\pi R}{N}$$

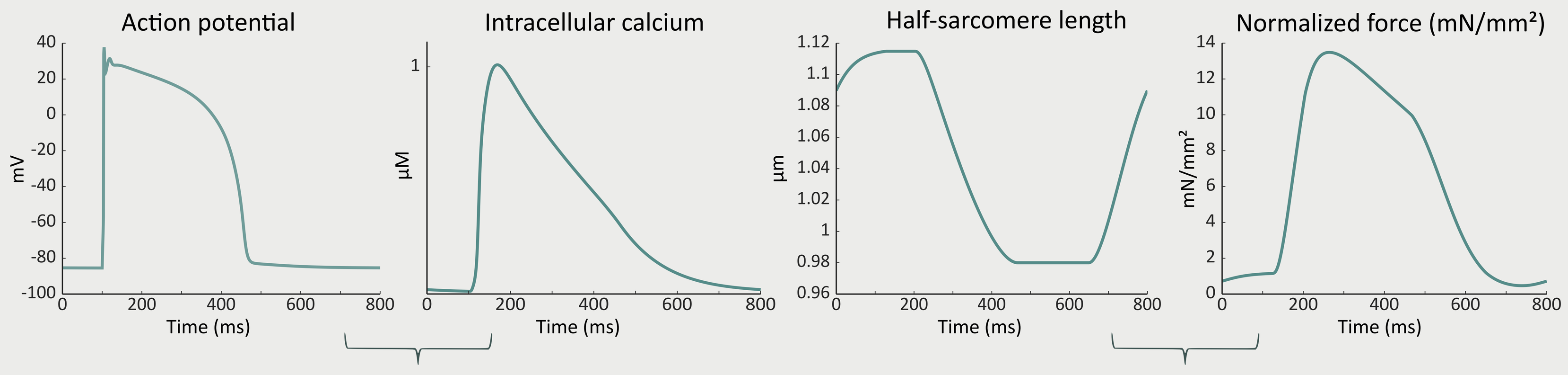
The equilibrium between the two half-spheres gives the relationship between the active pressure and the half-sarcomere normalized force:

$$P = F_m \frac{L_m}{L_r}\left(\left(\frac{r_{out}}{r_{in}}\right)^2 - 1\right)$$

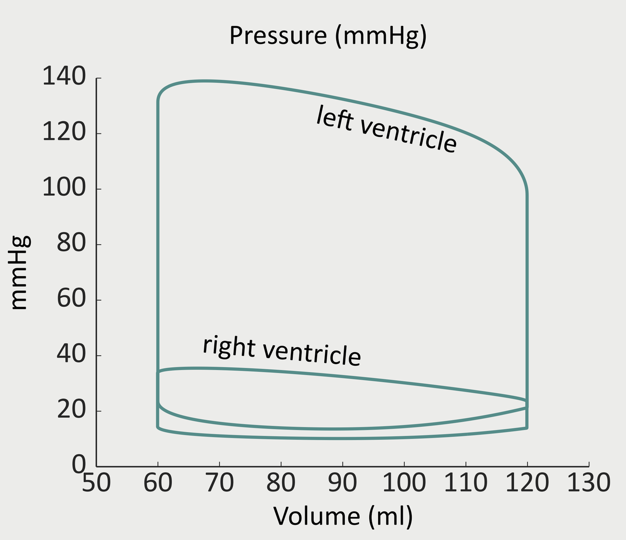
Ref: Shim, E.B. et al., 2007. The cross-bridge dynamics during ventricular contraction predicted by coupling the cardiac cell model with a circulation model. *J Physiol Sci*, 57(5), pp.275–285.

