MODELING BLOOD FLOW IN THE CARDIOVASCULAR SYSTEM

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The cardiovascular system:

- **Systemic circulation:**
  - Systemic arteries
  - Systemic veins

- **Pulmonary circulation:**
  - Pulmonary arteries
  - Pulmonary veins

- **Left and right heart:**
  - Atrium
  - Ventricle
Before 1628

Pliny the Elder (Roman), Galen (Greek),…;

Two distinct types of blood were thought to exist:

- **“Nutritive blood”** was thought to be made by the liver and carried through veins to the organs, where it was consumed.
- **“Vital blood”** was thought to be made at the heart and pumped through arteries to carry the “vital spirits.”

Blood was thought to be **produced and consumed** at the ends of a transport system whereas idea of a circulatory blood system was unthinkable.

It was believed that the heart acted not to pump blood, but to suck it in from the veins and that blood flowed through the septum of the heart from one ventricle to the other through a system of tiny pores.
This seemed *absurd* when compared to the *amount of blood* in a human body which in most humans is around 5 liters and even more absurd compared to the *amount of liquid intake* per day (in food and in drinking) which is less than 5 liter per day.

William Harvey’s 1628 modeling:
Stroke volume is 70 milliliters/beat
Heart beats 72 times/minute

Cardiac output of 7.258 liters/day
• Modeling gave birth to the view that blood must circulate. Harvey successfully announced the discovery of the circulatory blood system.

• Harvey discovered the circulation of blood 46 years before the discovery of the light microscope.

• Consequently Harvey changed the view of the world using a simple mathematical model making the inaccessible accessible.

1. In 1615 Harvey wrote (hand-written notes) that he was convinced that blood circulated.
2. Anton Van Leeuwenhoek’s microscope from 1674 (the first functioning light microscope) was sufficiently strong to make the capillaries visible.
3. Van Leeuwenhoek was the first to see and describe the capillaries of the circulatory system.
4. Marcello Malpighi, made the discovery simultaneously and independently, published his discovery of the capillaries in 1675. He is often credited the discovery of the capillaries by use of the microscope.
Systemic arteries:

- Large arteries (cm)
- Small arteries (mm)
- Arterioles (100 μ)
- Capillaries (50 μ)
Small arteries
Capillaries:
Pressure

![Diagram of blood pressure across the cardiovascular system.](Image)
The heart
How to model dynamics of the cardiovascular system?

**Cardiovascular models:**
- System models (ODE models)
  - Cardiovascular models including systemic and/or pulmonary arteries and veins
- Regional models (PDE models 1D, 2D, 3D)
  - Arterial or venous 1D models, e.g. large systemic arteries
  - Arterial or venous 2D/3D models, e.g. iliac bifurcation, coronary bypass models

**Heart Model:**
- System models (ODE models), e.g. cardiac ejection effect
- Regional models (PDE models 1D, 2D, 3D), e.g. blood flow through the aortic valve
Questions arising in cardiovascular physiology

- **Clinical applications:**
  - Anesthesia simulation
  - Surgery planning
  - Early screening for regulatory deficits

- **Understanding physiological mechanisms:**
  - Cardiac ejection effect
  - Autonomic regulation and autoregulation
  - Flow dynamics past stenosis
  - Fetal circulation
1. Using a mathematical model to predict blood flow after bypass surgery

2. Understanding mechanisms behind cerebral blood flow regulation
Mathematical models

- **System models:**
  - Windkessel model: Analyze effects of regulation using measured pressure as an input
  - Closed loop compartment model: Develop and test theories that can predict the interaction between autoregulation and autonomic regulation

- **Regional models:**
  - One-dimensional fluid dynamics model: Analyze effects of wave-propagation in young, elderly, and hypertensive people
Surgery planning

1. Extract contours from MRA
2. Assemble contours to construct model
Surgery planning

- Bypass graft inserted into the abdominal aorta
- Can we construct a computational model with 1 spatial dimension that can accurately predict the pressure and velocity distribution in the aorta?
- Blood flow measured at green lines with MRI (non-invasive)
- Blood pressure measured at yellow circles with transducer (invasive)
Fluid dynamics of blood flow

- **Navier-Stokes (NS) equations** describe momentum balance using Newton’s second law, $F = ma$. In one spatial dimension (along the vessel) one equation relates pressure $p$, volumetric flow rate $q$, and cross-sectional area $A$.

- **Volume conservation** relates volumetric flow rate $q$ and cross-sectional area $A$.

- **Constitutive equation** relates pressure $p$ and cross-sectional area $A$. 

