Image-based modeling of the cardiovascular system

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COLLEGE OF ENGINEERING & MEDICAL SCHOOL
COMPUTATIONAL VASCULAR BIOMECHANICS LAB
UNIVERSITY OF MICHIGAN

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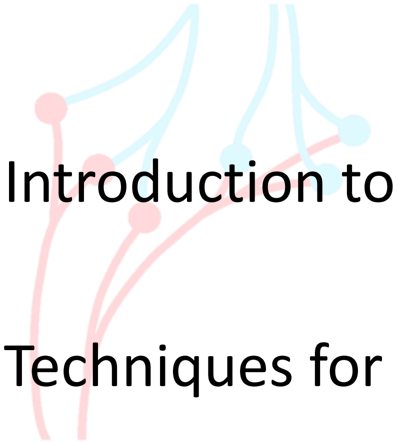
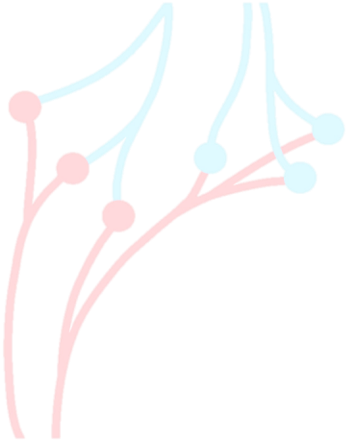
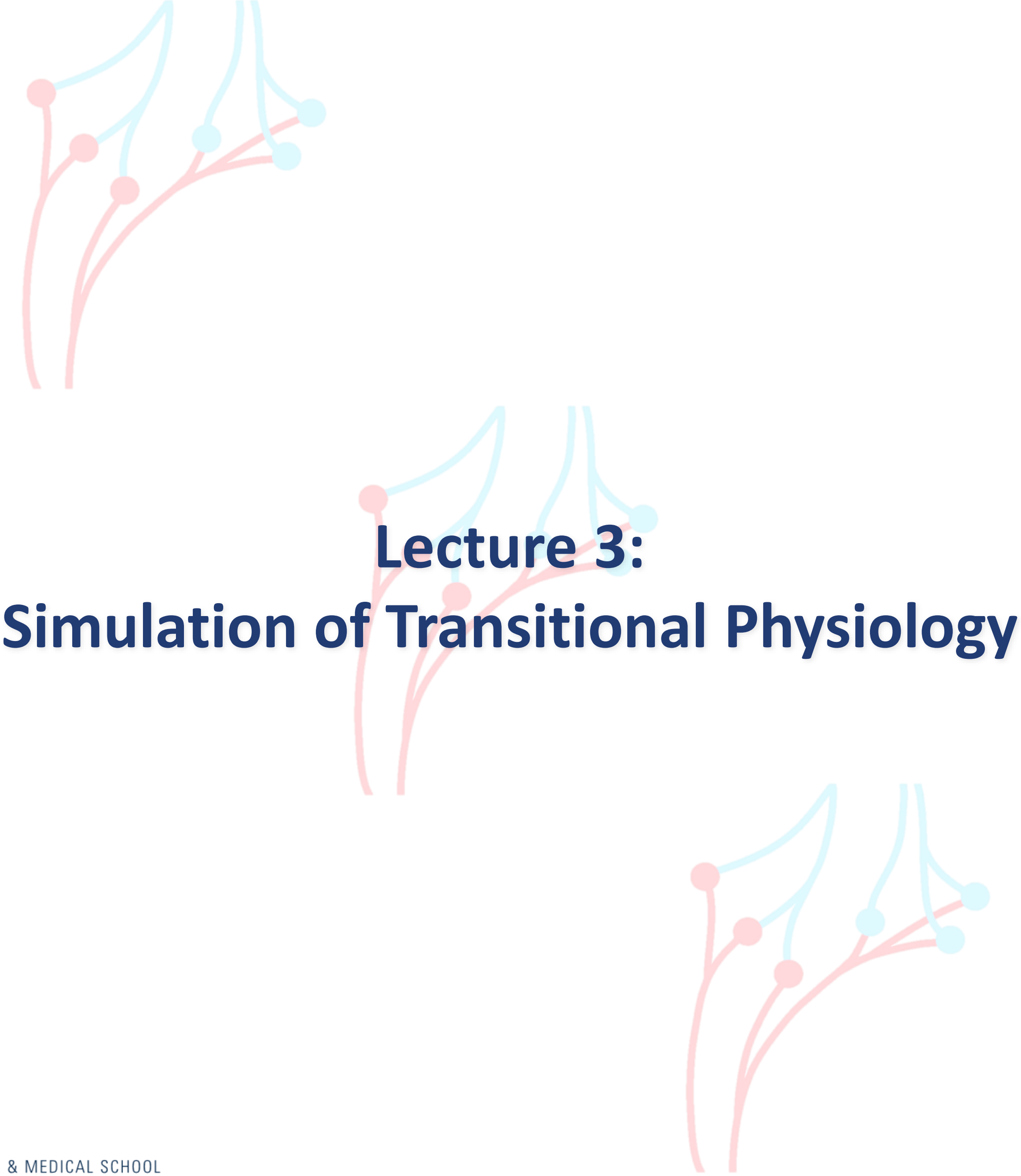
Outline



- Lecture 1: Introduction to function and modeling of the CV system
- Lecture 2: Techniques for Parameter Estimation in the CV system

- Lecture 3: Simulation of Transitional Physiology
- Lecture 4: Advanced Topics, Clinical Applications and Challenges





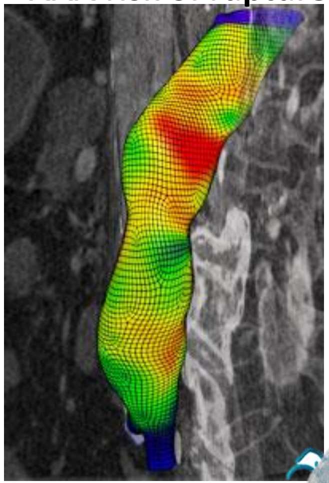
Lecture 3:
Simulation of Transitional Physiology

Time-scales in Cardiovascular Modeling

seconds → **minutes** → **months & years**

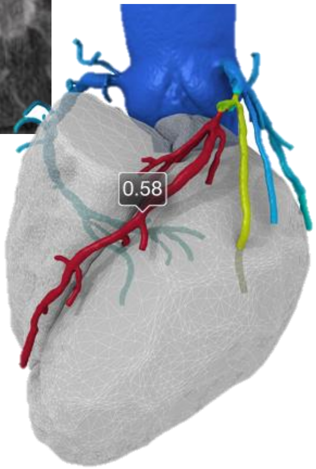
Single Cardiac Cycle

AAA risk of rupture



VASCOPS

FFR_{CT}

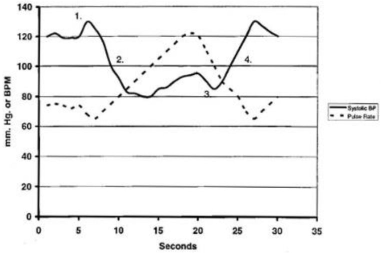


HEARTFLOW

Transitional Stages

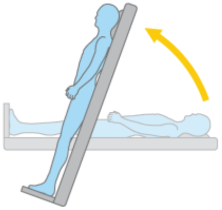
Arterial adaptations during surgery

Valsalva



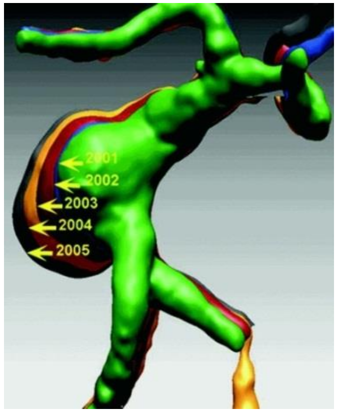
Micro-gravity

Tilt tests

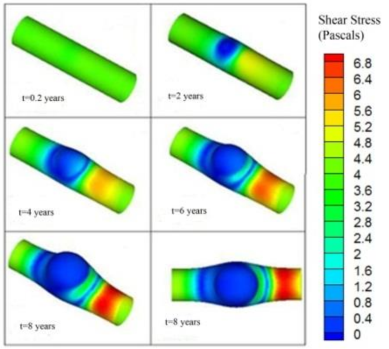


Exsanguination (trauma)

Tissue Growth & Remodeling



Acevedo-Bolton et al.



Watton et al.

Control Mechanisms of Flow and Pressure

Global control of Pressure

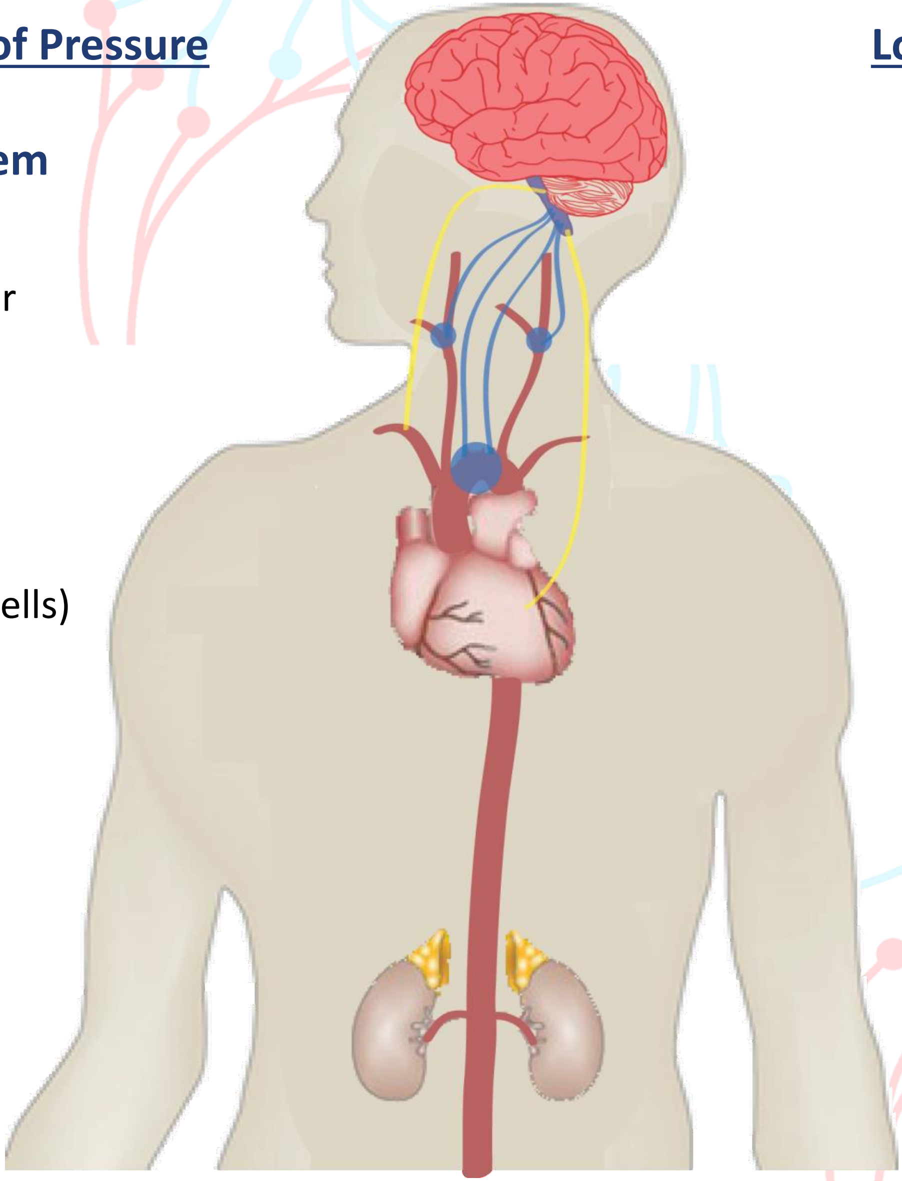
Baroreflex system

Vasomotor Center
(CNS)

Baroreceptors
(stretch sensing cells)

Afferent nerves
(to CNS)

Efferent nerves
(from CNS)

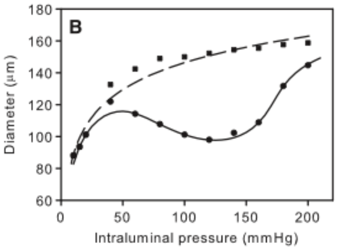


Local control of Flow and Pressure

Organ-specific Auto-regulations

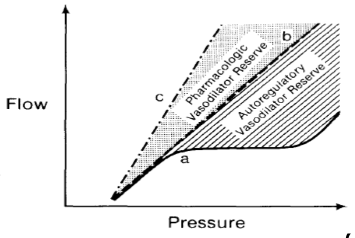
Cerebral Auto-regulation

Secomb

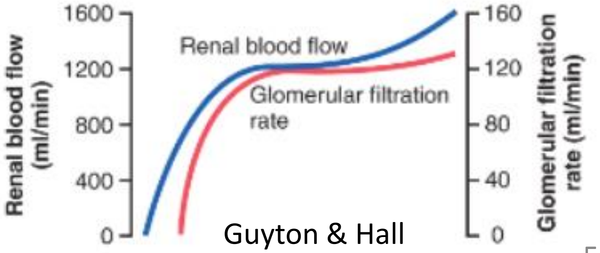


Coronary Auto-regulation

Dole



Renal Auto-regulation



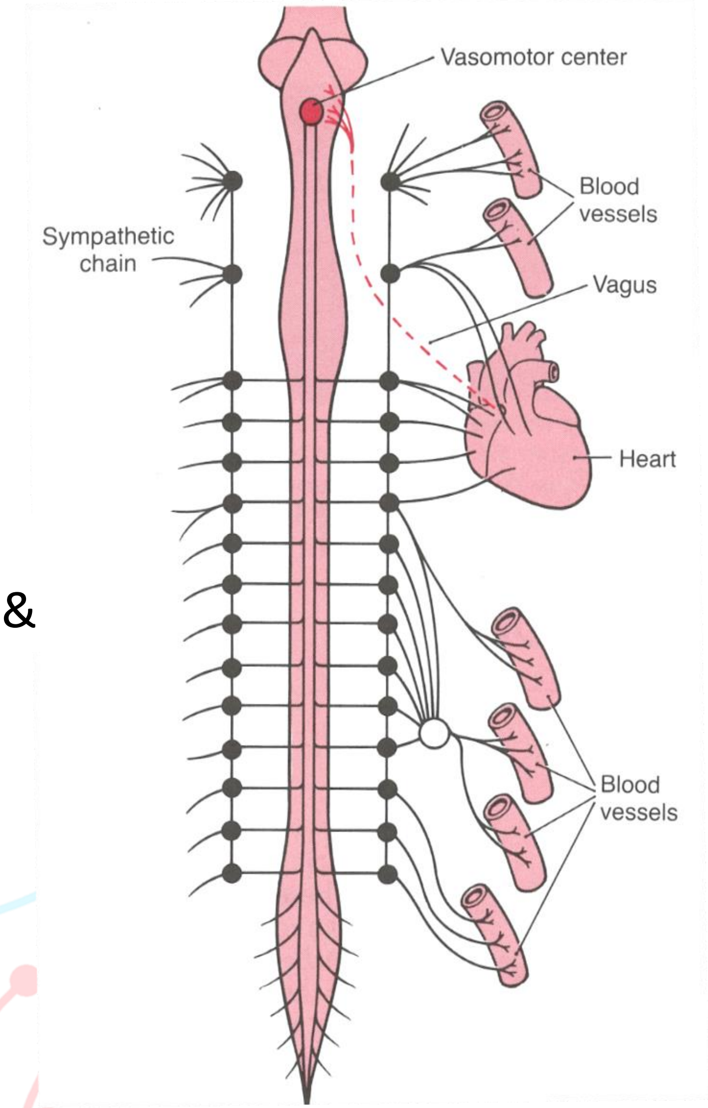
Guyton & Hall

Global control: modeling the baroreflex

Sympathetic system (the gas pedal)

- The sympathetic nerves innervate:
  - Small arteries & arterioles
  - Veins
  - Heart

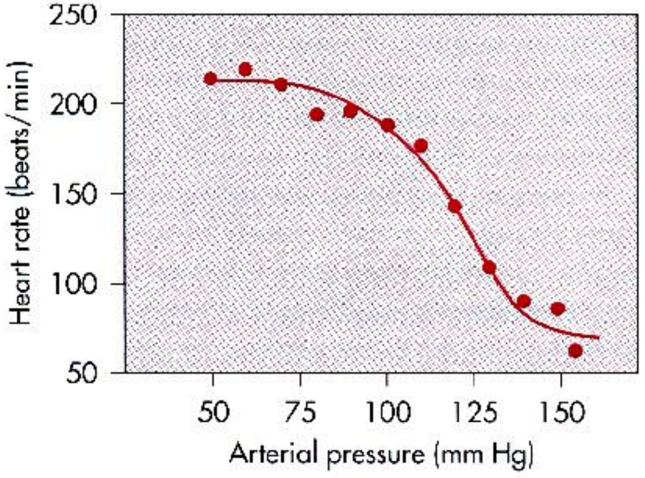
- Increased sympathetic activity stimulates:
  - Increase in vessel constriction in small arteries & arterioles and veins
  - Increase in heart rate
  - Increase in maximum heart contractility



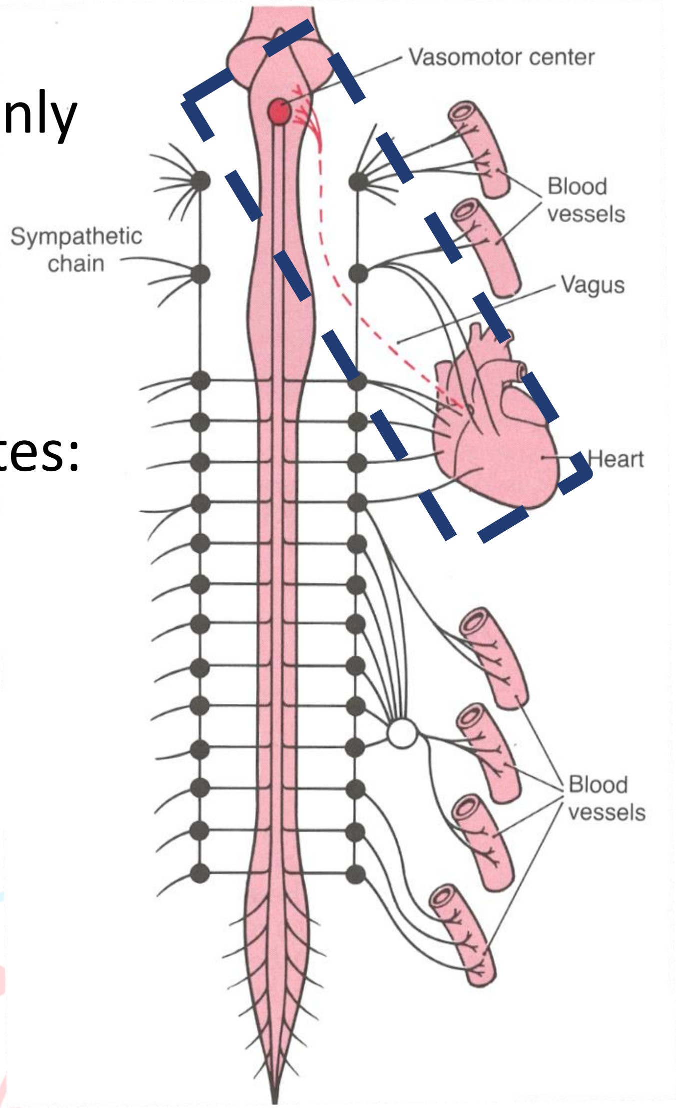
Guyton, Human Physiology and Mechanisms of Disease, 5th Ed.

