Multiscale model of the human cardiovascular system: healthy and pathological behaviors
Cardiovascular system model (CVS)
Hemodynamics

- Flow through the vessels

\[ Q = \frac{P_o - P_i}{R} \]

- Volume variation

\[ \frac{dV}{dt} = Q_{in} - Q_{out} \]

- Cardiac valves (mitral, tricuspid, aortic and pulmonary)

= unidirectionnality of the blood flow
Hemodynamics

- Pressure-volume relationship:
  - Passive chamber: \( P = E \cdot V \)
  - Active chamber (both ventricles): \( P \equiv E \cdot V \)

\[ P = E(t) \cdot V \]

Varying-elastance model

Input function

[Graph showing pressure-volume relationship with elastance of the chamber]
Cardiac contraction

- From macroscopic to microscopic scale

- From microscopic to macroscopic properties: Franck-Starling law


Adapted from Klabunde, R. (2011). Cardiovascular physiology concepts. Lippincott Williams & Wilkins.
Modeling cardiac contraction

- Varying elastance model
- Cell-based model

**Cardiac cell**

- Sarcomere contraction
- Calcium release from the sarcoplasmic reticulum
- Electrical stimulation (action potential)
Modeling cardiac contraction

Varying elastance model $\rightarrow$ cell-based model

Mechanical model (Negroni & Lascano 2008)

Electrophysiological model (ten Tusscher & Panfilov 2006)
Electrophysiology

\[ C_m \frac{dV}{dt} + \sum_{i} I_i + I_{stim} = 0 \]

\[ \frac{d[Ion]_i}{dt} = \frac{I_{in} - I_{out}}{z_{ion} V_c F} \]

Intracellular calcium (µM)
Sarcomere contraction

\[ L = X + h \]

- Elastic length
- Inextensible length
- Thick filament
- Thin filament
\[ L = X + h \]

- Elastic length
- Inextensible length

\[ F_m \propto h \]

\[ \frac{dX}{dt} = B \cdot (h - h_c) \]

- Sliding velocity

\[ \Delta h = \Delta L \]

- Steady elongation

\[ h_c \]
Excitation-contraction coupling

\[
[TS] = [TS]_{tot} - [TSCa_3] - [TSCa_3^\sim] - [TSCa_3^*] - [TS^*]
\]

\[
\frac{d[TSCa_3]}{dt} = g \times [TSCa_3^\sim] - f \times [TSCa_3]
+ Y_b \times [Ca_i]^3 \times [TS] - Z_b \times [TSCa_3]
\]

\[
\frac{d[TSCa_3^\sim]}{dt} = f \times [TSCa_3] - g \times [TSCa_3^\sim]
- Y_p \times [TSCa_3^\sim] + Z_p \times [TSCa_3^*]
\]

\[
\frac{d[TSCa_3^*]}{dt} = Z_r \times [Ca_i]^3 \times [TS^*] - Y_r \times [TSCa_3^*]
+ Y_p \times [TSCa_3^\sim] - Z_p \times [TSCa_3^*]
\]

\[
\frac{d[TS^*]}{dt} = Y_r \times [TSCa_3^*] - Z_r \times [Ca_i]^3 \times [TS^*] - g_d \times [TS^*]
\]

\[
f = f_0 \exp(-R_{La} \times (L - L_a))
\]

\[
g = Z_a + Y_v \times (1 - \exp(-\gamma \times (h - h_{wr})^2))
\]

\[
g_d = Y_d \exp(-Y_c \times (L - L_c))
\]

\[F_m \propto [TSCa_3^\sim], [TSCa_3^*], [TS^*]\]
From cell to organ

Both ventricles are assimilated to simple spheres and the pressure and volume can be related to the force and half-sarcomere length:

\[ N \text{ half-sarcomeres are aligned along a circle of radius } R: \]

\[ L_m = \frac{2\pi R}{N} \]

\[ V_{int} = \frac{4}{3} \pi r_{int}^3 \]

Blood volume inside the ventricular cavity is given by:

\[ V_{int} + V_{wr} = \frac{4}{3} \pi R^3 \]

\[ \Rightarrow L_m \text{ and } V_{int} \text{ are linked} \]

The wall stress \( \sigma \) is considered constant and is related to the pressure inside the ventricular cavity:

\[ P = \sigma \left( \frac{r_{out}^2}{r_{in}^2} - 1 \right) \]

The wall stress is also related to the normalized force \( F_m \) given by the sarcomere model:

\[ \sigma = F_m \frac{L_m}{L_r} \]

\[ \Rightarrow P \text{ and } F_m \text{ are linked} \]

Cardiovascular system model (CVS)

Results: Baseline

- Force (mN/mm²), Calcium (10⁻¹ μM)
- Action potential (mV)
- Sarcomere length (µm)
- Left ventricular volume (ml)

Graphs showing the changes in force, calcium, action potential, sarcomere length, and left ventricular volume over time.
Cardiovascular system model (CVS)

Results: Fogarty balloon

\[ P_{pa} V_{pa} \quad P_{pu} V_{pu} \]
\[ P_{pv} V_{pv} \quad P_{pv} V_{pv} \]
\[ P_{rv} V_{rv} \quad P_{rv} V_{rv} \]
\[ P_{lv} V_{lv} \quad P_{lv} V_{lv} \]
\[ P_{vc} V_{vc} \quad P_{vc} V_{vc} \]
\[ P_{ao} V_{ao} \quad P_{ao} V_{ao} \]

\[ R_{pul} \quad R_{mt} \quad R_{sys} \quad R_{av} \quad R_{tc} \quad R_{pv} \]

Active contraction

\[ \text{Pressure (mmHg)} \]
\[ \text{Volume (ml)} \]
Cardiovascular system model (CVS)

Results: Fogarty balloon

\[ \begin{align*}
    P_{pa} & = V_{pa} \\
    & \text{Pul. Art.} \\
    R_{pul} & \\
    P_{pv} & = V_{pv} \\
    & \text{Right V.} \\
    R_{pv} & \\
    P_{rv} & = V_{rv} \\
    & \text{Active contraction} \\
    R_{t} & \\
    P_{vc} & = V_{vc} \\
    & \text{Vena cava} \\
    R_{sys} & \\
    P_{ao} & = V_{ao} \\
    & \text{Aorta}
\end{align*} \]
Cardiovascular system model (CVS)

Results: Ventricular failure
Future perspectives:

- Fluid therapy: « Will a patient be fluid responsive? »

  -> Need for indicators of fluid responsiveness
Future perspectives:

• Fluid therapy: « Will a patient be fluid responsive ? »
  -> Need for indicators of fluid responsiveness

• Contractility index: « What is the contractile state of a patient’s heart ? »
  -> Need for a contractility index that is not load dependent (and preferably available with non-invasive measures)
  -> comparison of different proposed indices