Assumptions

- Blood flow is Newtonian
- Fluid is incompressible, the fluid density ($\rho$ [g/cm$^3$]) is constant
- Fulfills no-slip condition, i.e. the velocity of fluid particles located next to the wall follows the velocity of the wall
- Flow is axisymmetric and is without swirl
  \[ u = (u_r(r,x,t), u_x(r,x,t), t), \text{no q dependence and no q component} \]
- Vessel wall is elastic
- Vessel is tethered in the longitudinal direction, it only undergoes radial motion
Assumptions

- Unstressed vessels are tapered longitudinally,
  \[ 0 < r < R \]
Constitutive equation

- Elastic properties of the vessel walls

\[ p = \frac{4}{3} \frac{Eh}{r_0} \left(1 - \sqrt{\frac{A_0}{A}}\right), \]

\[ \frac{Eh}{r_0} = k_1 \exp(k_2 r_0) + k_3 \]
Kelvin’s Model

\[ s + \tau_\varepsilon \frac{ds}{dt} = \frac{Eh}{r_0} \left( p + \tau_\sigma \frac{dp}{dt} \right), \]  
\[ s = 1 - \sqrt{\frac{A_0}{A}}, \]

\[ \tau_\sigma = \frac{\eta_1}{\mu_0} \left( 1 + \frac{\mu_0}{\mu_1} \right), \quad \tau_\varepsilon = \frac{\eta_1}{\mu_1}, \quad \frac{Eh}{r_0} = \mu_0 \]

\( \mu_0 \) - spring constant  
\( \mu_1 \) - spring constant  
\( \eta_1 \) - dashpot constant  
\( s \) - strain  
\( p \) - pressure  
\( A \) - area
Kelvin’s Model

\[
\frac{dA}{dt} = \frac{\mu_0 \left( \sqrt{\frac{A_0}{A}} - 1 \right) + p + \tau_\sigma \frac{dp}{dt}}{\mu_0 \tau_\varepsilon \sqrt{A_0} / 2A^{3/2}}
\]

- \(A\) - area
- \(p\) - pressure
- \(\mu_0\) - spring constant
- \(\mu_0\) - spring constant
- \(\mu_1\) - spring constant
- \(\eta_1\) - dashpot constant
Kelvin’s Model

- The Kelvin Viscoelastic Model can be rewritten in an integral form.
- Thus after some calculations, we have in our model an exponent that represents one type of tissue in the arteries.

\[
s(t) = \frac{r_0}{E_h \tau_\varepsilon} \left\{ \tau_\sigma p(t) + \left( \frac{\tau_\sigma - \tau_\varepsilon}{\tau_\varepsilon} \right) \int_{-\infty}^{t} e^{-(t-\gamma)/\tau_\varepsilon} p(\gamma) d\gamma \right\}
\]

\[
s(t) = \frac{r_0}{E_h} \left\{ (1 + A_1) p(t) - \left( \frac{A_1}{B_1} \right) \int_{-\infty}^{t} e^{-(t-\gamma)/B_1} p(\gamma) d\gamma \right\}
\]

where \( A_1 = \frac{\tau_\sigma - \tau_\varepsilon}{\tau_\varepsilon} \) and \( B_1 = \tau_\varepsilon \).
Model Validation
Model Validation

[Diagram showing a model validation setup involving a reservoir, chamber, ultrasonic crystals, pressure microtransducer, sonomicrometer, and oscilloscope.]
Model Validation

- Used nonlinear optimization to compute model parameters that minimized the difference between computed and measured values of the cross-sectional area using blood pressure as input:

\[
J = \frac{1}{NA} \sum_{i=1}^{N} \left( A_i^d - A_i^c \right)^2
\]
1D Model Summary

- **Momentum equation**

\[
\frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{q^2}{A} \left( 1 + \frac{2}{3} \frac{\delta}{R} \right) \right) + \frac{A}{p} \frac{\partial p}{\partial x} = -\frac{2R\pi
q}{\delta A}
\]

- **Continuity equation**

\[
\frac{\partial A}{\partial t} + \frac{\partial q}{\partial x} = 0
\]

- ** Constitutive equation**

\[
p = \frac{4}{3} \frac{Eh}{r_0} \left( 1 - \sqrt{\frac{A_0}{A}} \right), \quad \frac{Eh}{r_0} = k_1 \exp(k_2 r_0) + k_3
\]
Boundary Conditions

- 1D model forms a second order hyperbolic PDE, for each vessel segment
  - Initial conditions for $p, q, A$
  - Three conditions at bifurcations
  - One inflow boundary condition at inlets
  - One outflow boundary condition at outlets
1D model boundary conditions