Parasympathetic system (the brake)

- The parasympathetic nerve (vagus nerve) only innervates:
  - Heart
- Increased parasympathetic activity stimulates:
  - Decrease in heart rate
  - Decrease in maximum heart contractility

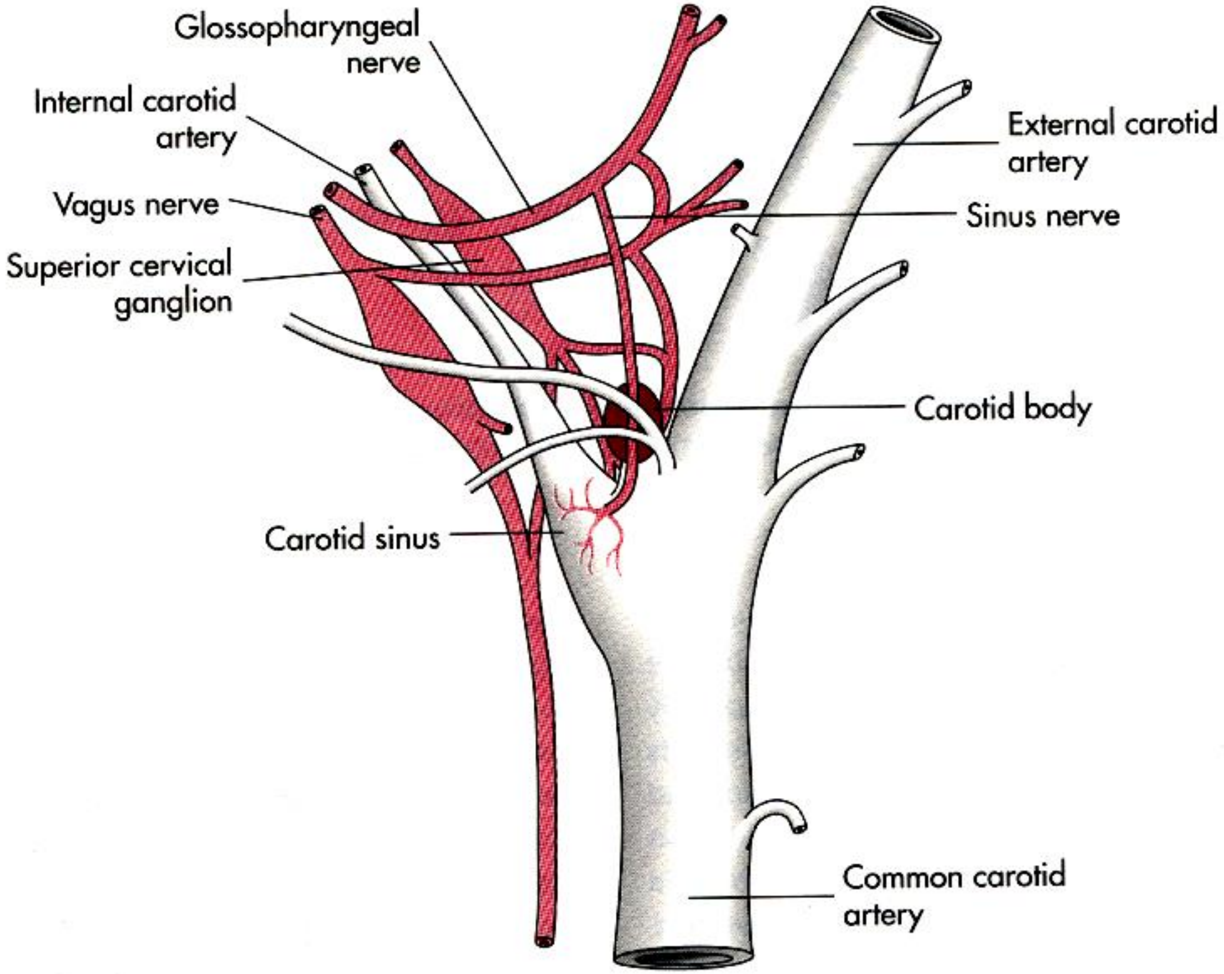


Berne and Levy, 6th edition



Guyton, Human Physiology and Mechanisms of Disease, 5th Ed.

The baroreceptors



Berne and Levy, 6th edition

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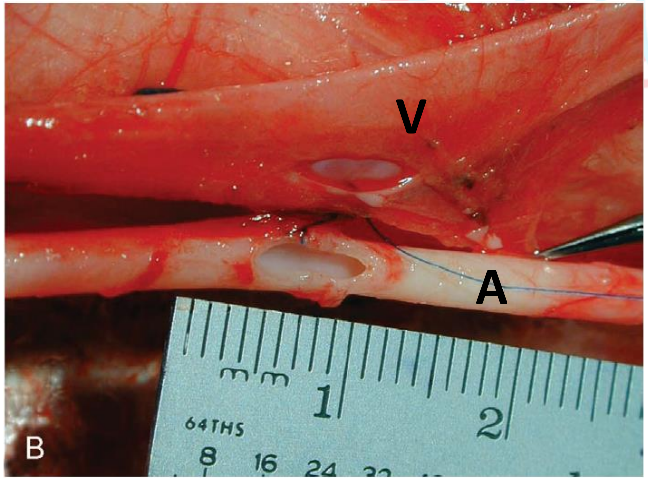
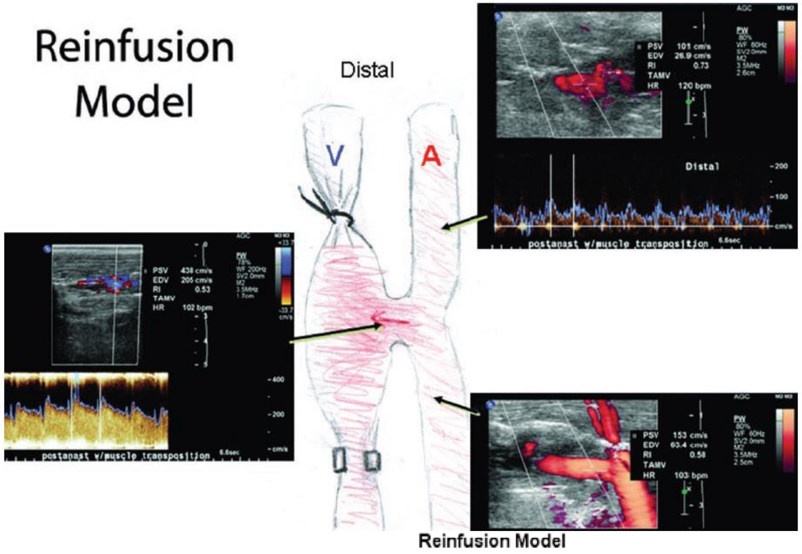
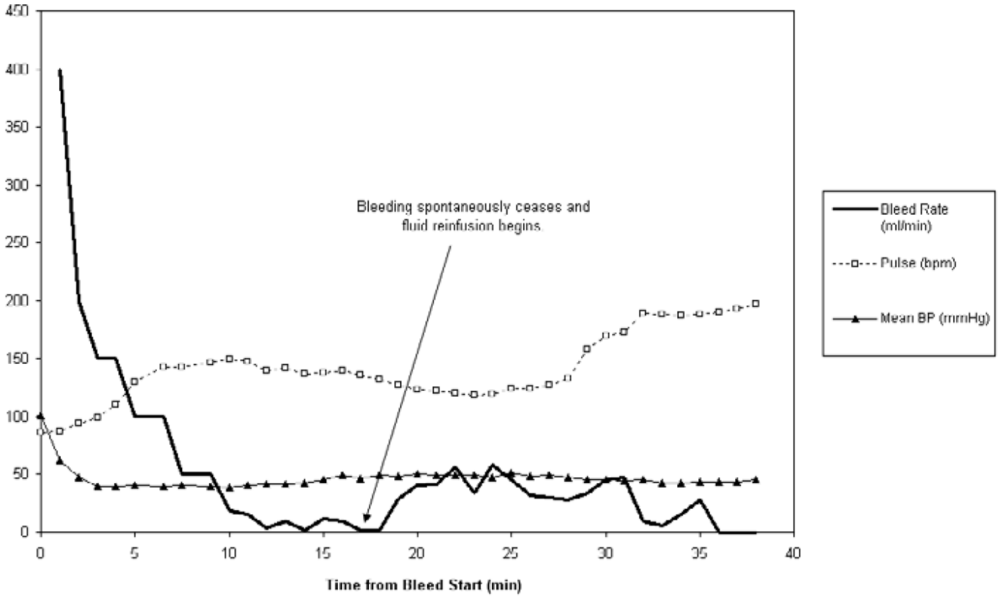
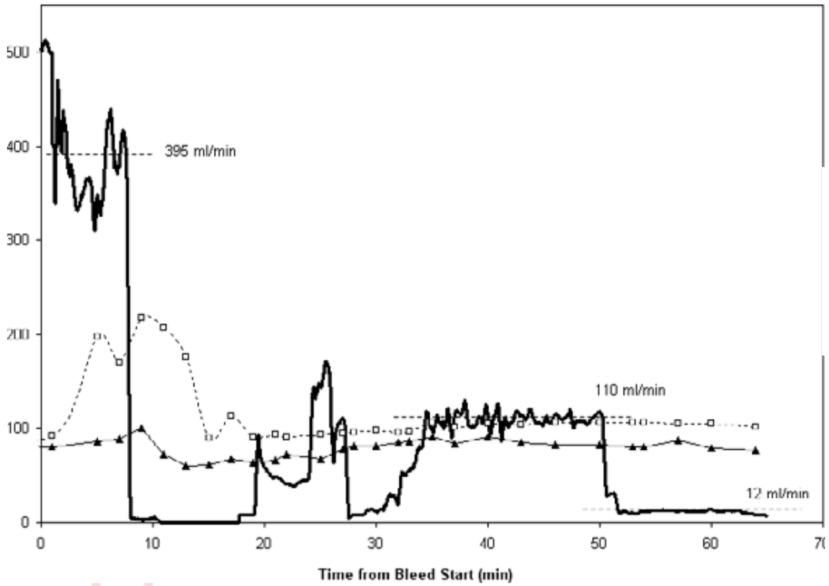
Example: Hemodynamic changes during trauma



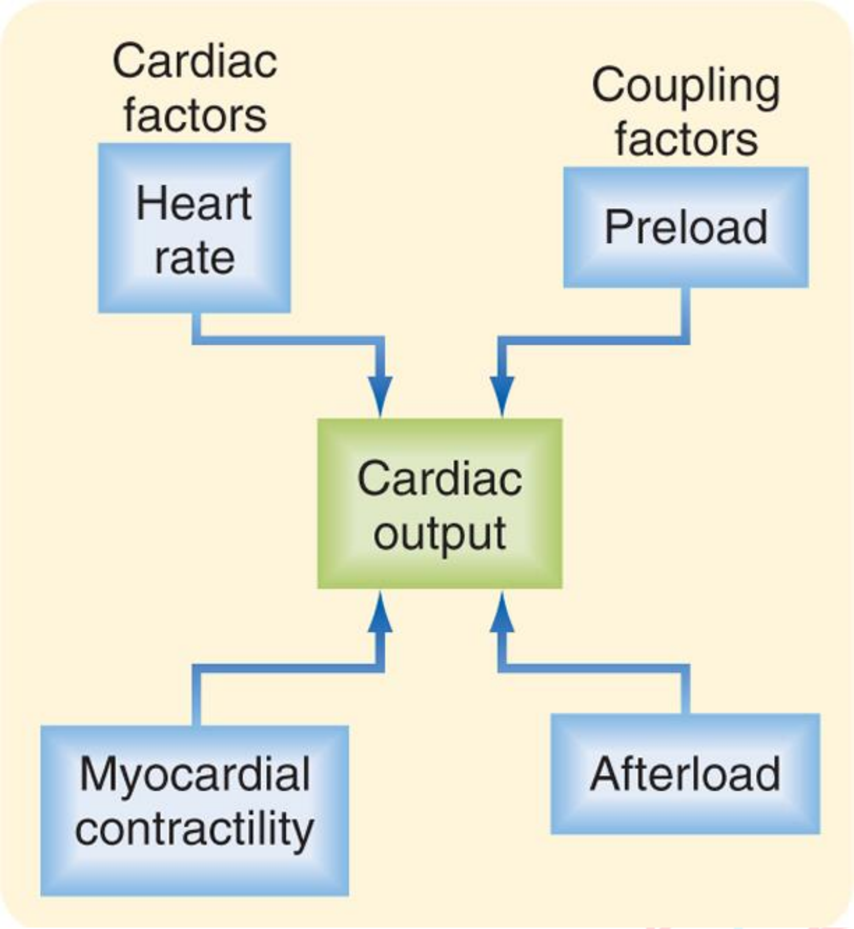






Haick et al. Polish Journal of Surgery 2011

Regulation of cardiac output



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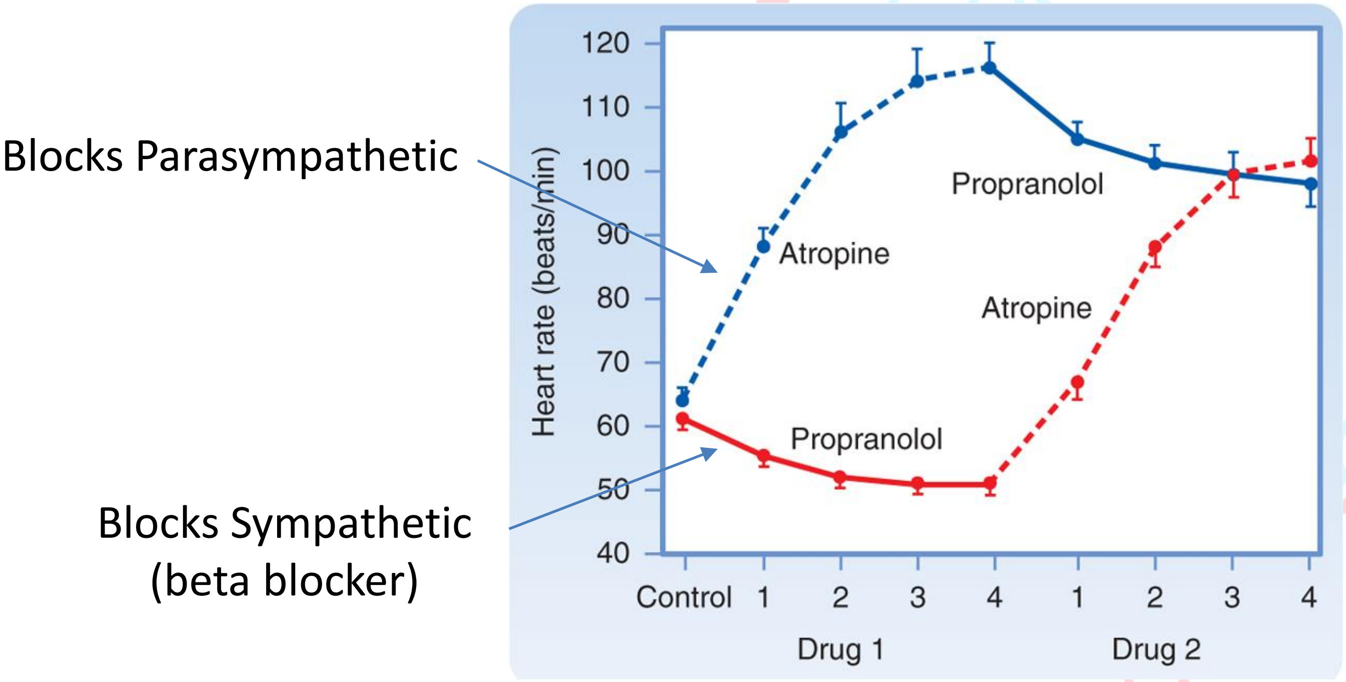
Control of heart rate

- Heart rate is principally controlled by autonomic nervous system through sympathetic (increase heart rate) and parasympathetic (decreases heart rate) pathways.

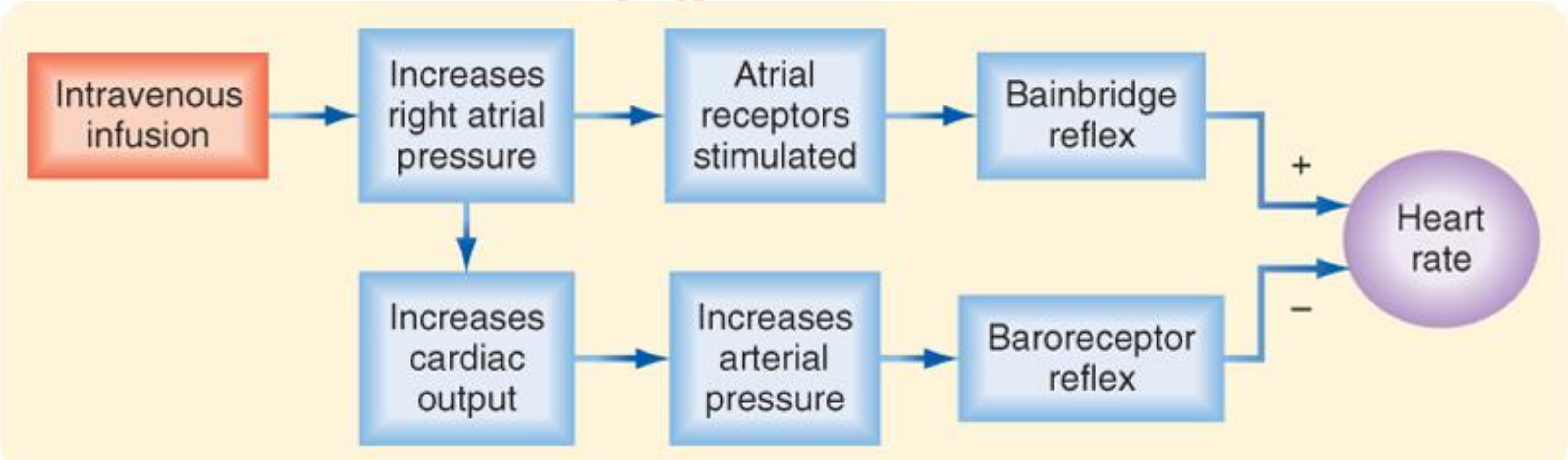
- Parasympathetic tone dominates in healthy individuals, so blocking these mechanisms increases heart rate.



Berne and Levy, 6th edition

Brainbridge reflex

- The Bainbridge reflex, also called the **atrial reflex**, is an increase in heart rate due to an increase in central venous pressure
- Increased blood volume is detected by stretch receptors (baroreceptors) located in both atria at the venoatrial junctions
- The baroreceptor reflex can correct for a change in arterial pressure by increasing or decreasing heart rate. In contrast, the Bainbridge reflex responds to changes in blood volume



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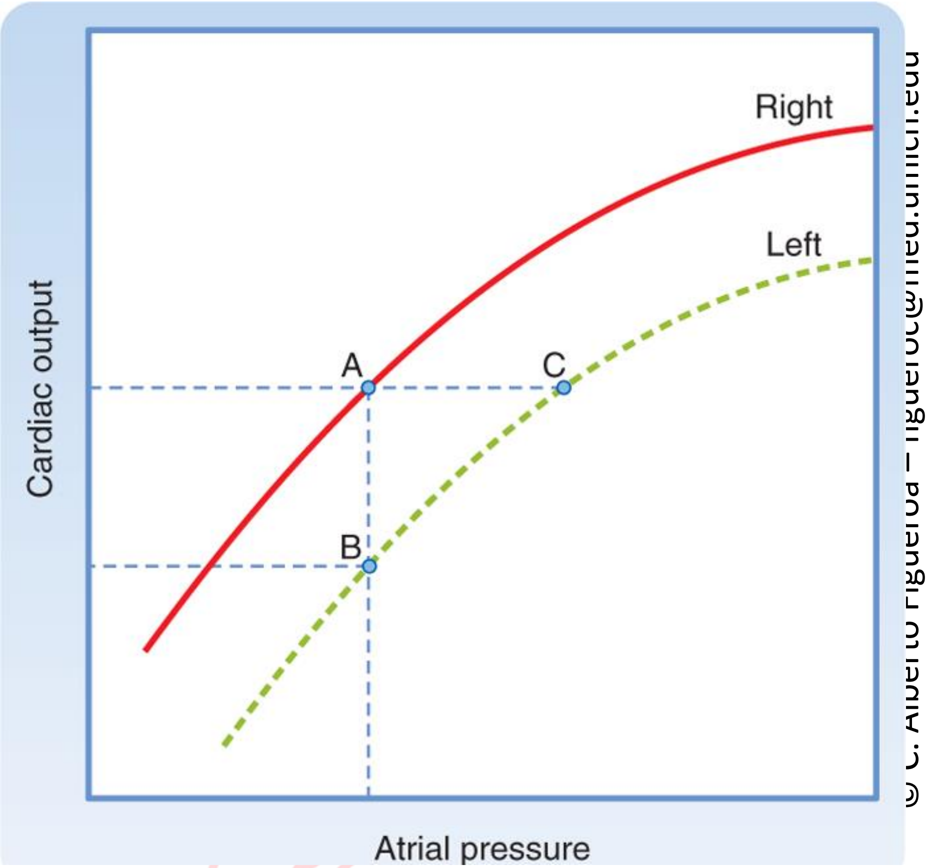
Control of Stroke Volume

- Myocardium can adapt to changing hemodynamic conditions by intrinsic mechanisms (know this from experiments in denervated hearts).
- **Frank-Starling mechanism** is one important way that stroke volume changes.
- Increased preload (right ventricular filling pressure just before ventricular contraction) causes increased SV, EDV, but HR constant.
- Dilation of heart due to increased EDV increases myocardial fiber length which increases contractility.
- Increased afterload (aortic pressure the heart pumps against) causes decreased HR, but constant SV.

Frank-Starling mechanism

- Also known as the “Law of the heart”
- Maintains balance between right and left ventricles.
- If the atrial pressures were the same, then the output of the right side would exceed the left leading to an increase in left ventricular diastolic volume, which would increase left ventricular output, resulting in equilibration of cardiac outputs.