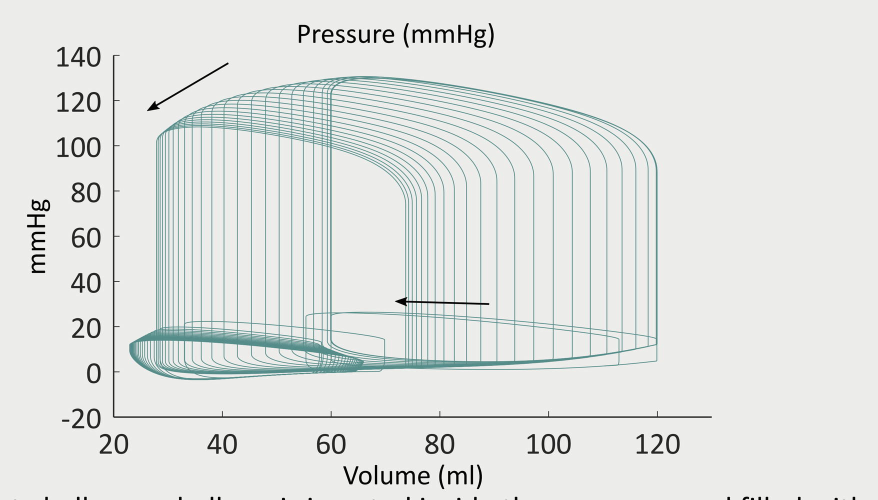
Normal heart

Cellular variables



Hemodynamics variables



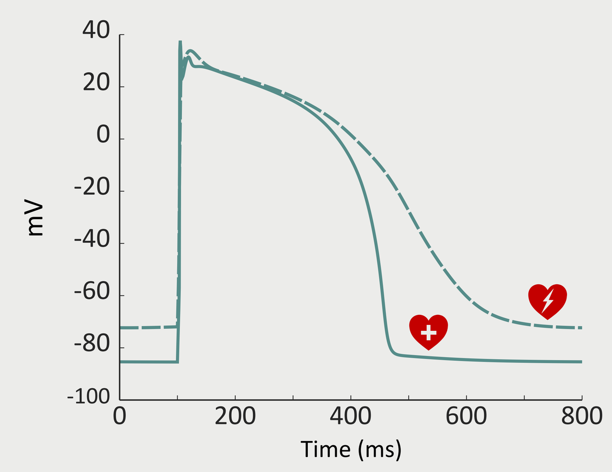


Fogarty balloon: a balloon is inserted inside the vena cava and filled with air. The pressure-volume loops are shifted towards the lower left corner.

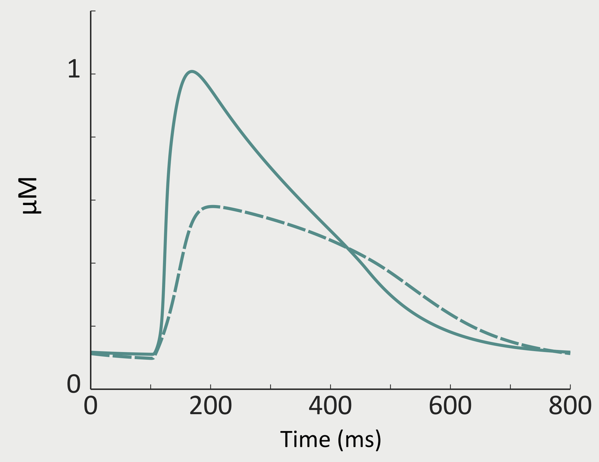
Failing heart

Perturbations occur at the cellular scale (ionic currents are altered)

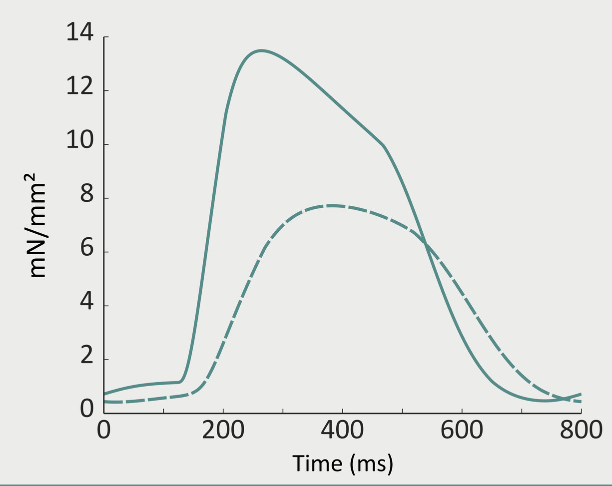
Action potential is prolonged ...



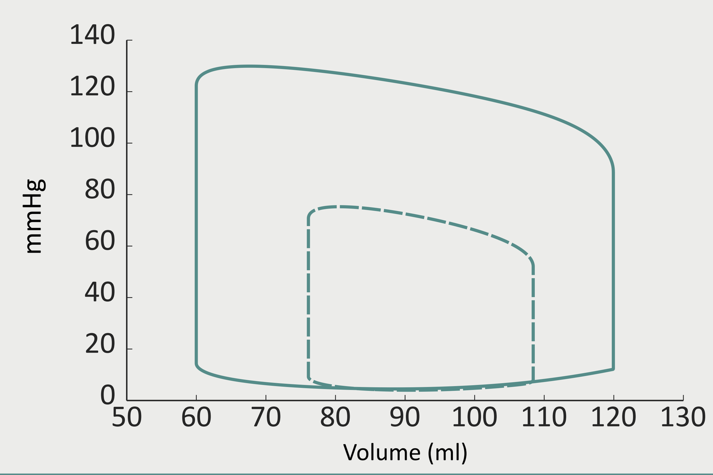
Intracellular calcium decreases ...



Maximal sarcomere force decreases ...



Pressure-volume loop gets smaller !



Our multiscale model can account for a healthy behaviour and for basic hemodynamic experiments like preload variations. More importantly, it is able to reproduce pathological behaviours that originate at the cellular scale, like heart failure, and their consequences on the whole CVS.

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