- Bifurcation conditions

\[ q_p(L,t) = q_{d1}(0,t) + q_{d2}(0,t) \]
\[ p_p(L,t) = p_{di}(0,t) - \rho K \frac{U_p^2(L,t)}{2}, \quad i = 1,2 \]
1D model boundary conditions

- **Inflow boundary condition**, measured flow (periodic)

- **Outflow condition**, computed

\[
p(x_L, t) = \frac{1}{T} \int_{0}^{T} z(x_L, t - \tau) q(x_L, t) \, d\tau
\]

or

\[
P(x_L, \omega) = Q(x_L, \omega) Z(x_L, \omega)
\]
Model validation

The model is validated against MRI blood flow measurements at 10 locations. Data measured from a 32 year old male, 65 kg and 178 cm.
Postural change: sit-to-stand

- **Objective:** Study short term regulation by analyzing arterial finger pressure and cerebral flow velocity during postural change from sitting to standing.

- **Measurements:** Cerebral blood flow velocity is measured in the middle cerebral artery.
  
  Arterial finger pressure is measured in the middle finger, which is held at heart level to eliminate effects of gravity.
Effects of postural change

- Approximately 500 cc of blood is pooled in lower extremities as a result of gravitational force

- Venous return is reduced leading to a decrease in stroke volume

- Arterial blood pressure in the trunk and upper extremities drop, while blood pressure in the lower extremities is increased

- Blood flow to the brain is reduced leading to build up of CO\textsubscript{2}
Autonomic baroreflexes, mediated by CNS restore heart rate, arterial BP, and cerebral BF.

- **Sympathetic response:** Increased sympathetic activity increases release of noradrenaline, which increases heart rate, cardiac contractility, vascular resistance, compliance (6-8 cardiac cycles).

- **Parasympathetic response:** Decreased parasympathetic activity decreases release of ach, which increases heart rate and cardiac contractility (1-2 cardiac cycles).

- **Cholinergic response:** Parasympathetic release of ach in the brain may lead to a decrease of cerebrovascular resistance.
Cerebral autoregulation maintain cerebral perfusion.

- **Myogenic control**: A decrease in pressure relaxes muscles in the vessel wall, which makes vessels dilate to maintain cerebral perfusion.

- **Oxygen demand control**: A decrease in cerebral perfusion increases CO$_2$ and decreases metabolites related to O$_2$ supply. To maintain cerebral perfusion cerebrovascular resistance is decreased.
Short-term regulation
Measured data

Young subject

Hypertensive subject
Modeling objective

- Develop mathematical models to:
  - Understand how postural change alters cerebral and systemic vascular resistances, compliance, heart rate, and cardiac contractility
  - Study how these factors change in young, healthy elderly, and hypertensive elderly subjects
System model
Mathematical model

- **Change in volume:**
  \[
  \frac{dV_i}{dt} = q_{in} - q_{out}
  \]

- **Kirchhoff’s current law:**
  \[
  q_i = \frac{p_{in} - p_{out}}{R_i}
  \]

- **Pressure volume relation:**
  \[
  V_i = C_i p_i \quad \Leftrightarrow \quad C_i \frac{dp_i}{dt} + p_i \frac{dC_i}{dt} = q_{in} - q_{out}
  \]
Ventricular pressure equation

\[ p = a(V - b)^2 + (cV - d)g(t) \]

- \( a \) - ventricular elastance during relaxation
- \( b \) - ventricular volume for zero diastolic pressure
- \( c,d \) - volume dependent and volume independent components of the pressure

\[ f(t) = \begin{cases} 
0 & , \quad 0 \leq t \leq \alpha \\
p_p(H) \frac{(t - \alpha)^n(\beta(H) - t)^m}{n^m m^m[(\beta(H) - \alpha)/(m + n)]^{m+n}} & , \quad \alpha \leq t \leq \beta(H) \\
0 & , \quad \beta(H) \leq t \leq T 
\end{cases} \]

- \( T \) - length of the cardiac cycle
- \( H \) - heart rate
- \( \alpha, \beta \) - time representing the onset of contraction and relaxation, respectively
- \( p_p \) - peak value of the activation function
Model parameters