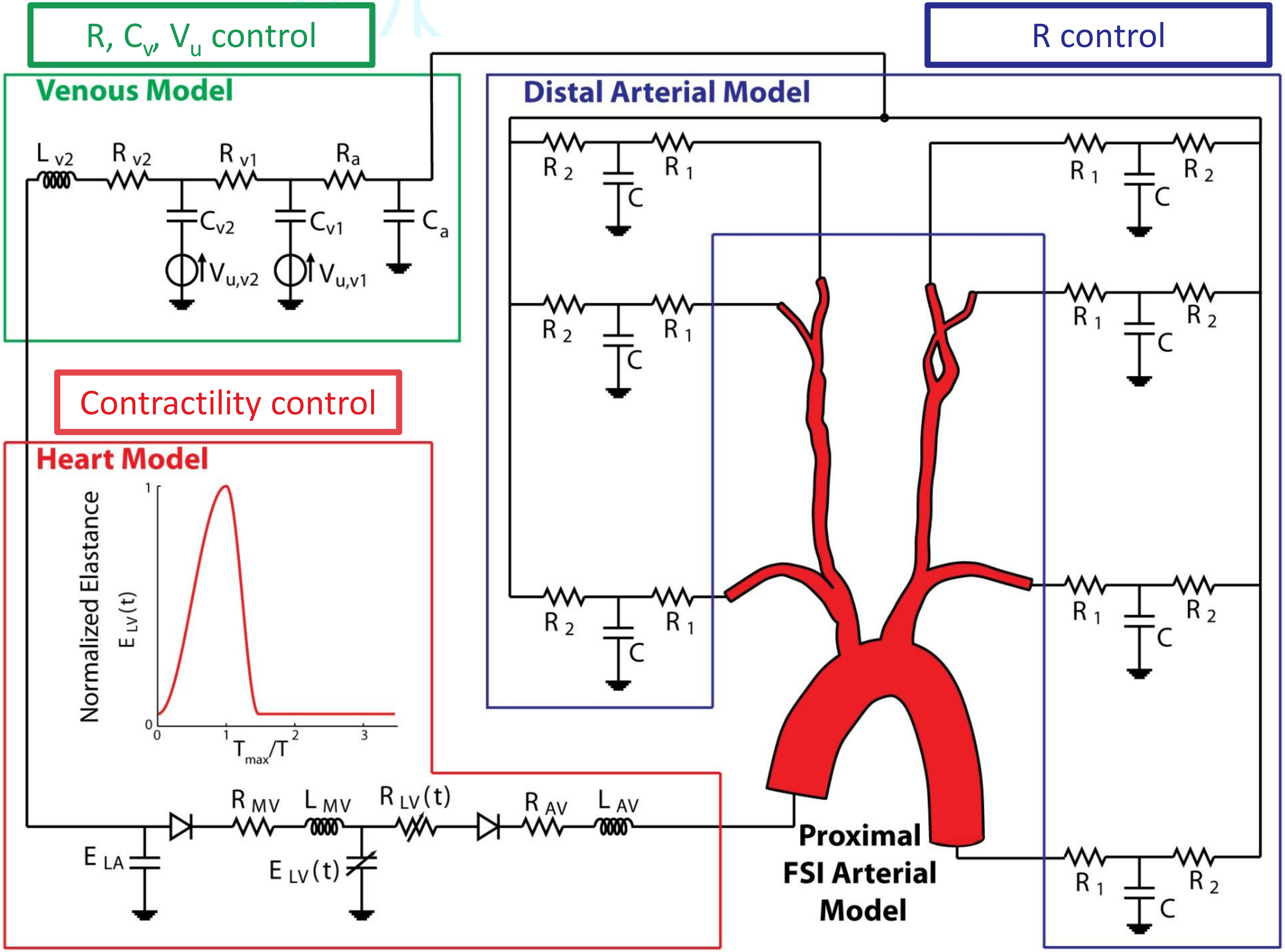
Berne and Levy, 6th edition

Modeling the baroreflex

- To model the baroreflex mechanism the minimum set of components required are:
  - Heart
  - Large arteries
  - Small arteries and arterioles
  - Veins

- The effect of the baroreflex requires the control of:
  - Arterial resistance (small arteries and arterioles)
  - Peripheral blood volume (veins)
  - Heart rate
  - Heart contractility

Modeling the baroreflex



R, C_v, V_u control

R control

Contractility control

Venous Model

Distal Arterial Model

Heart Model

Proximal FSI Arterial Model

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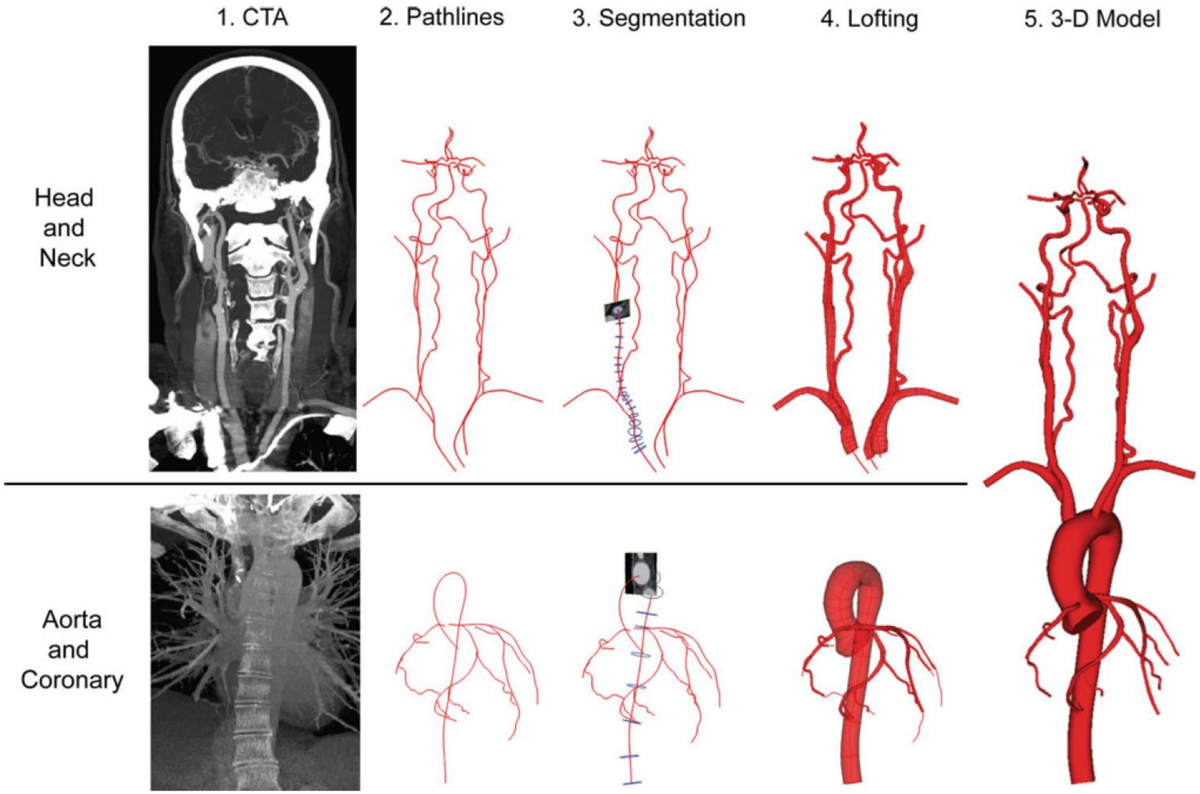
Patient Specific Geometry

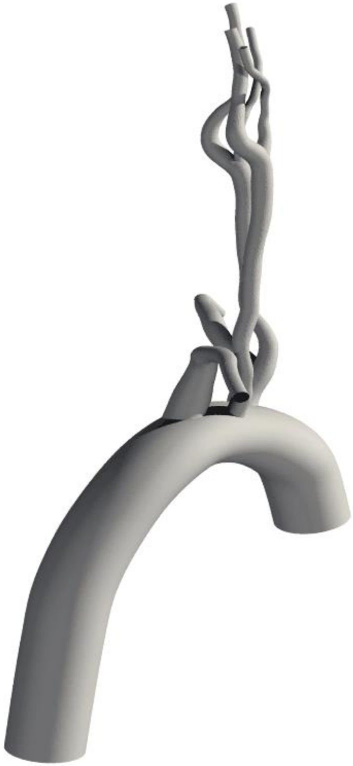
- The basis of the geometry is taken from a previously published model



J.S. Coogan, J.D. Humphrey, C.A. Figueroa. BMMB 2013

Patient Specific Geometry

- Here the geometry has been reduced to 7 branches:
  - Right subclavian
  - Right internal carotid
  - Right external carotid
  - Left internal carotid
  - Left external carotid
  - Left subclavian
  - Descending aorta



Patient-specific geometry

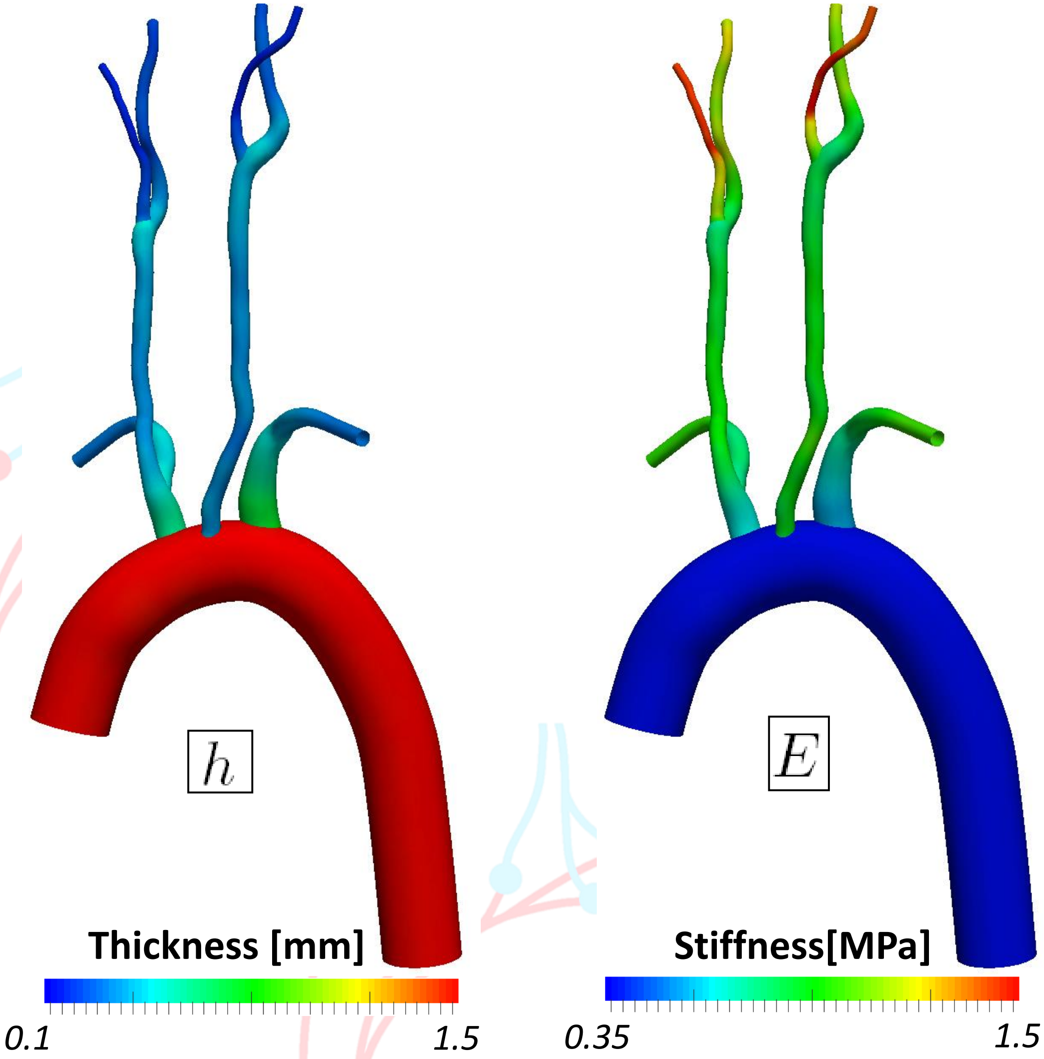
- Wall thickness and elastic modulus derived from a vessel diameter, pulse wave velocity relationship

$$c\left(\bar{d}\right) \approx \frac{a_2}{\bar{d}^{b_2}}$$

$$h = 0.1R$$

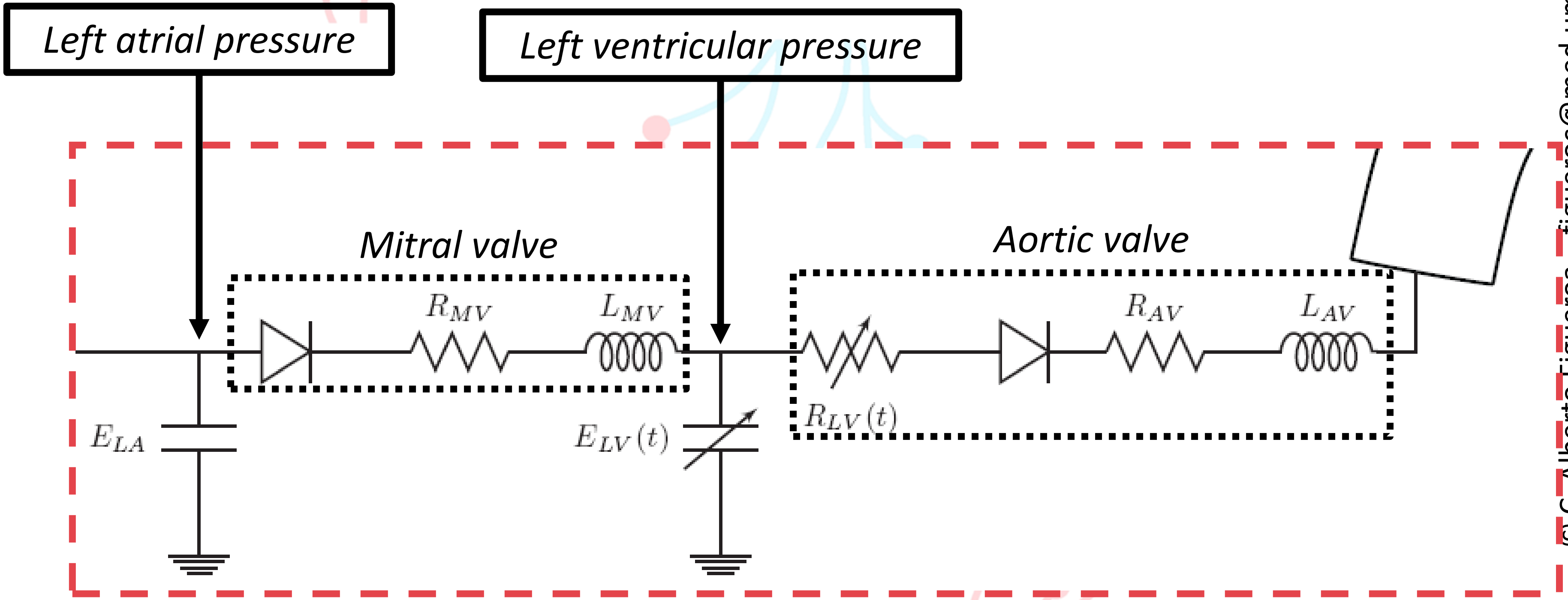
$$E = \frac{3\rho R c^2}{2h}$$

Reymond et al.
Am J Physiol Heart Circ Physiol, 2009



Inflow BC – the heart model

- The inlet of the 3D geometry is implicitly coupled to a 0D model of the left heart



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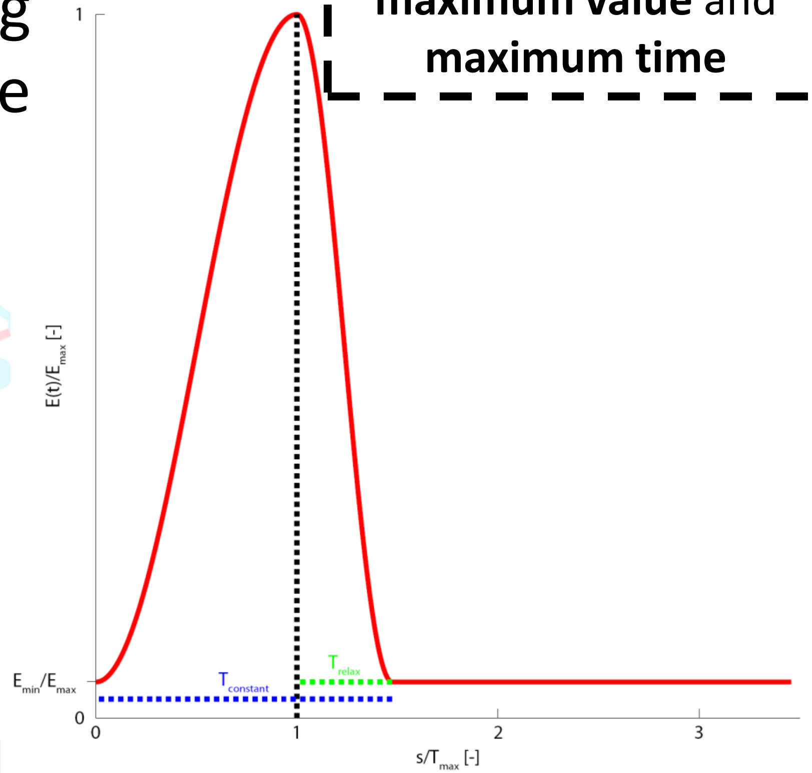
Inflow BC – the heart model

- The time varying pumping action of the left ventricle is modelled using via an non-dimensional elastance function

$$\boxed{P_{LV}(t) = E_{LV}(t)\,(V_{LV}(t) - V_{u,LV})}$$

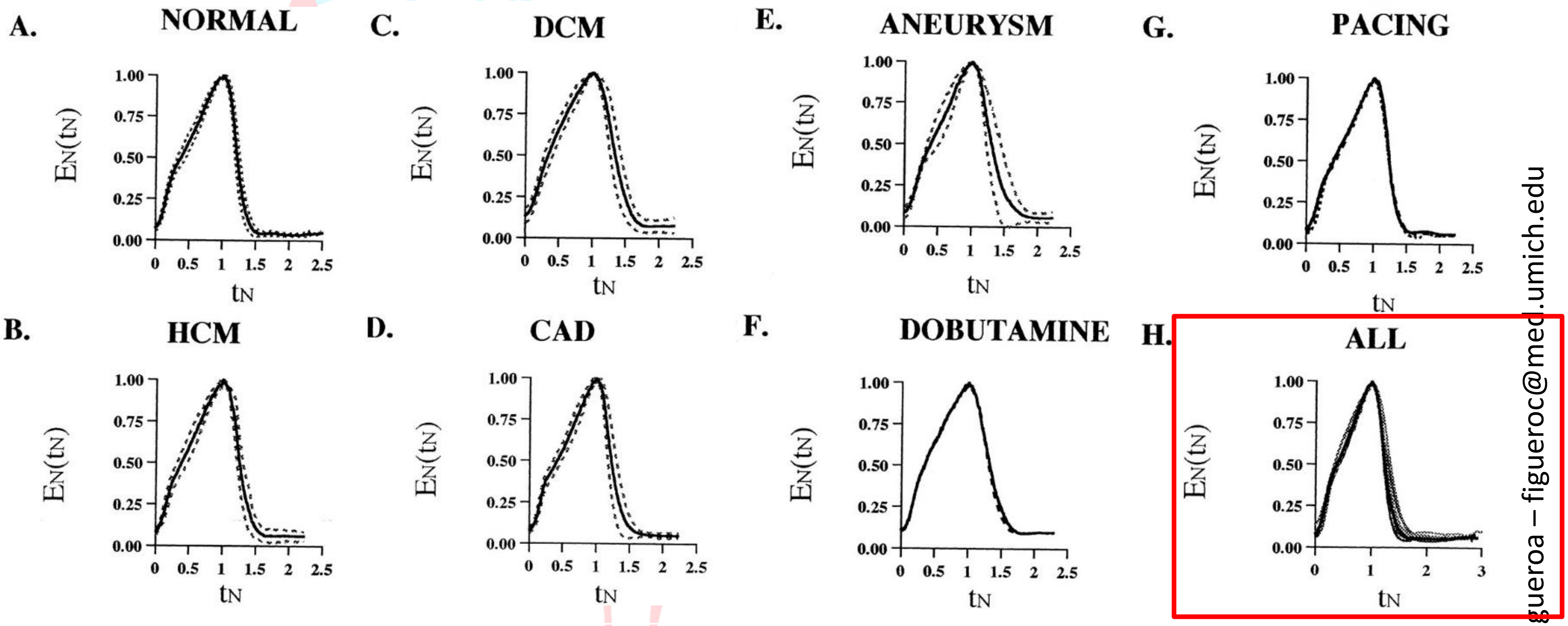
Pope et al., Math Biosci Eng, 2009

The baroreflex controls **maximum value** and **maximum time**



$$E_{LV}(t) = \begin{cases} E_{min} + \dfrac{E_{max} - E_{min}}{2}\left[1 - \cos\left(\dfrac{s\pi}{T_{max}}\right)\right], & 0 \leq s < T_{max} \\ E_{min} + \dfrac{E_{max} - E_{min}}{2}\left[\cos\left(\dfrac{\pi(s - T_{max})}{T_{relax}}\right) + 1\right], & T_{max} \leq s < T_{max} + T_{relax} \\ E_{min}, & T_{max} + T_{relax} \leq s < T \end{cases}$$

Universal functional form for the elastance function



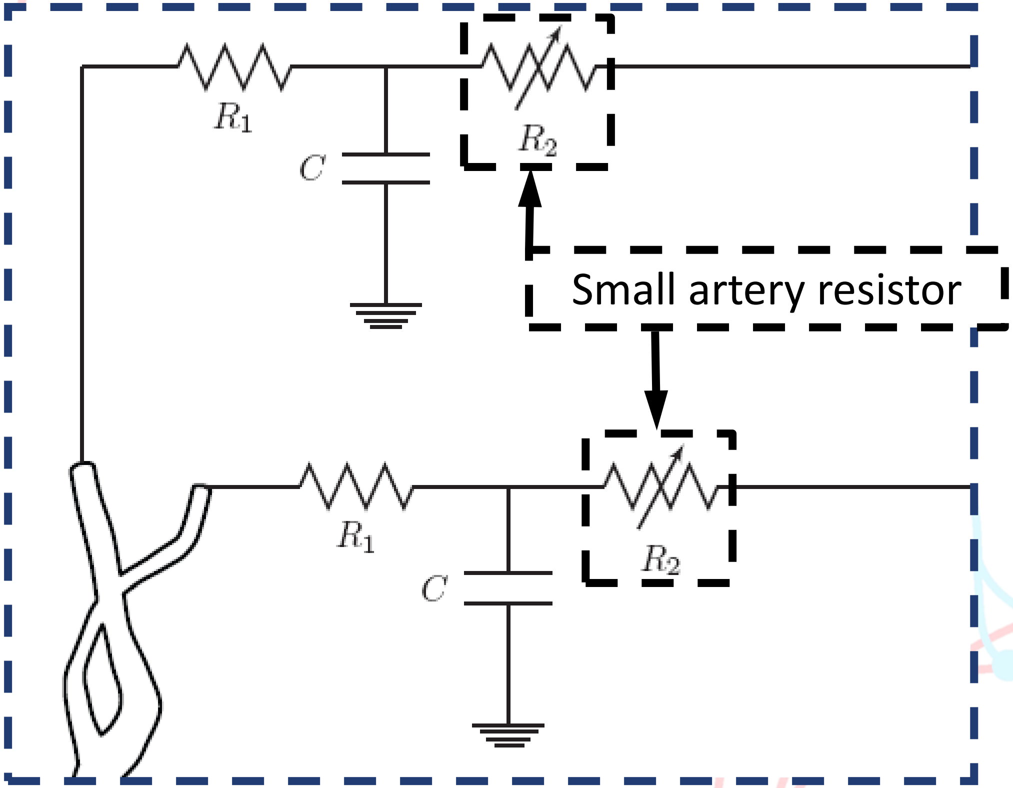
HCM hypertrophic cardiomyopathy
DCM dilated cardiomyopathy
CAD coronary artery disease with normal LV function

Senzaki et al. Circulation. 1996

- Once normalised, the elastance function is <u>**self similar**</u> under a wide range of conditions.

Arterial outflow BCs

- Each vessel branch in 3D is implicitly coupled to a 3-element Windkessel



Small artery resistor

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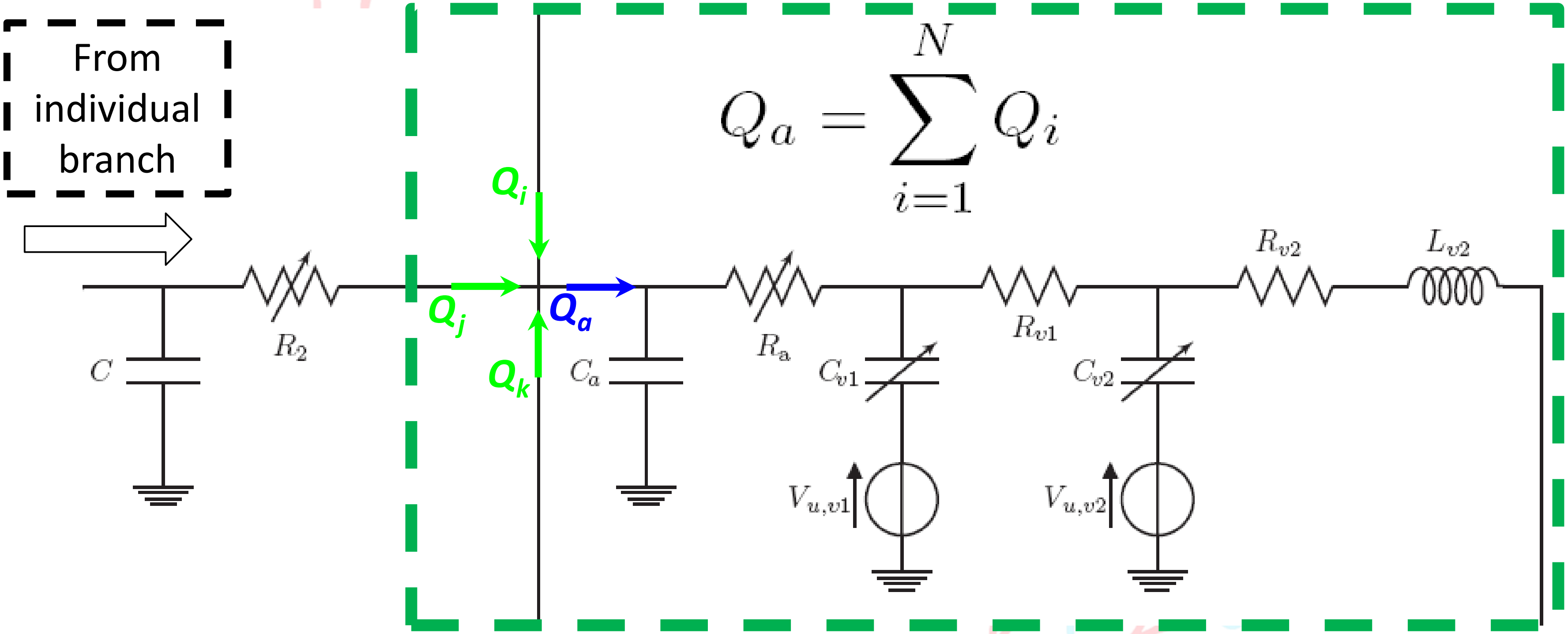
Arterioles and veins

- Each Windkessel is attached a circuit that represents the arterioles, venules and small veins



$$Q_a = \sum_{i=1}^{N} Q_i$$

- The flow from each Windkessel branch is added and passed to the arterioles and veins circuit

Pressure feedback

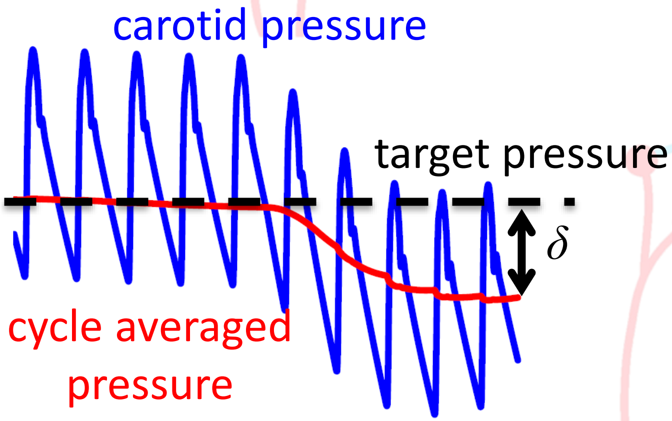
- The average pressure at each carotid branch is compared to its target value, the maximum difference is used as the control signal

$$n_s(\delta) = \frac{1}{1+\delta^{+\nu}}$$

Sympathetic Activity

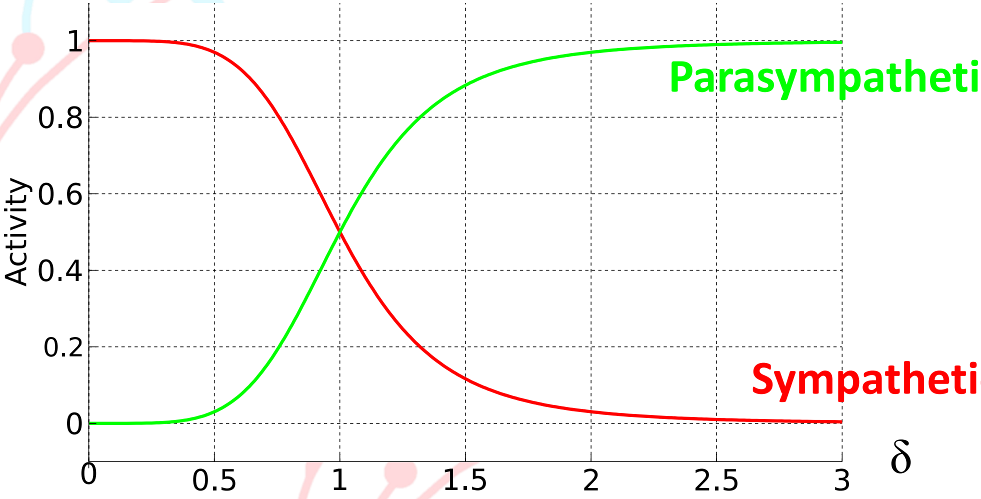
$$n_p(\delta) = \frac{1}{1+\delta^{-\nu}}$$

Parasympathetic Activity



$$j = \operatorname{argmax}_i = \frac{|\overline{p}_i - p_{i,target}|}{p_{i,target}}$$

$$\delta = \frac{\overline{p}_j}{p_{j,target}}$$

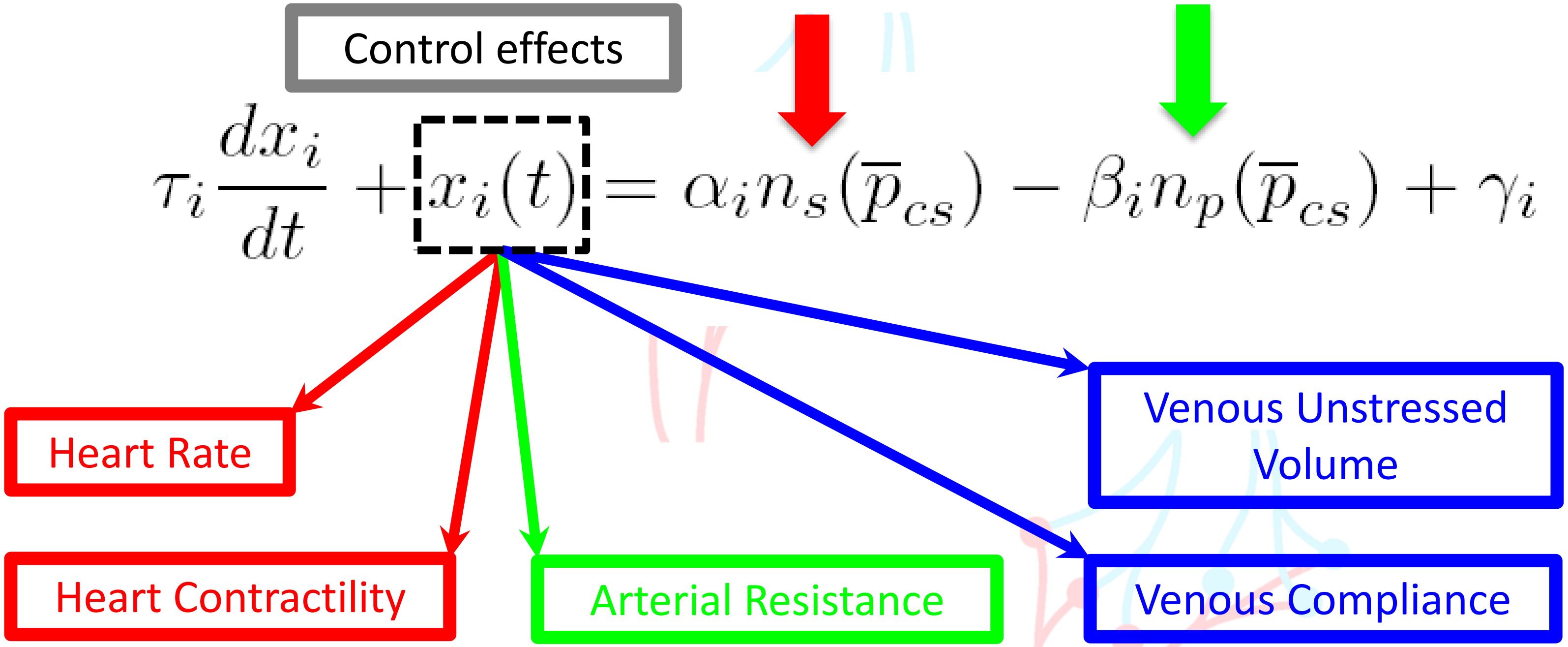


Decreasing δ ⟺ *Increasing δ*

Ottesen, J, Olufsen, M. & Larsen, J., Applied Mathematical Models in Human Physiology, 2004.

Control response

- The baroreflex is modelled as a 1st order ODE whose RHS depends on the sympathetic n_s and parasympathetic n_p activity



Control effects

$$\tau_i \frac{dx_i}{dt} + \boxed{x_i(t)} = \alpha_i n_s(\bar{p}_{cs}) - \beta_i n_p(\bar{p}_{cs}) + \gamma_i$$

Heart Rate

Heart Contractility

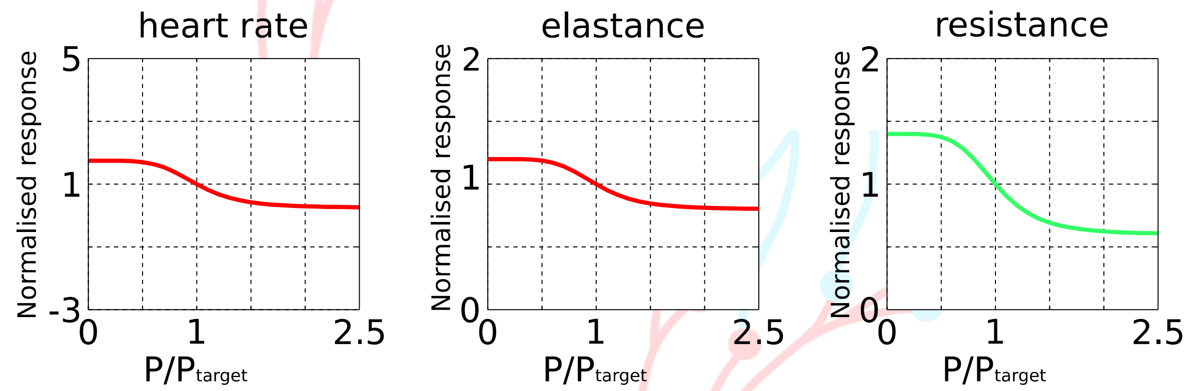
Arterial Resistance

Venous Unstressed Volume

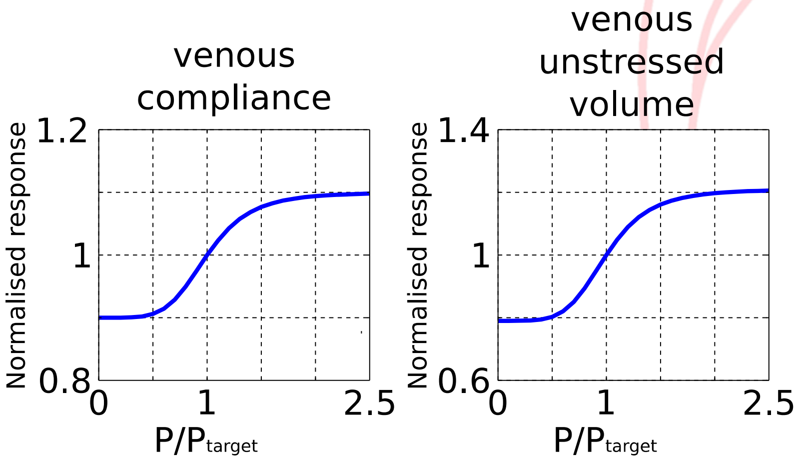
Venous Compliance

Control parameters

- Gain parameters (α and β) have been fitted to steady state values from literature



Heart rate, elastance and arterial resistance time constant $\tau = 3$ s

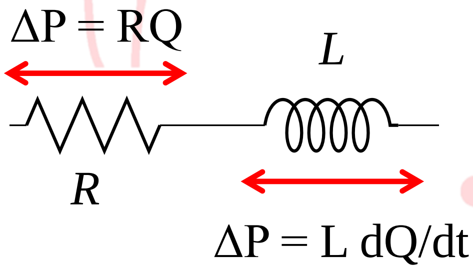


Venous compliance unstressed volume time constant $\tau = 30$ s

Ottesen, J, Olufsen, M. & Larsen, J., Applied Mathematical Models in Human Physiology, 2004.

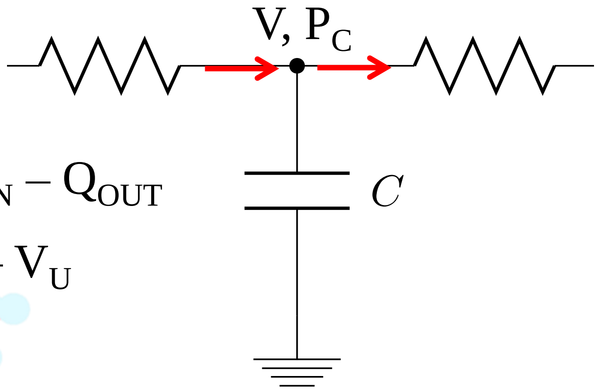
Systemic circuit

- The circuit is numerically implemented by using the following relationships



$dV/dt = Q_{IN} - Q_{OUT}$

$CP_C = V - V_U$



- The resulting algebraic system has the form

$$\mathbf{A}\mathbf{x}^{n+1} = \mathbf{B}\mathbf{x}^{n} + \mathbf{C}\mathbf{q}^{n+1} + \mathbf{D}$$

0D variables $\mathbf{x}^T = [P_i, \ldots, P_n, P_{i,c}, \ldots, P_{n,c}, V_a, V_{v1}, V_{v2}, Q_{v2}, V_{la}, Q_{mv}, V_{lv}]$

3D flows $\mathbf{q}^T = [Q_i, \ldots, Q_n]$

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Baroreflex assessment: the tilt test

- Controlled assessment of the baroreflex is clinically examined by controlling the orientation of the patient

- The change in orientation triggers the baroreflex due to a gravitational pressure change