- Initial parameters obtained from literature data
- Optimal parameters obtained using non-linear optimization minimizing the error between computed and measured values

\[ J = \alpha_1 \sum \left( \frac{p_{af} - p_{afd}}{Np_{af}} \right)^2 + \alpha_2 \sum \left( \frac{v_{acp} - v_{acpd}}{Nv_{acp}} \right)^2 + \alpha_3 \sum \left( \frac{p_{af,sys} - p_{afd,sys}}{Np_{af,sys}} \right)^2 + \alpha_4 \sum \left( \frac{p_{af,dia} - p_{afd,dia}}{Np_{af,dia}} \right)^2 + \alpha_5 \sum \left( \frac{v_{acp,sys} - v_{acpd,sys}}{Nv_{acp,sys}} \right)^2 + \alpha_6 \sum \left( \frac{v_{acp,dia} - v_{acpd,dia}}{Nv_{acp,dia}} \right)^2 \]
Results
Postural change from sitting to standing facilitates redistribution of blood volumes from the upper body to the legs

- Adding gravity effects lower compartments

\[ q_{al} = \frac{p_{au} - p_{al} + \rho gh}{R_{al}}, \quad q_{vl} = \frac{p_{vl} + \rho gh - p_{vu}}{R_{vl}} \]

\[ h(t) = \begin{cases} 
0, & t < t_{st} \\
\alpha(t - t_{st}), & t_{st} \leq t \leq t_{st} + T_S \\
h_M, & t > t_{st} + T_S 
\end{cases} \]

- \( t_{st} \) - onset of standing
- \( T_S \) - transition from sitting to standing
- \( h_M \) - maximum height
- \( \alpha = h_M / T_S \) - slope of the curve
Nonlinear (passive) resistances

- Poiseuille’s law for flow in a cylinder

\[ R = \frac{8\eta l}{\pi r^4} \quad \Leftrightarrow \quad \frac{1}{R} \equiv r^4 \equiv v^2 \equiv p^2 \]

- Resistances in the large arteries (Rau, Ral, Raf, Rac) exhibit saturation

\[ R = (R_M - R_m) \frac{\alpha_2^k}{p^k + \alpha_2^k} + R_m \]
Control equations

- Controlled parameters modeled using set-point functions

\[
\frac{dx(t)}{dt} = \frac{-x(t) + x_{ctr}(\bar{p})}{\tau}
\]

- \( x(t) \): controlled parameter
- \( \tau \): time constant characterizing the time it takes to obtain full effect

\[
x_{ctr}(\bar{p}) = (x_{\text{max}} - x_{\text{min}}) \frac{\bar{\alpha}_2^k}{\bar{p}^k + \bar{\alpha}_2^k} + x_{\text{min}}
\]

- \( \bar{\alpha}_2 \): pressure needed to obtain the mean value \( \frac{x_{\text{min}} + x_{\text{max}}}{2} \)
- \( k \): steepness of the sigmoid
Mean pressure

- The mean pressure is computed as a weighted average of the instantaneous (pulsatile) values

\[
\bar{p} = \frac{1}{N} \int_0^t e^{-\alpha(t-s)} p(s) \, ds, \quad N = \int_0^t e^{-\alpha(t-s)} \, ds = \frac{1 - e^{-\alpha t}}{\alpha}
\]

*N* - normalization constant, ensures \( \bar{p} = 1 \) when \( p(s) = 1 \)

- Corresponding differential equation

\[
\frac{d\bar{p}}{dt} = -\bar{p} + \frac{p(t)}{N}
\]
“Modeling” autoregulation

- The Cerebrovascular (Racp) and aortic (Rau) resistances are modeled as piecewise linear “hat” functions

\[
R(t) = \sum_{i=1}^{n} \gamma_i H_i(t)
\]

\[
f(t) = \begin{cases} 
\frac{t - t_{i-1}}{t_i - t_{i-1}}, & t_{i-1} \leq t \leq t_i \\
\frac{t_{i+1} - t}{t_{i+1} - t_i}, & t_i \leq t \leq t_{i+1} \\
0, & \text{otherwise}
\end{cases}
\]

\[\gamma_i \quad \text{- optimized unknown parameters}\]
Autoregulation

Graph showing time [sec] on the x-axis and Racp [mm Hg s/cm³] on the y-axis. The data points are marked with asterisks.
Model validation
Model parameters

- **Uncontrolled parameters**, resistances and capacitors used from steady state simulation.

- **Controlled parameters**, gravity and non-linear resistances, regulated resistances and capacitors, and autoregulation equation give rise to 110 parameters.

- **Parameters identified** using Nelder-Mead non-linear optimization to identify parameters that minimize the error between data and model.
Autoregulation
Magnetic Resonance Angiograms

Healthy Adult

Type II Diabetes Mellitus
Models

Veins

Arteries

Brain

Heart

Finger

Upper Body

Lower Body
References


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