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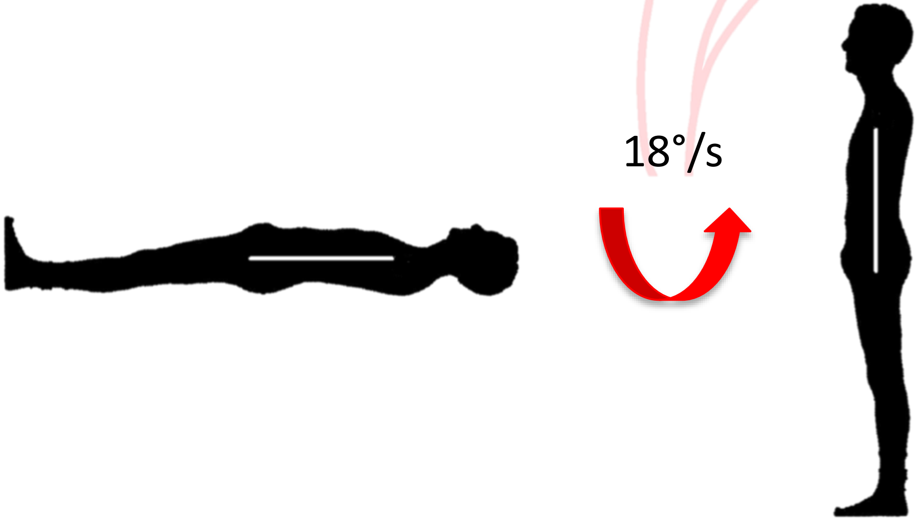
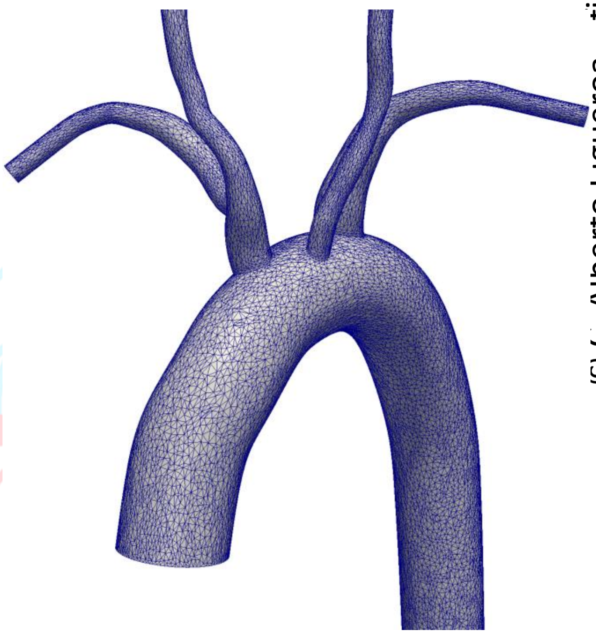
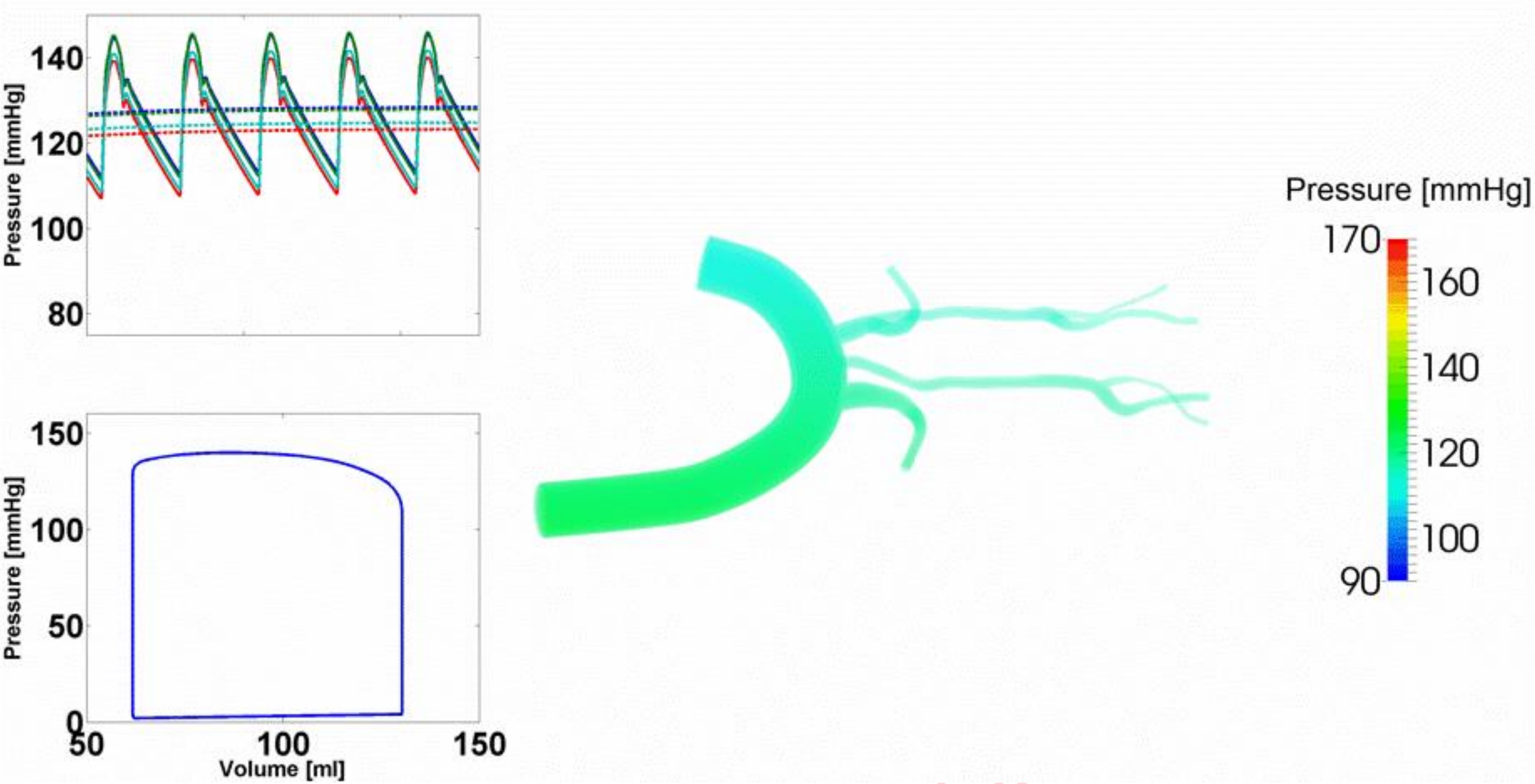
Simulating the tilt test

- Using a time step Δt = 0.0001 s, **25 s of physical time were simulated**
- Two sets of simulations were performed:
  - 90° tilt over 5 s with gravity, with baroreflex control
  - 90° tilt over 5 s with gravity, without baroreflex control

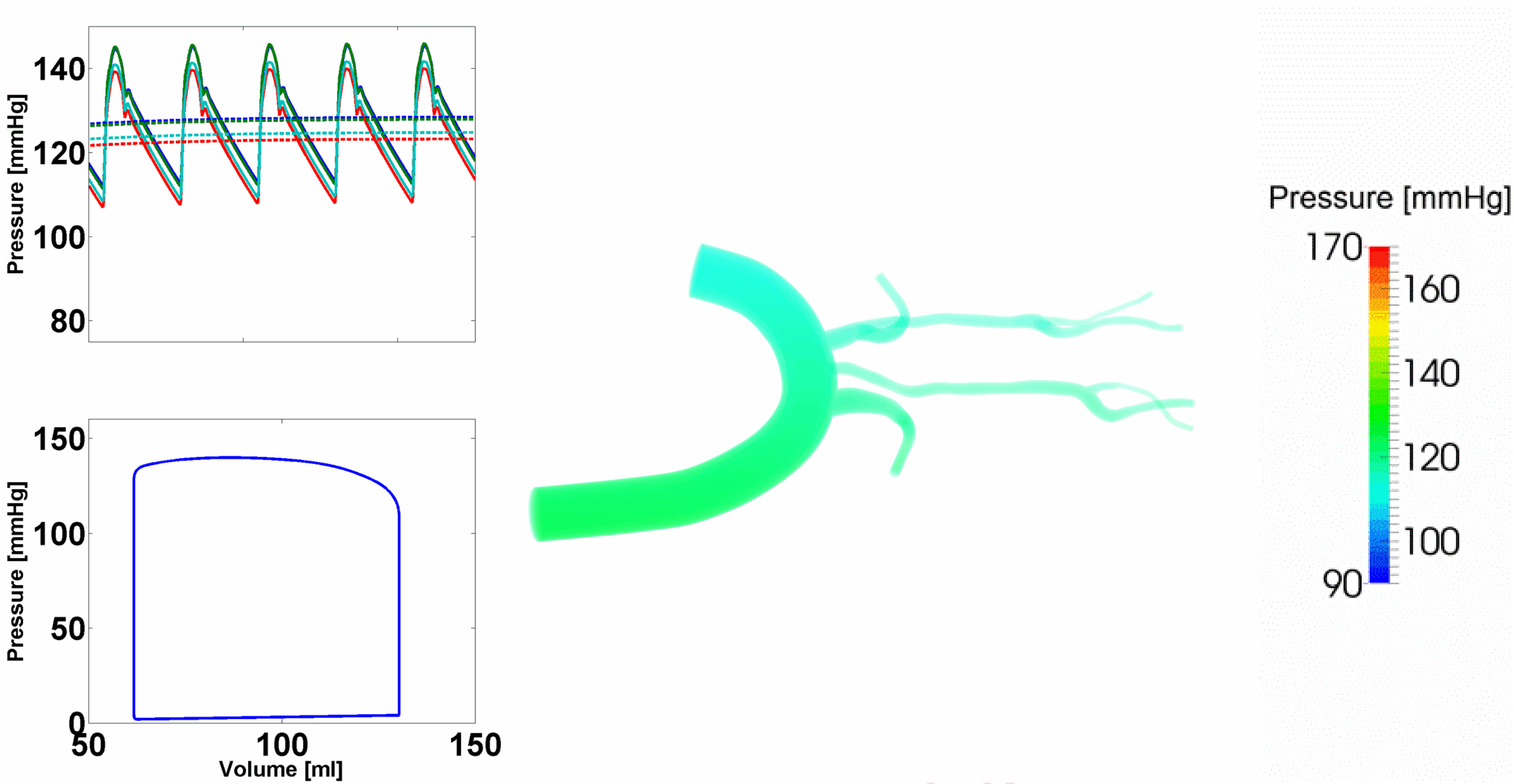




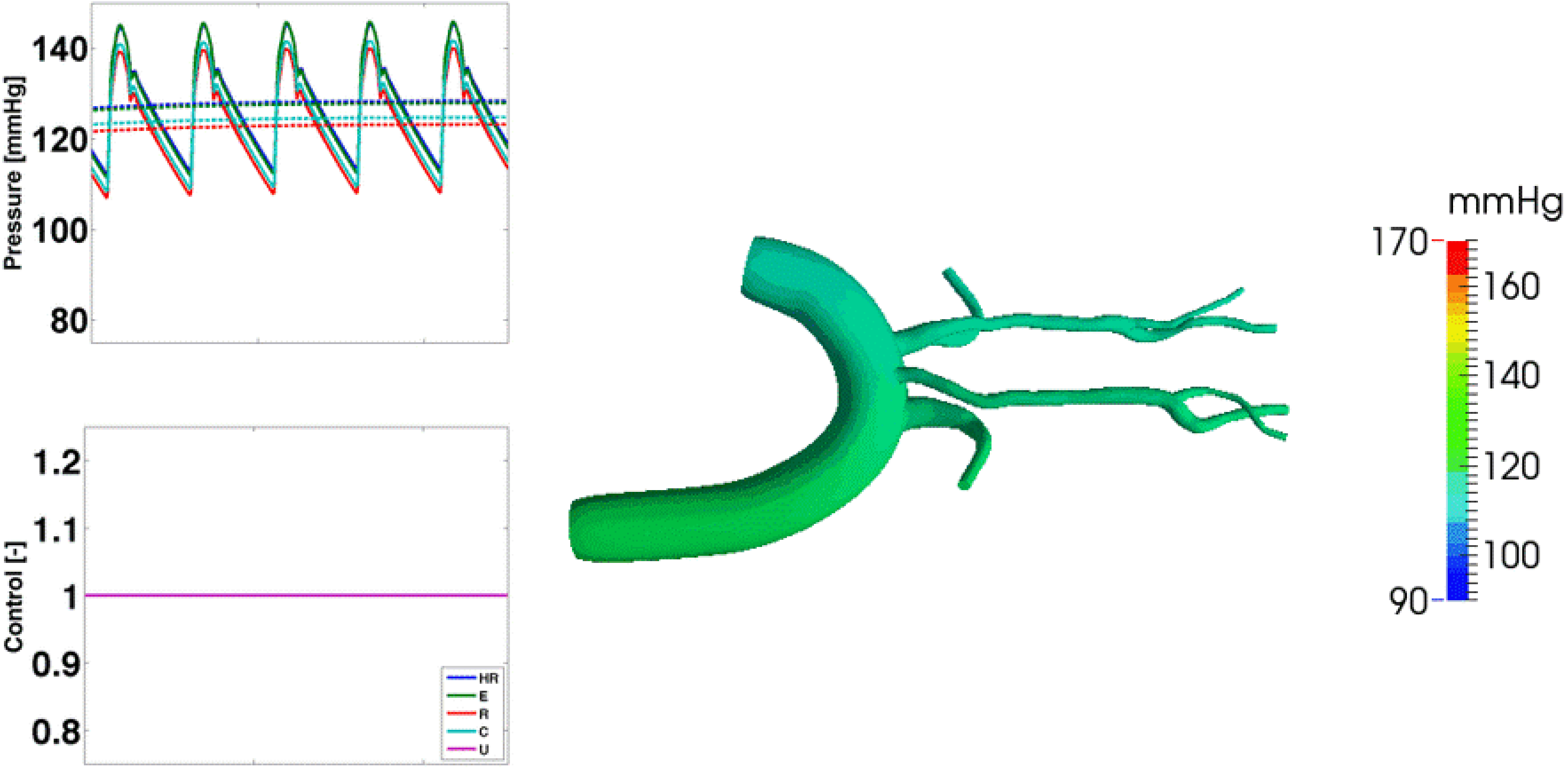
Effect of feedback on Pressure-Volume loop



Effect of feedback on Pressure-Volume loop



Effect of feedback on control



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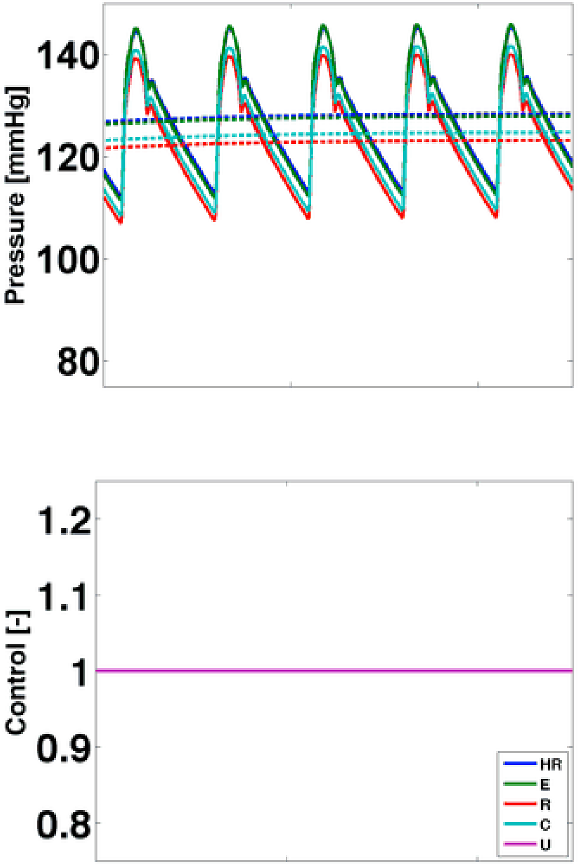
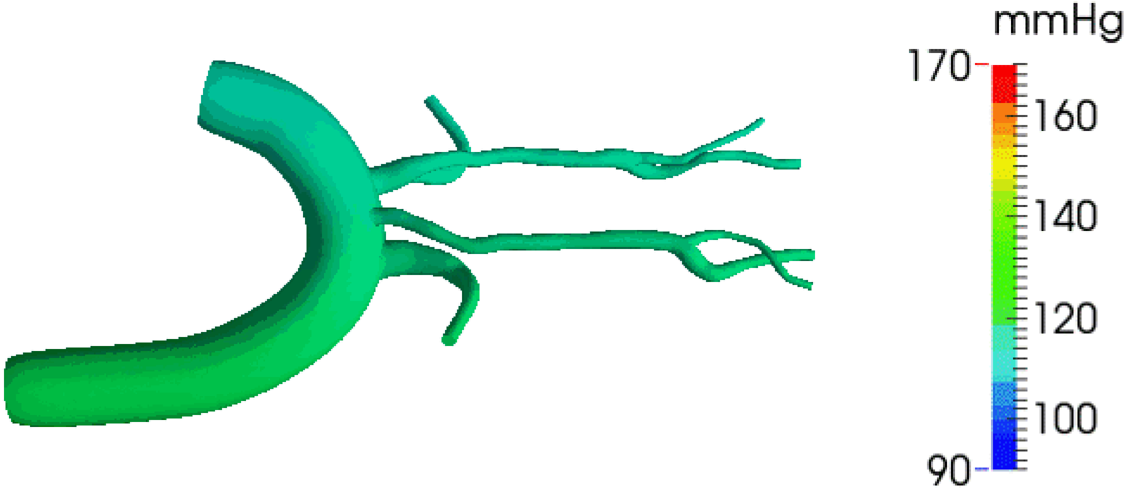
Effect of feedback on control





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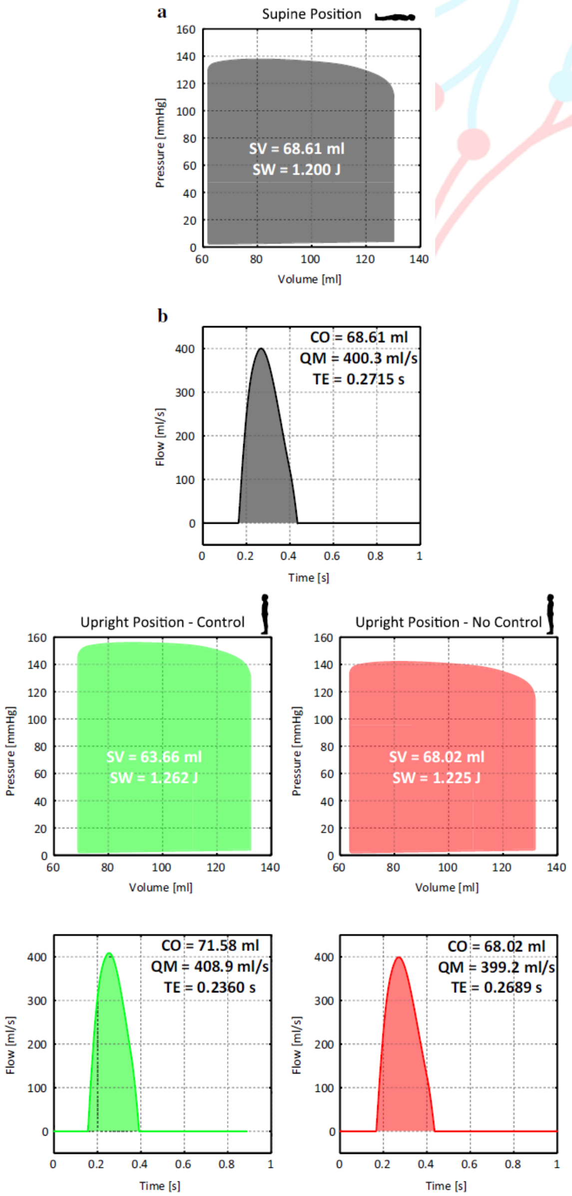
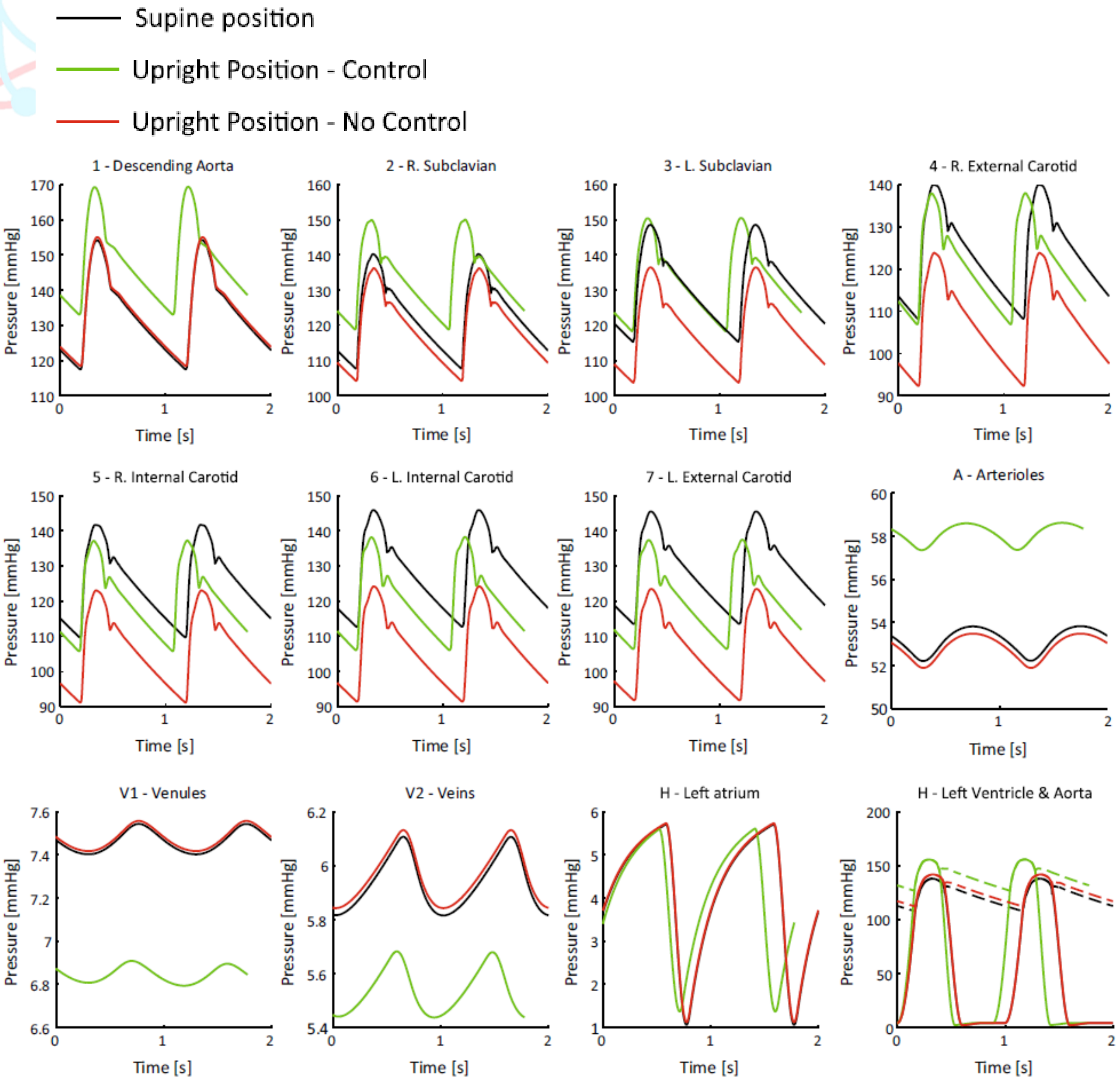
Effect of feedback on control



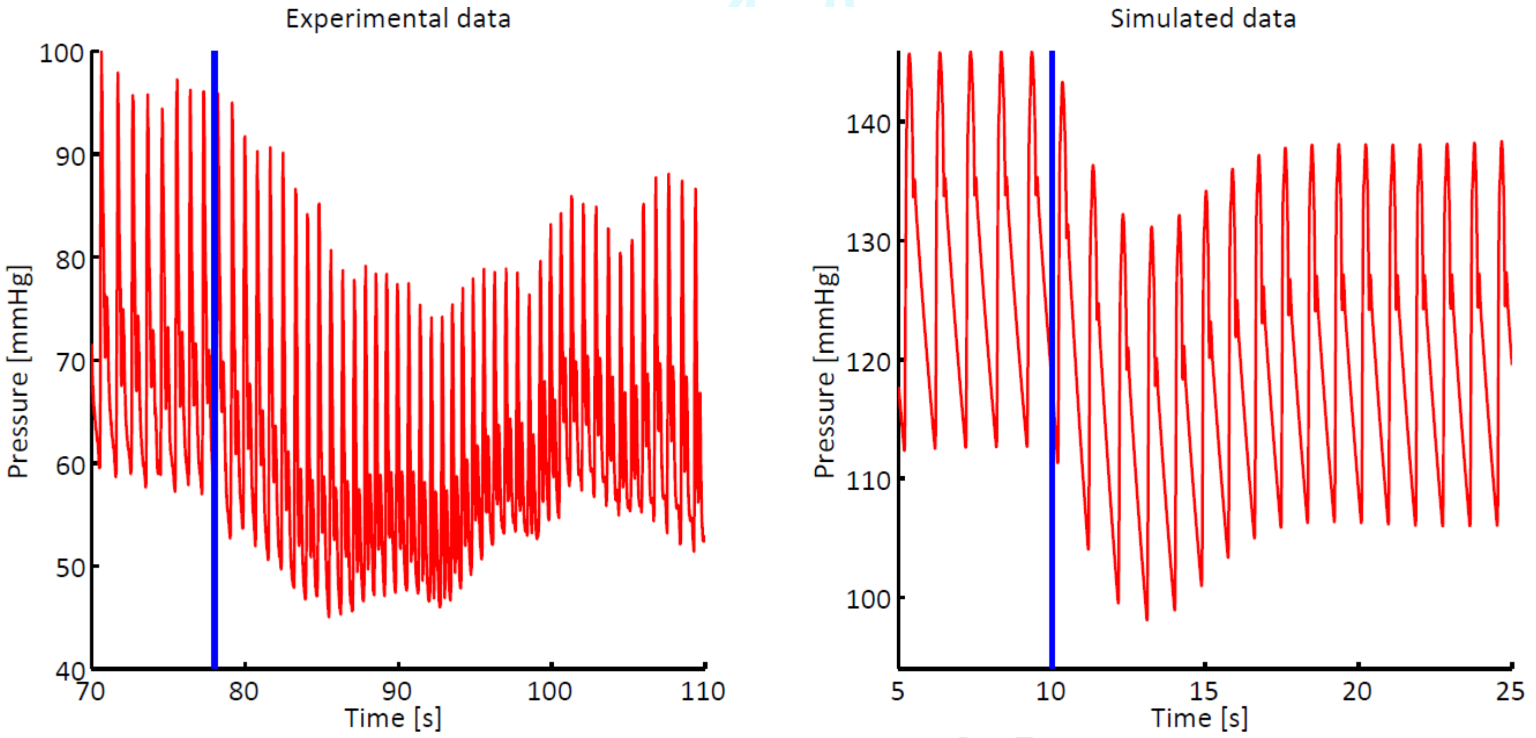


http://bloodflow.engin.umich.edu/

Validation against clinical data

- Fitting the baroreflex response to physiological data

- Experimental data exhibit difference in pressure waveforms during head up tilt



Williams et al., “Patient-specific modelling of head-up tilt”, Math Med Biol. 2013.

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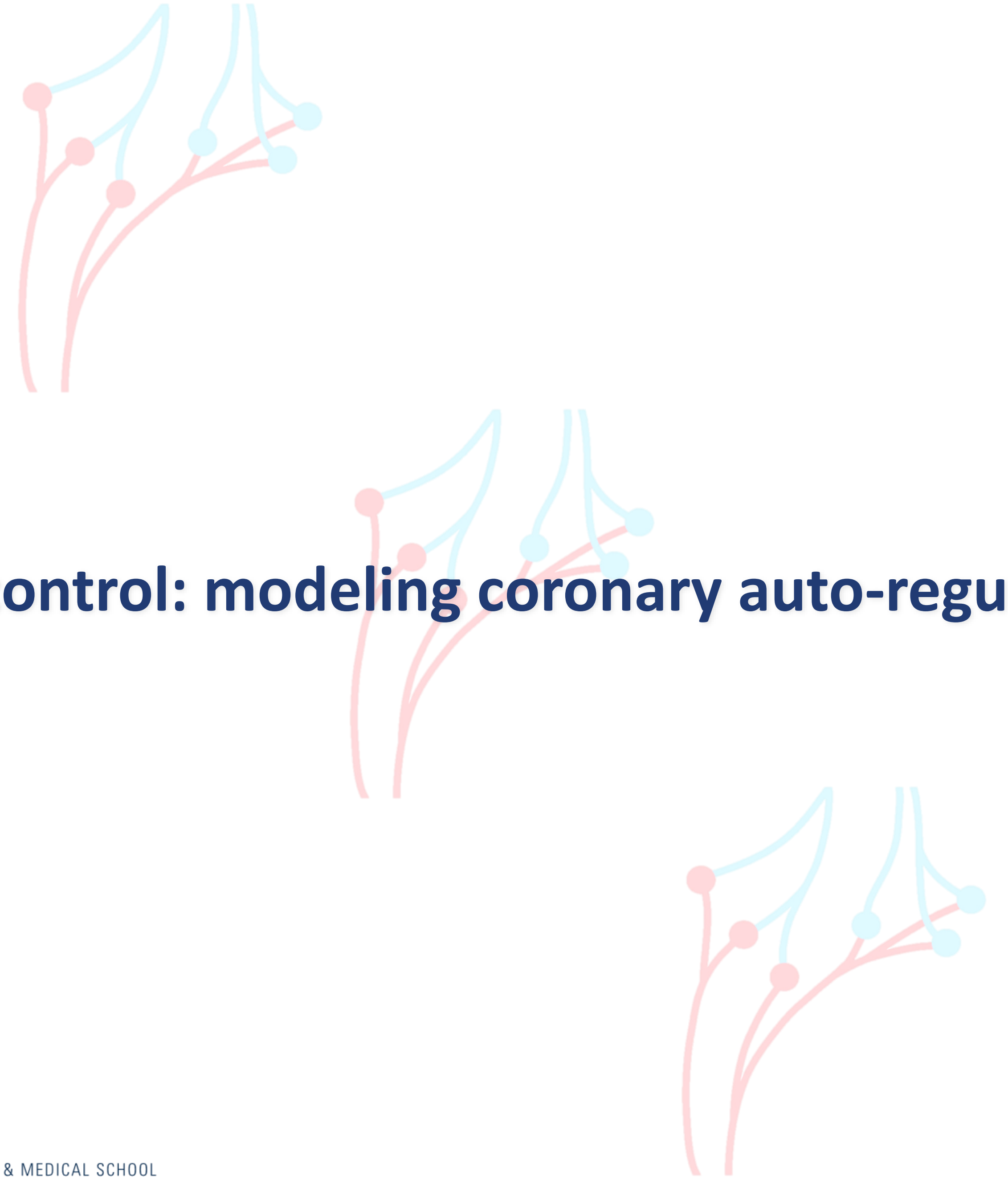
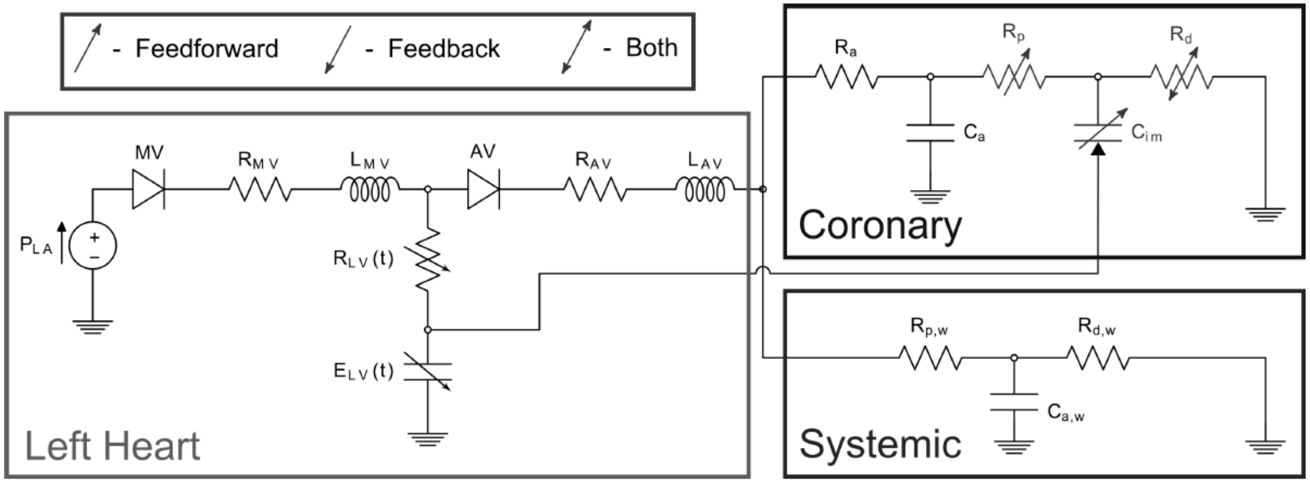


Local control: modeling coronary auto-regulations

Local control: Coronary auto-regulation

Simulation of alpha and beta adreno-receptors and metabolic feedback in coronary vessel SMC



$H(t)$: myocardial hunger

$$\frac{dQ(t)}{dt} = \underbrace{k_{fb}\gamma^{-1}H(t) + g\gamma^{-1}\frac{dH(t)}{dt}}_{\text{Feedback: Damped oscillations of myocardial hunger}} + \underbrace{\gamma^{-1}\frac{dMVO2(t)}{dt}}_{\text{Feedforward: Oxygen demand}}$$

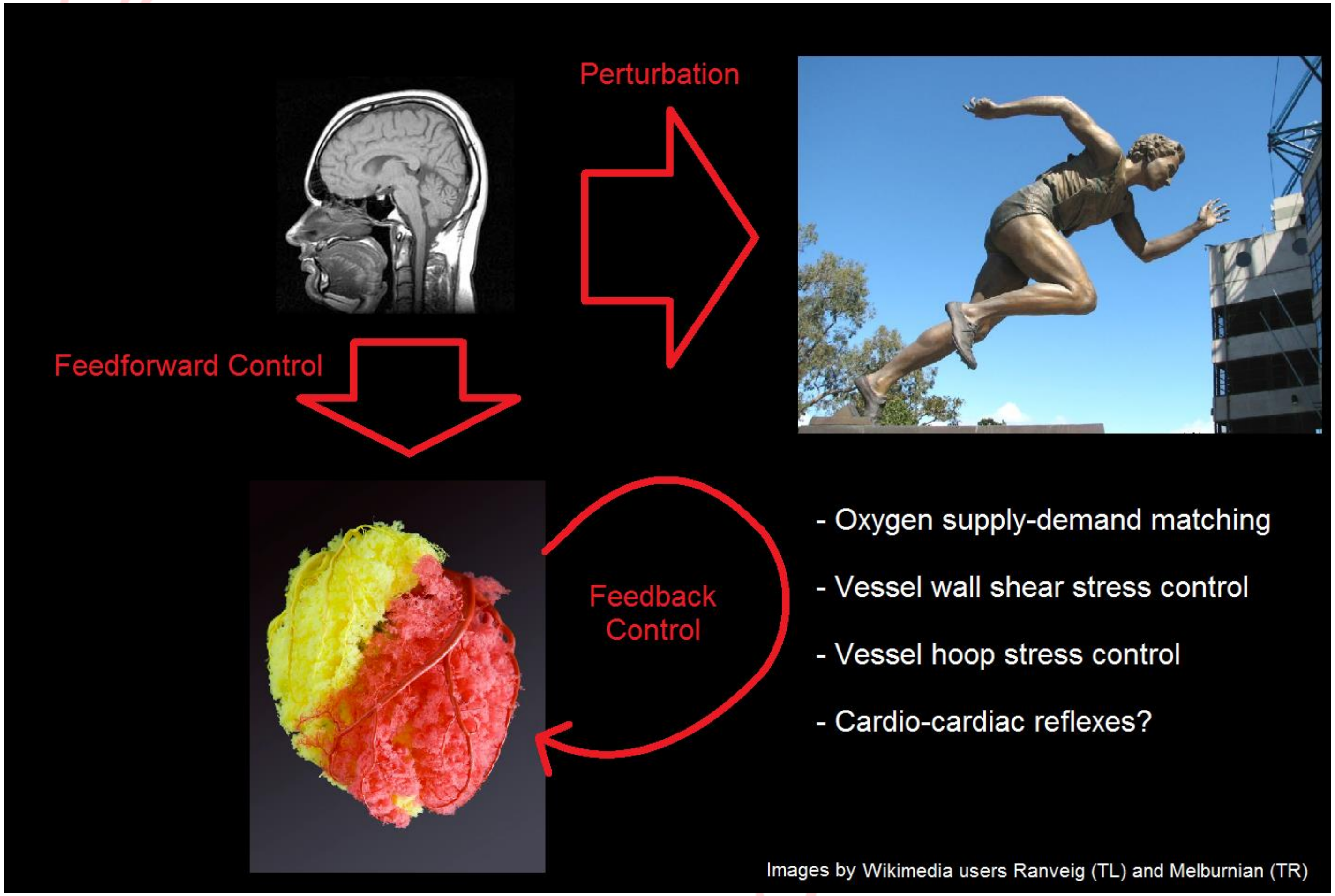
Coronary Flow Control Systems

Feedforward Control = **Parallel** Control

Images by Wikimedia users Ranveig (TL) and Melburnian (TR)

Coronary Flow Control Systems

Feedback control requires an error signal

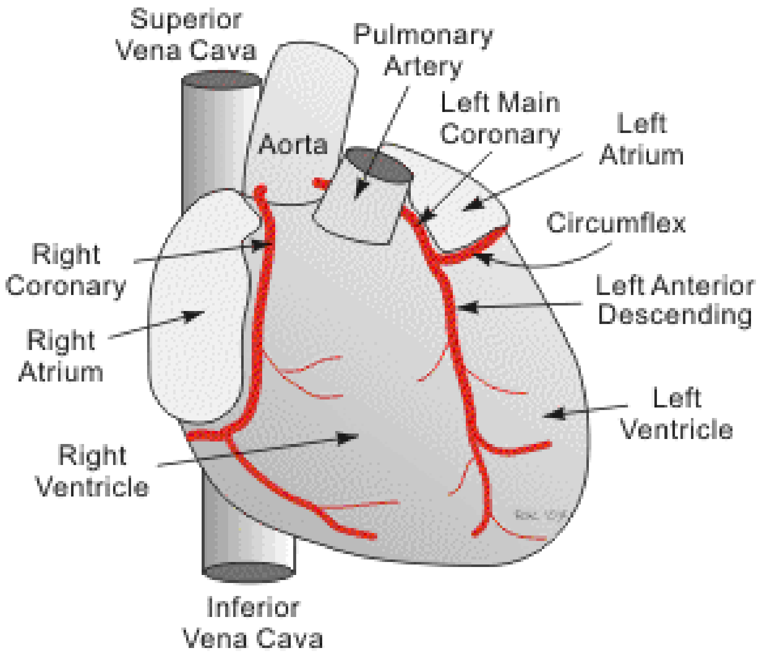


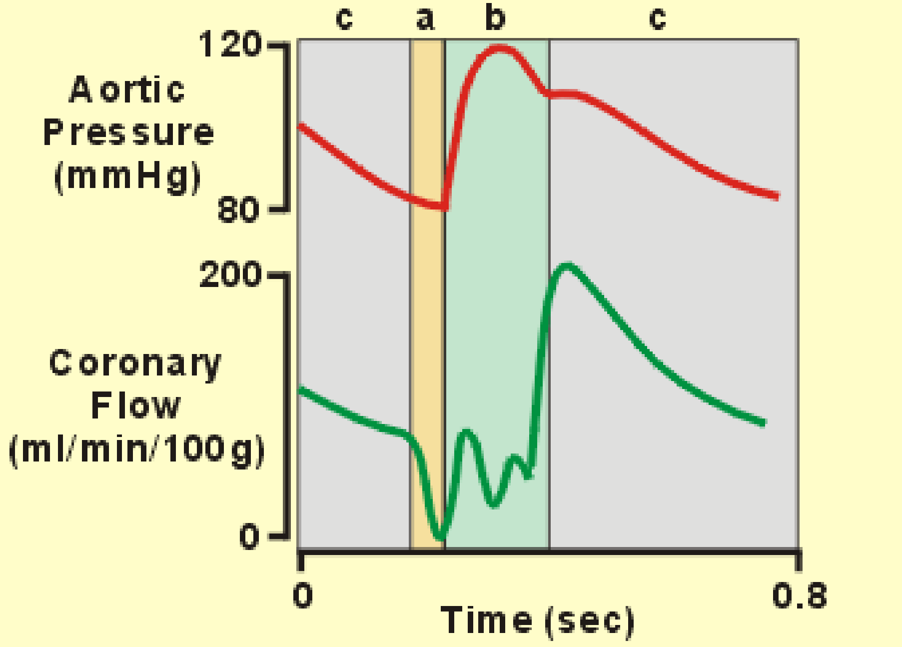
- Oxygen supply-demand matching
- Vessel wall shear stress control
- Vessel hoop stress control
- Cardio-cardiac reflexes?

Images by Wikimedia users Ranveig (TL) and Melburnian (TR)

What’s special about the coronary circulation?

- The flow occurs primarily in diastole to the contraction of the myocardium in systole!





Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c).

http://www.cvphysiology.com/

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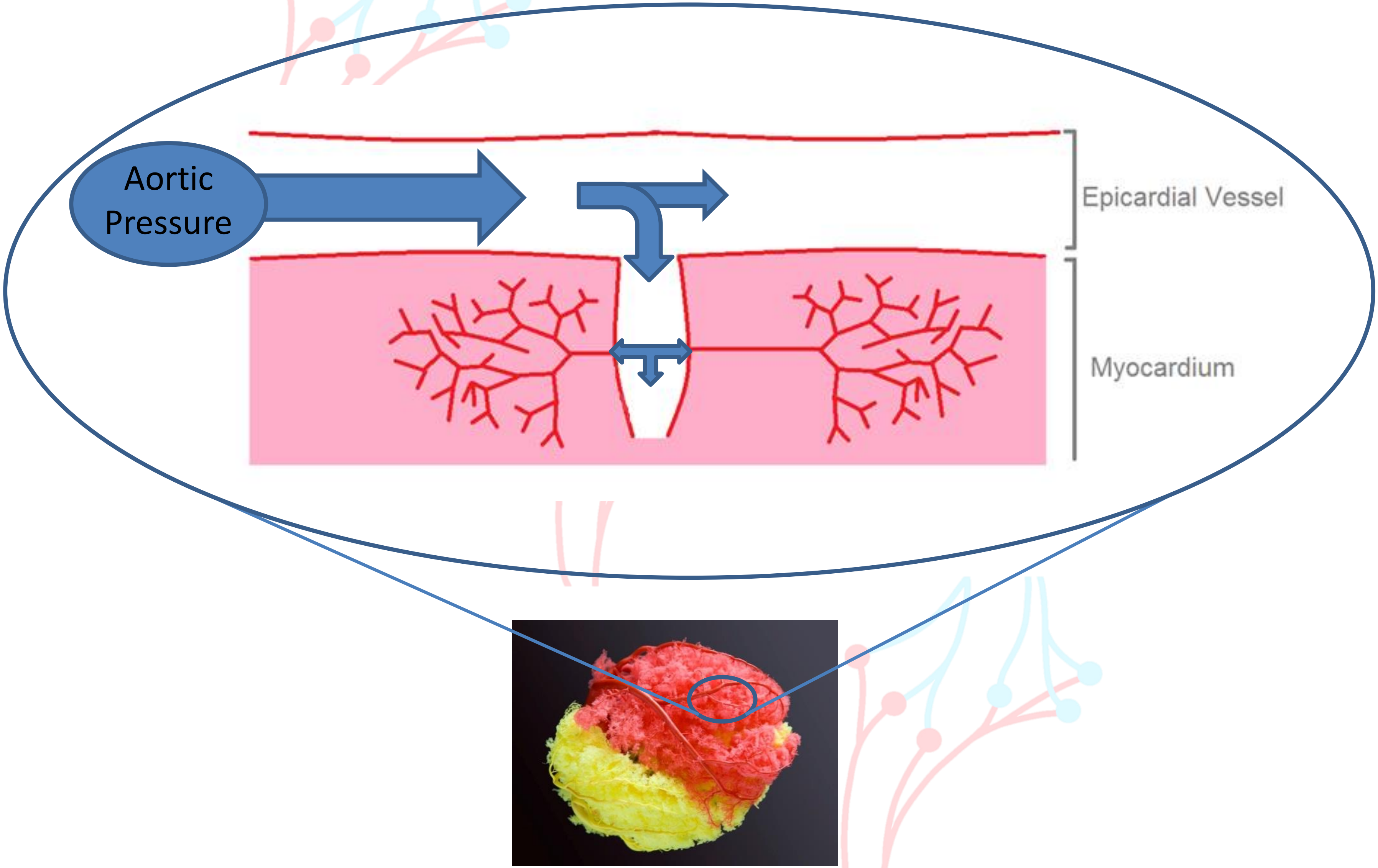
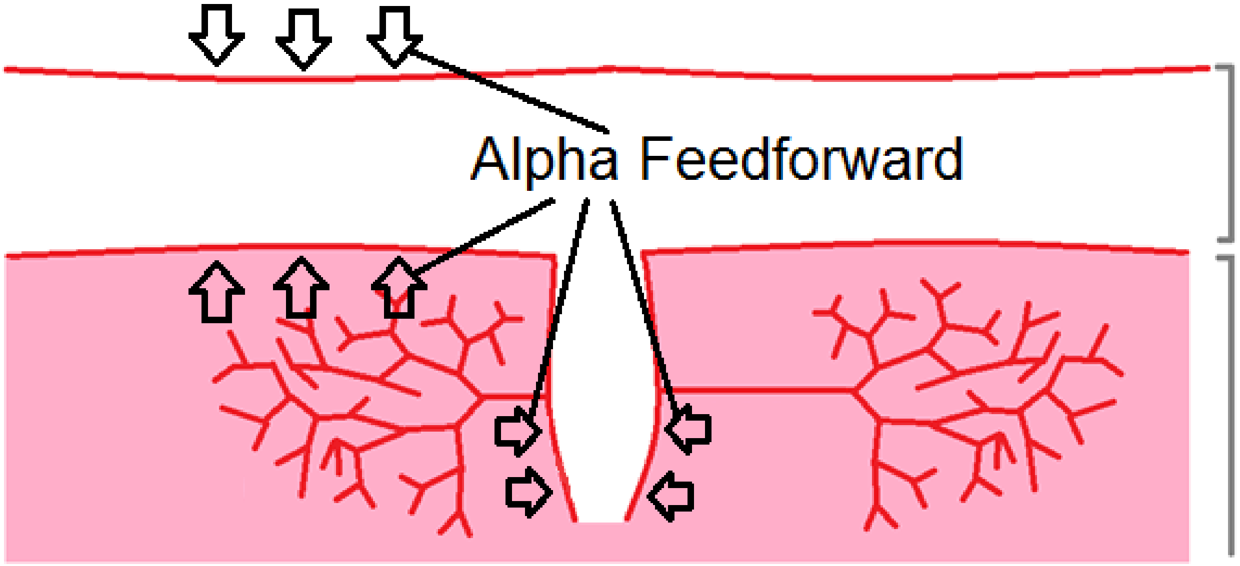
Modeling Coronary Flow Control



Feedforward Control: α-Vasoconstriction

Vessels of diameter > 100 µm

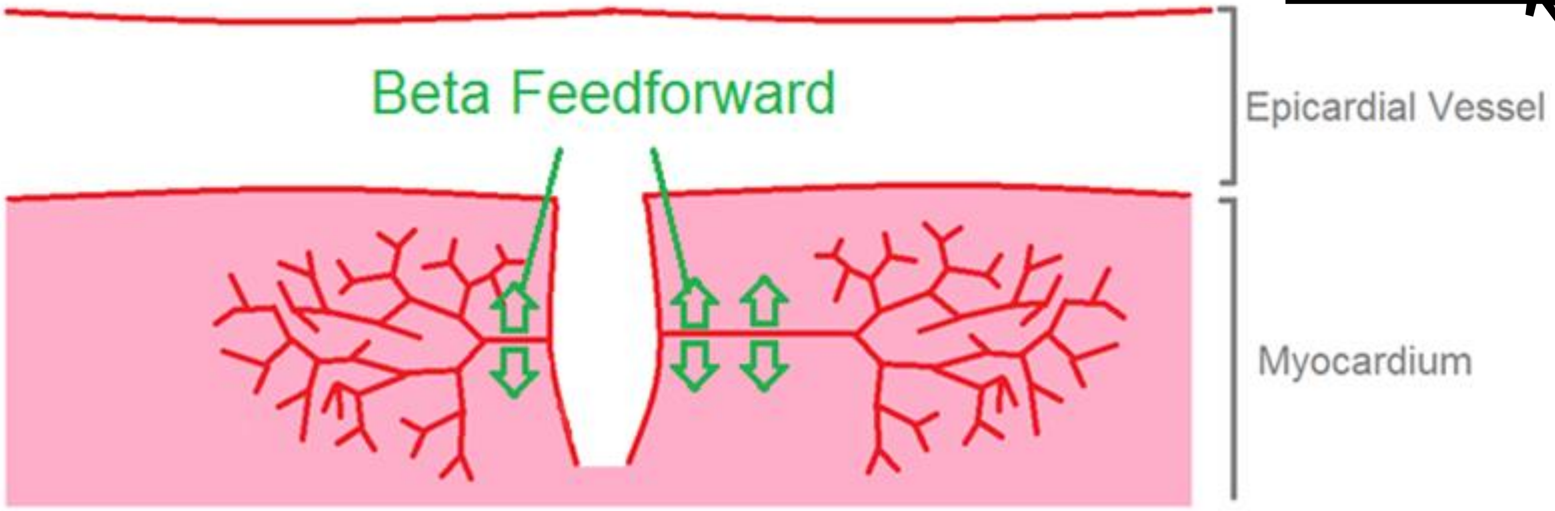


α-vasoconstriction has been described as “paradoxical”: it has been postulated that it acts to improve coronary perfusion by reducing retrograde systolic flow.

This mechanisms also affects vascular compliance reduction.

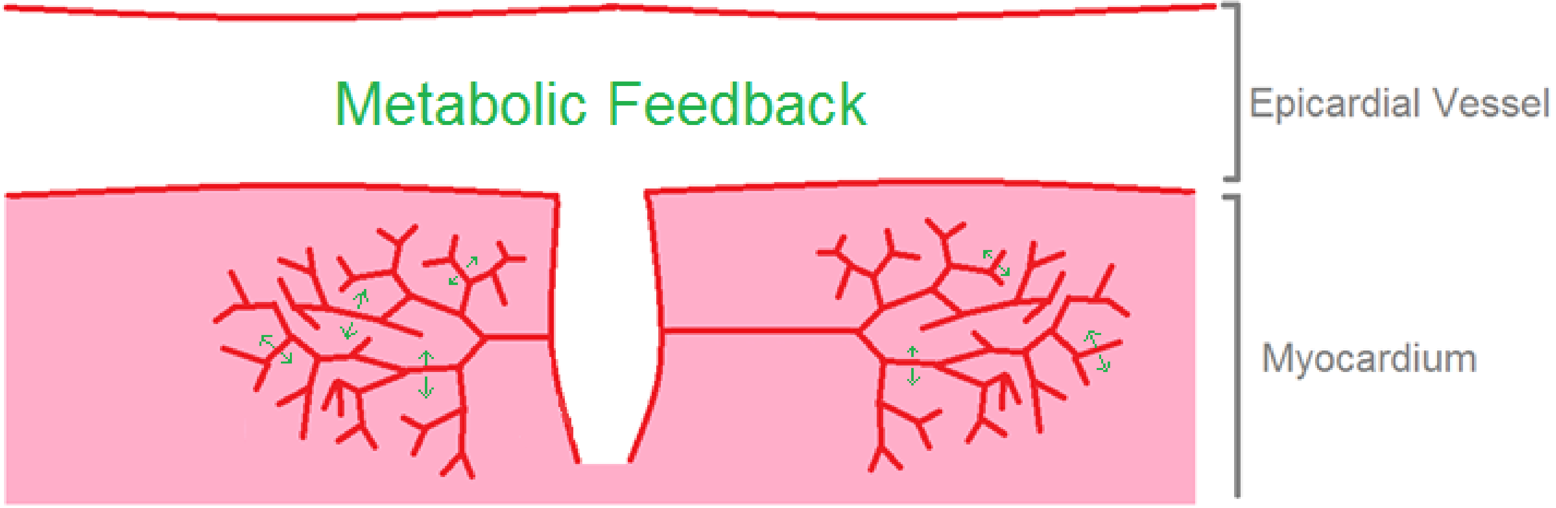
Feedforward Control: β-Vasodilation

Vessels of diameter < 100 μm



Feedback Control: Vasodilation

Vessels of diameter < 100 µm



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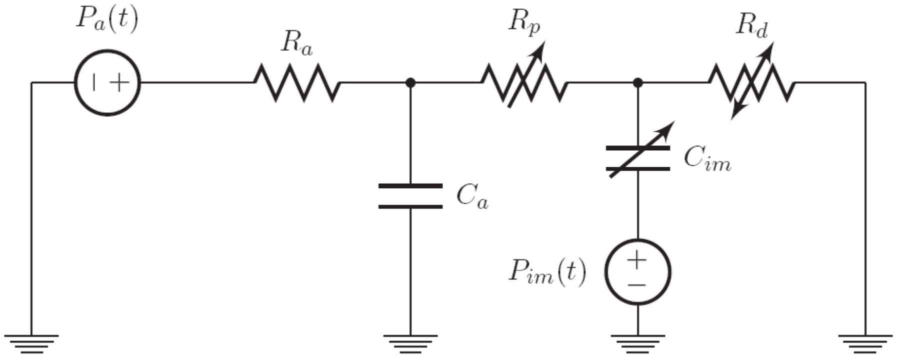
Coronary Vascular Model

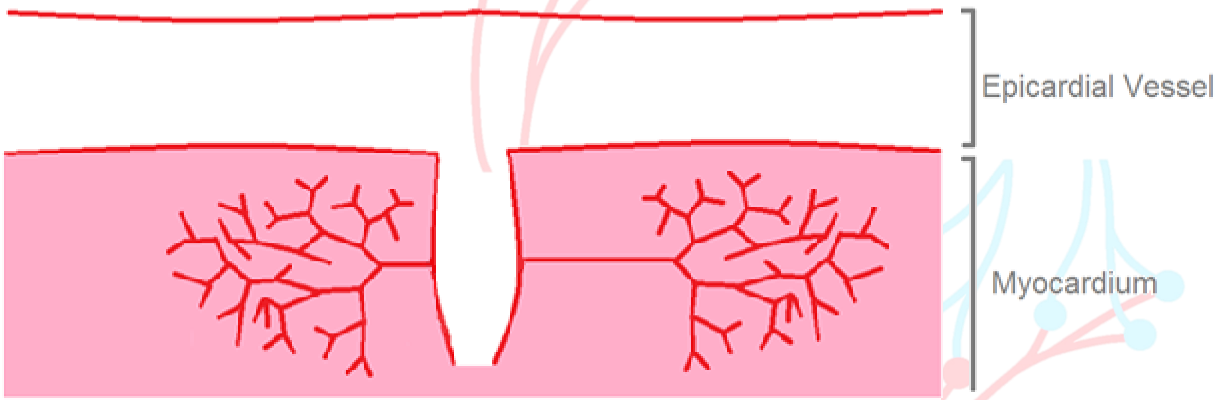


↗ - Feedforward

↙ - Feedback

⤢ - Both

Aortic Pressure



A Model of Coronary Microvasculature Resistance Control

- Key assumptions of the model:
  - Myocardial oxygen supply should closely match myocardial oxygen demand
  - Coronary flow control should primarily be via a **feedback** mechanism which evaluates and acts to counter discrepancies in oxygen demand
  - The control system should take into account the "historical" state of the system, such that repayments of any oxygen "debts" are possible
  - All changes in myocardial oxygen delivery are due to changes in flow: we assume that coronary venous blood oxygen content and myocardial oxygen extraction are constant

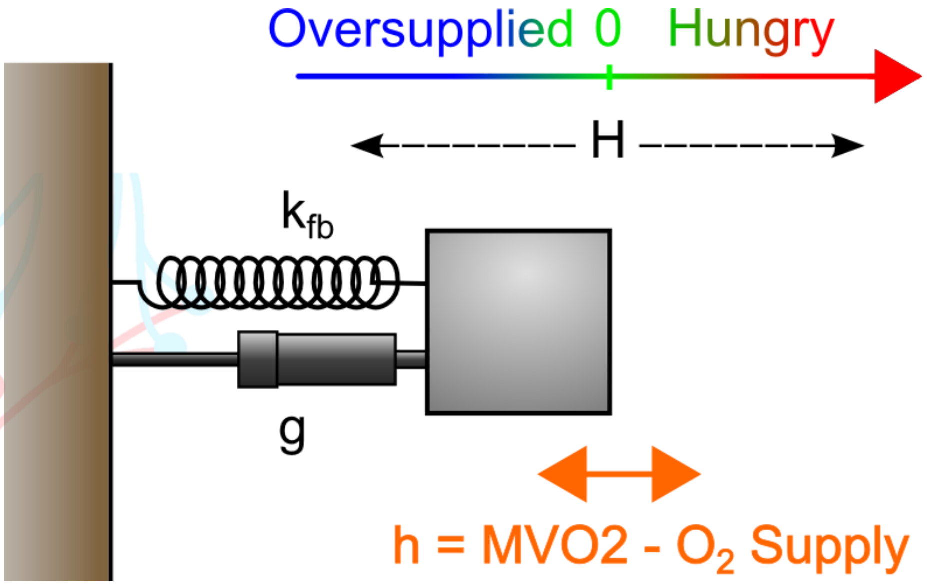
A Model of Coronary Microvasculature Resistance Control

Instantaneous O2 Demand - Supply Discrepancy:

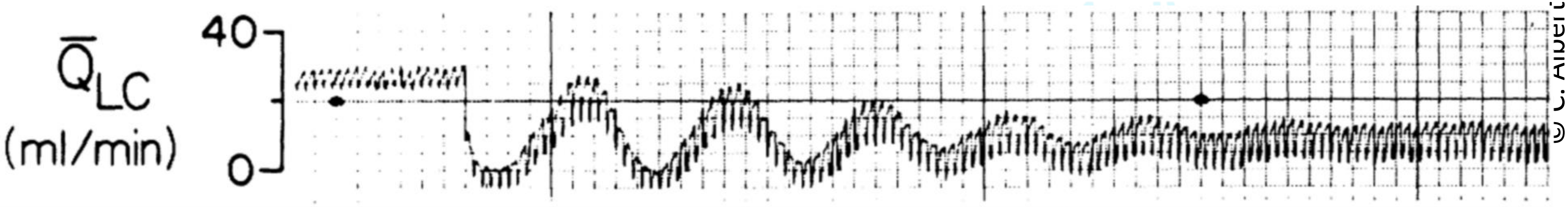
$$h(t) = MVO2(t) - \gamma Q(t)$$

Myocardial Hunger:

$$H(t) := \int_0^t h(\tau)d\tau,$$



Damped Harmonic Motion:



Canty and Klocke, *Circulation*, 1985.
Reduced Myocardial Perfusion in the Presence of Pharmacologic Vasodilator Reserve

A Model of Coronary Microvasculature Resistance Control

Combining the equations on the previous slide:

$$\frac{dQ(t)}{dt} = k_{fb}\gamma^{-1}H(t) + g\gamma^{-1}\frac{dH(t)}{dt} + \gamma^{-1}\frac{dMVO2(t)}{dt}$$

$$\text{define } S(t) = [R(t)]^{-1}$$

$$S(t)P(t) = Q(t)$$

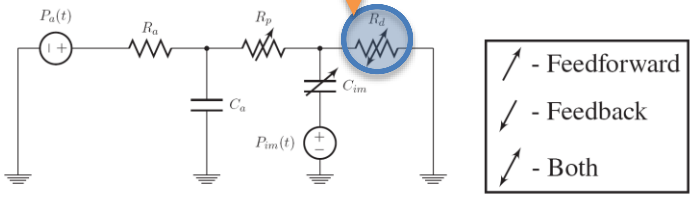
Differentiating this, and combining with the top-line equation:

$$\boxed{\boxed{\frac{dS(t)}{dt}\bar{P}} = \boxed{k_{fb}\gamma^{-1}H(t) + g\gamma^{-1}\frac{dH(t)}{dt}} + \boxed{\gamma^{-1}\frac{dMVO2(t)}{dt}}.}$$

to Figueroa – figueroc@med

A Model of Coronary Microvasculature Resistance Control

Arthurs, Lau, Asrress, Redwood & Figueroa, submitted to AJP - Heart and Circulatory Physiology



Time Derivative of 1/Coronary Resistance (distal)

Error Signal (Myocardial Hunger)

Arterial O_2 Content

Time Derivative of Myocardial O_2 Demand

$$\frac{dS(t)}{dt}\bar{P} = k_{fb}\gamma^{-1}H(t) + g\gamma^{-1}\frac{dH(t)}{dt} + \gamma^{-1}\frac{dMVO2(t)}{dt}.$$

Coronary Perfusion Pressure

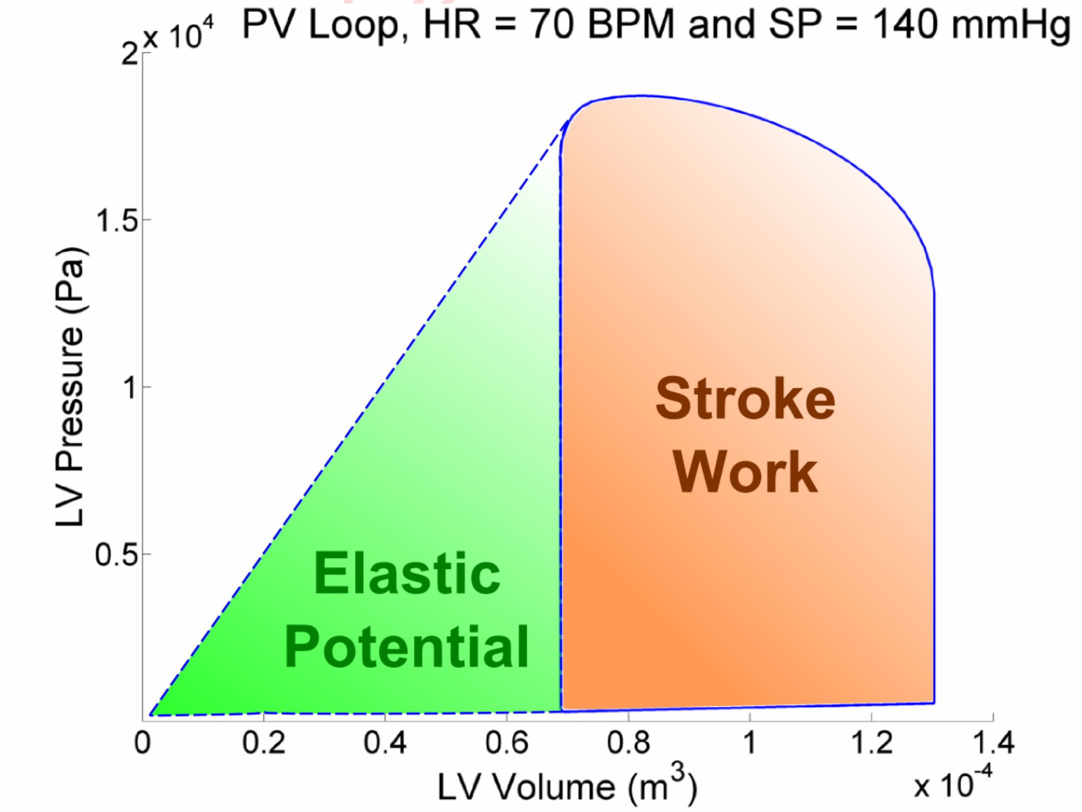
Damping Coefficient

Feedback Term

Beta Feedforward Term

Computing Myocardial Oxygen Demand, MVO2

- The amount of oxygen required by the myocardium should be related to the cardiac work



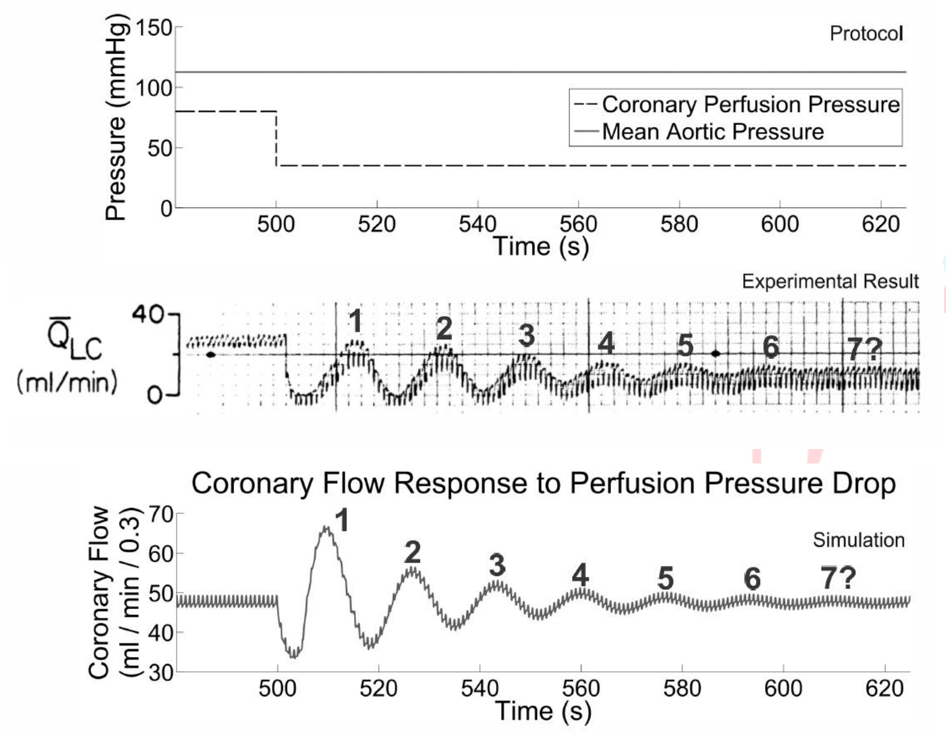
- Pressure Volume Area = EP + SW
- Total energy per beat = 3*PVA Joules [1]
- O$_2$ demand per beat
- = 3*PVA / 20 ml [2]

Kameyama et al., *Circulation*, 1992. Energy Conversion Efficiency in Human Left Ventricle
Coulson, *J Physiol,* 1976. Energetics of Isovolumic Contractions of the Isolated Rabbit Heart

Classic Examples of Coronary Auto-regulation

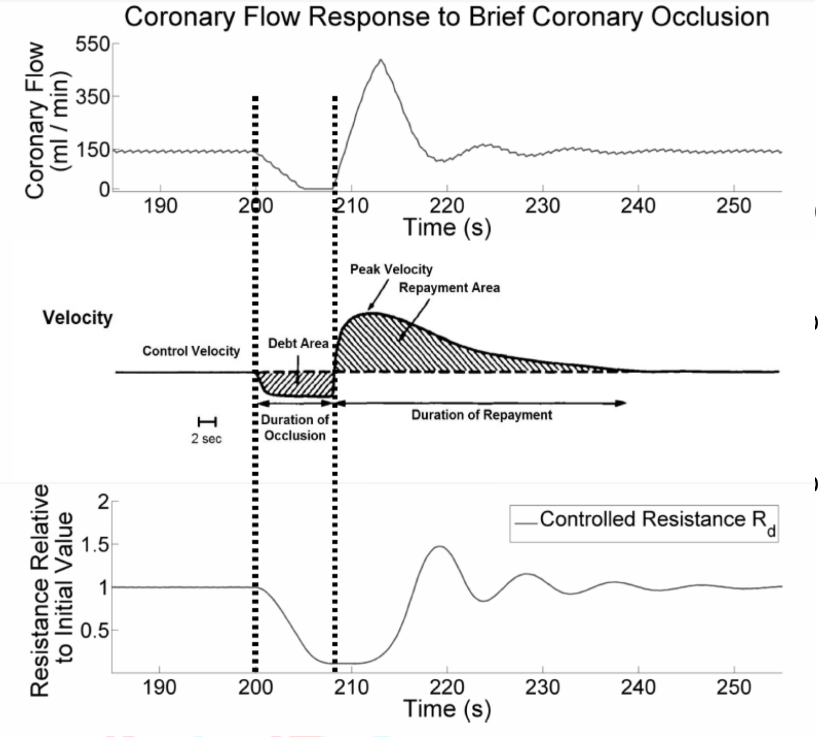
The model reproduces classic results in coronary physiology

Simulation of Perfusion Pressure Perturbation



Canty & Klocke, Circulation 1985

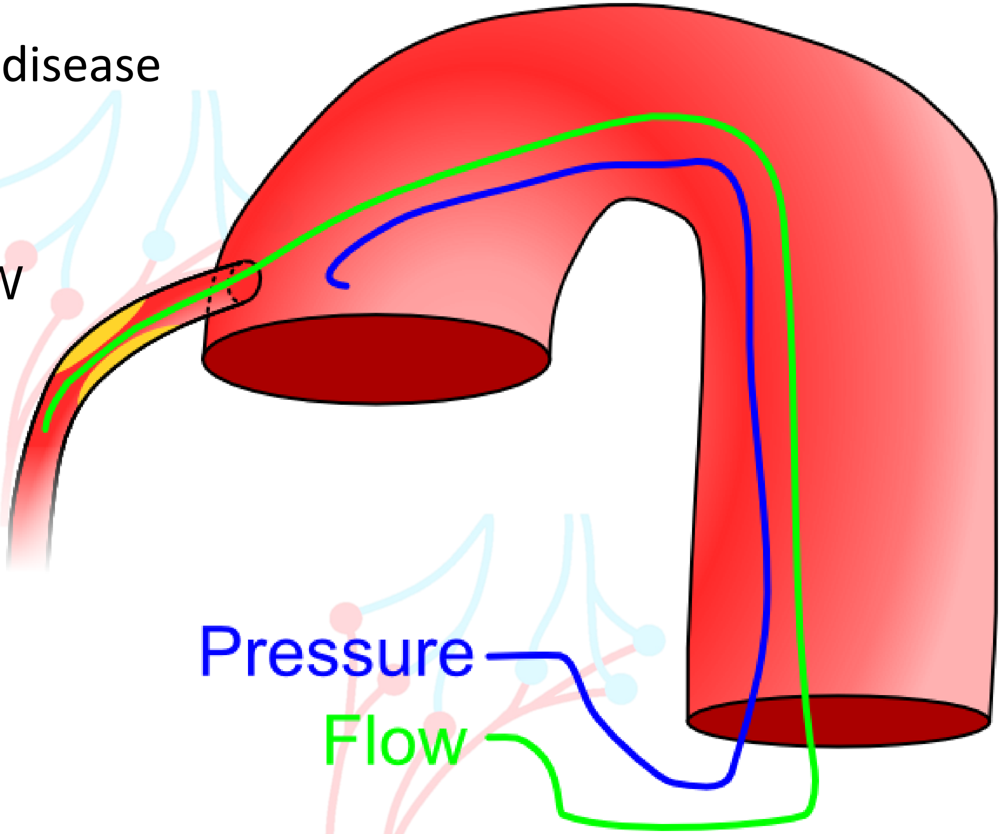
Simulation of Reactive Hyperemia



Marcus et al., Circ Research 1981

Patient Data - Acquisition

- Percutaneous coronary intervention patient
  (St Thomas' Hospital, London, UK)
  - Exertional angina
  - Documented coronary artery disease
    - Stenosis severity <80%
  - Exercise on a supine cycle
    - Intensity increments of 20 W
    - Recording:
      - Coronary Flow
      - Aortic Pressure
      - ECG



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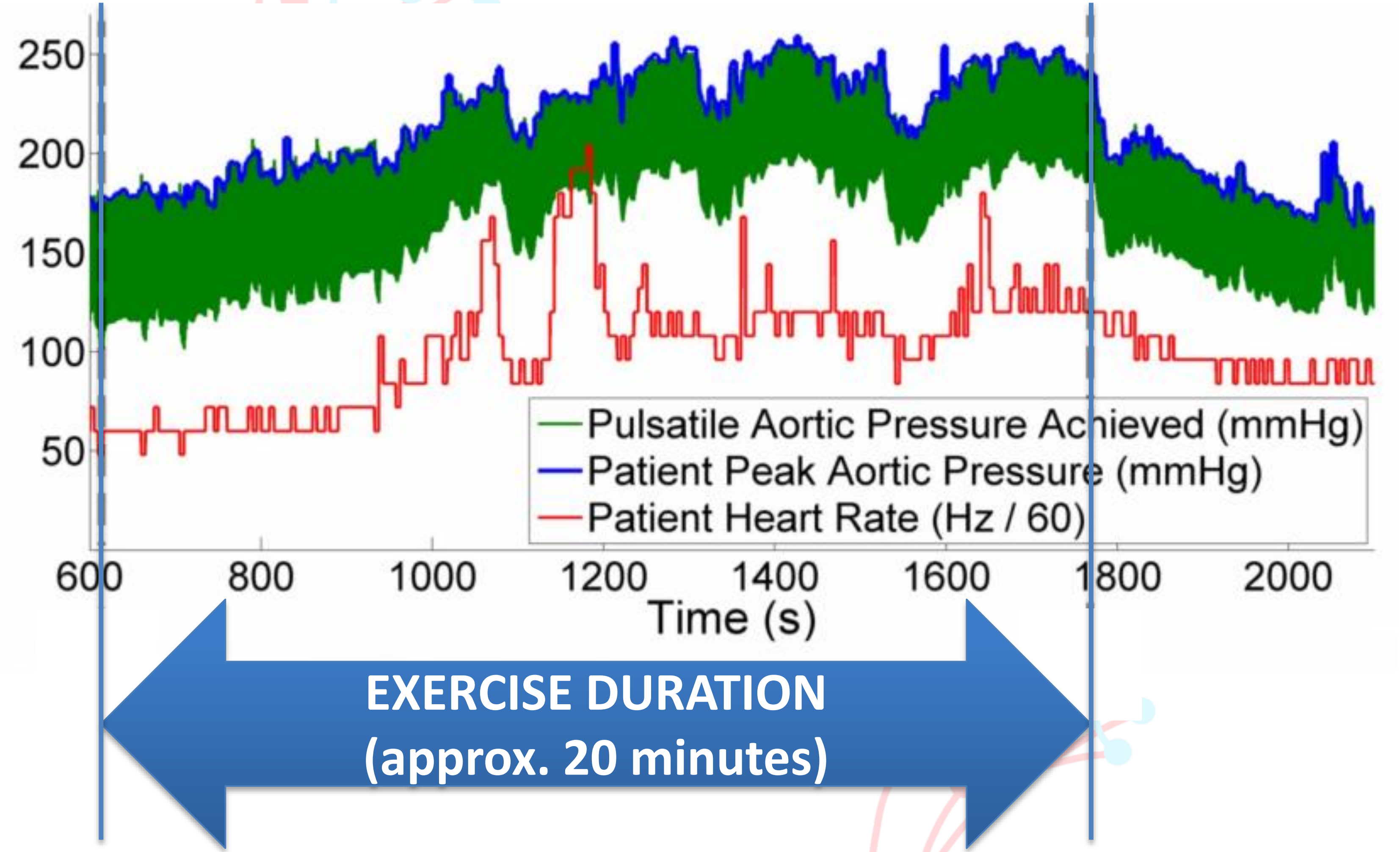
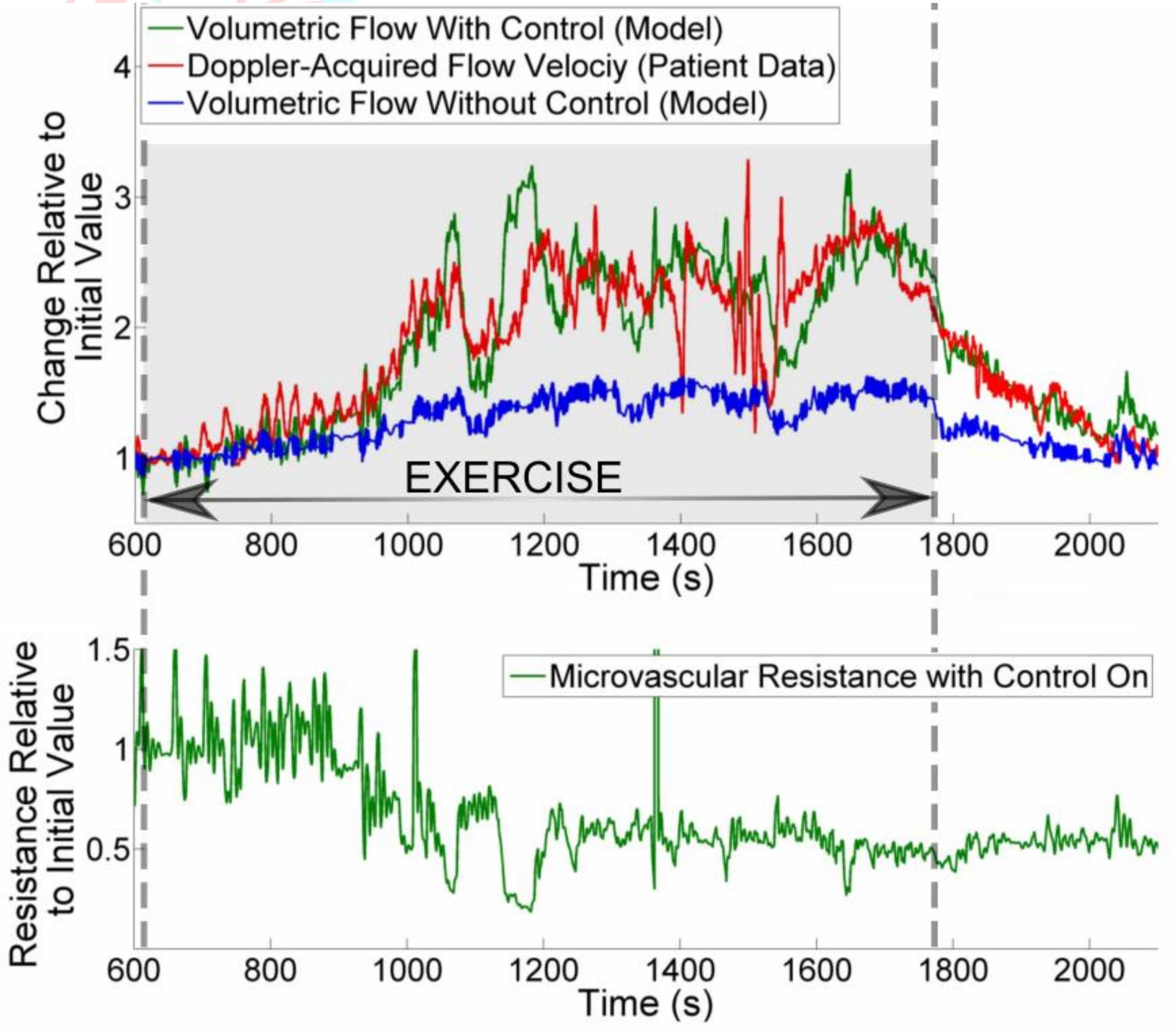
Patient Data



EXERCISE DURATION
(approx. 20 minutes)

Results: Coronary Auto-regulation via microvasculature control

The model reproduces human stress data acquired in the cath. lab



Arthurs, Lau, Asrress, Redwood & Figueroa, in preparation

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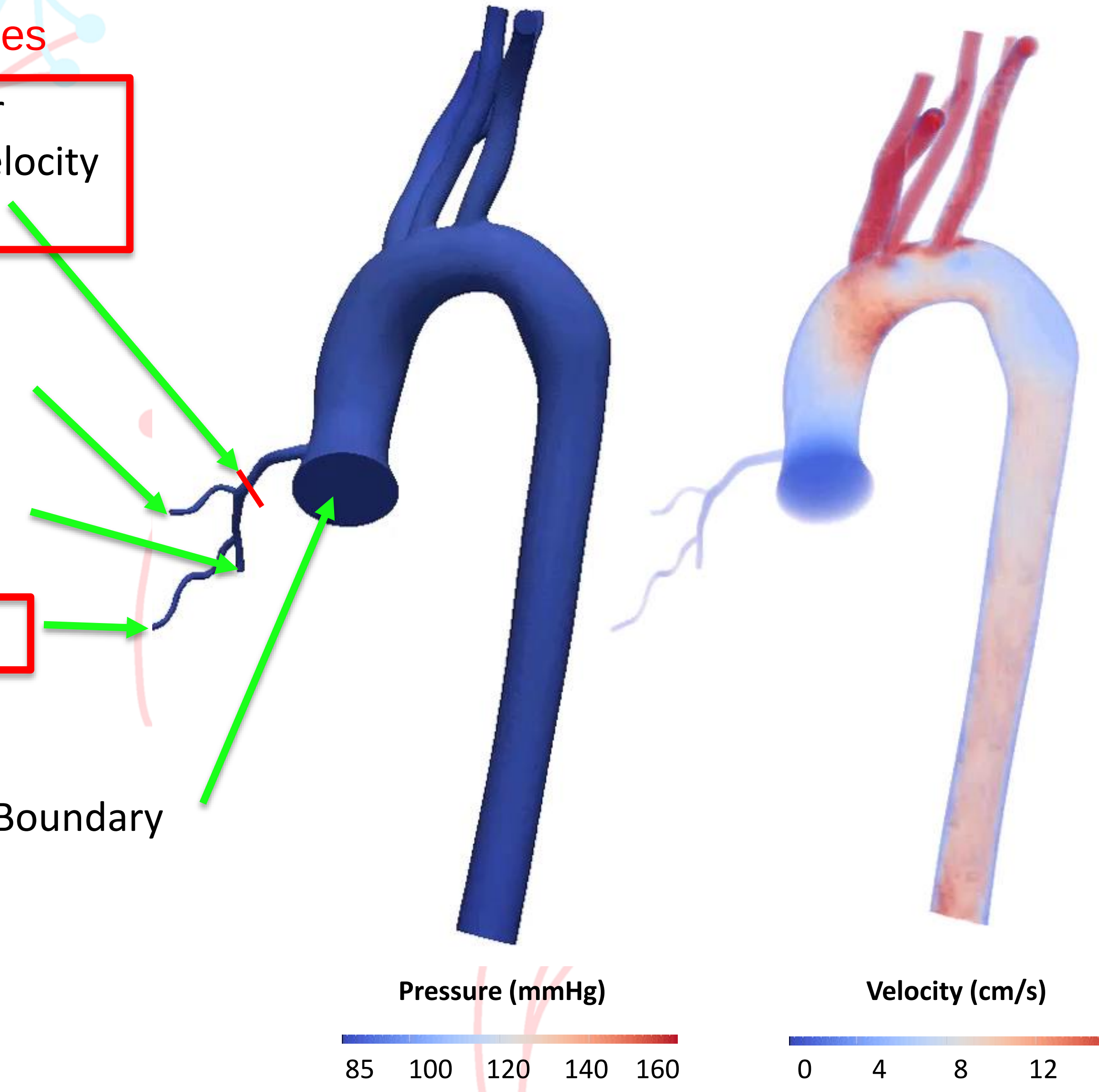
Results – 3D Simulations



Flow Velocities

Location For
Coronary Flow Velocity
Averaging

Coronary Boundary A

Coronary Boundary B

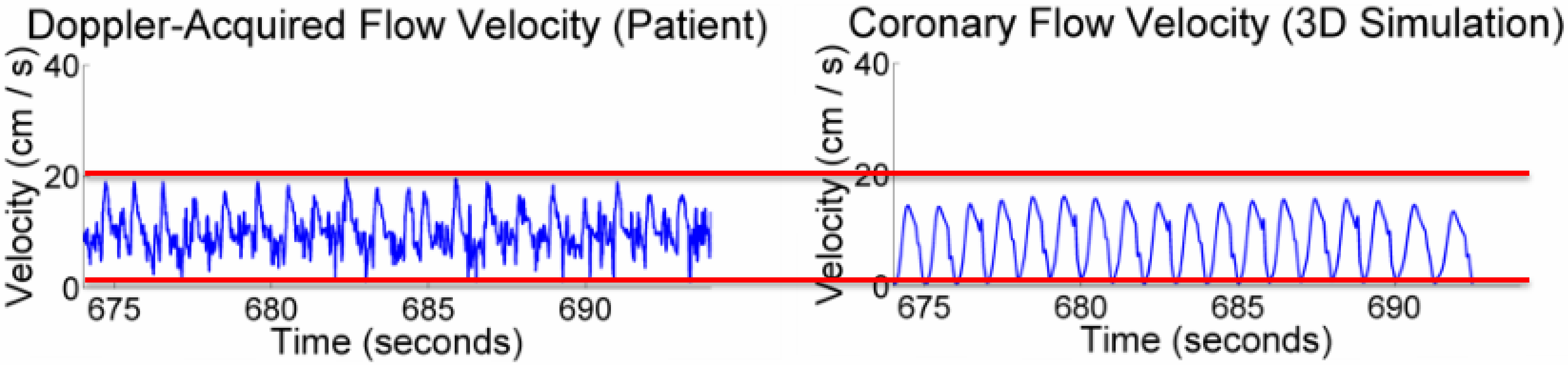
Coronary Boundary C

Volumetric Flow

Aortic Inlet Boundary

Results – 3D Simulations

Early Exercise



Late Exercise