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TDK THESIS

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Modelling the metabolic and myogenic control in human blood
circulation

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Notations

Notations, abbreviations

Notation	Name	(Value), Dimension
A	Cross section	m^2
C	Compliance	$\frac{\text{m}^3}{\text{Pa}}$
C_c	Plasma O_2 concentration	$\frac{\text{m}^3(O_2)}{\text{m}^3(plasma)}$
$C_{c,p}$	Plasma O_2 concentration in pulmonary capillaries	$\frac{\text{m}^3(O_2)}{\text{m}^3(plasma)}$
C_t	Tissue O_2 concentration	$\frac{\text{m}^3(O_2)}{\text{m}^3(tissue)}$
C_{RBC}	RBC conrentration in blood	$\frac{1}{\text{m}^3}$
E	Elastance	$\frac{\text{Pa}}{\text{m}^3}$
k_1	Parameter of a mathematical model	$1.200 \cdot 10^5 \frac{\text{kg}}{\text{s}^2\text{m}}$
k_2	Parameter of a mathematical model	$-4.793 \cdot 10^2 \frac{1}{\text{m}}$
k_3	Parameter of a mathematical model	$7.522 \cdot 10^4 \frac{\text{kg}}{\text{s}^2\text{m}}$
L	Inductance	$\frac{\text{Pa s}^2}{\text{m}^3}$
O_2	Oxygen molecule	-
p	Pressure	Pa
PWV	Pulse wave velocity	$\frac{\text{m}}{\text{s}}$
$P_{O_2,p}$	Partial pressure of O_2 dissolved in plasma	Pa
$P_{O_2,t}$	Partial pressure of O_2 dissolved in tissue	Pa
q	Volumetric flowrate	$\frac{\text{m}^3}{\text{s}}$
R	Resistance	$\frac{\text{Pa s}}{\text{m}^3}$
t	Time	s
v	Velocity	$\frac{\text{m}}{\text{s}}$
x	Axial coordinate	m
ATP	Adenosine triphosphate	-
CBF	Cerebral blood flow	$\frac{\text{m}^3}{\text{s}}$
HB	Haemoglobin	-
HB_{O_2}	Haemoglobin O_2 saturation	1
MAP	Mean arterial pressure	Pa
RBC	Red blood cell	-
ν	Kinematic viscosity	$\frac{\text{m}^2}{\text{s}}$
ρ	Density	$\frac{\text{kg}}{\text{m}^3}$
σ	Mechanical tension	Pa

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1 Introduction

1.1 Objectives

The study of biological processes through mathematical modeling could become a cornerstone in understanding complex physiological phenomena in the future. Hemodynamics, the dynamics of blood flow, is a fundamental aspect of cardiovascular physiology, directly influencing the delivery of nutrients and oxygen to tissues. Autoregulation is responsible for maintaining constant blood flow to organs and tissues despite changes in conditions such as blood pressure [6]. This thesis aims to introduce and explore mathematical models that accurately represent processes in connection with autoregulation within the context of low-dimensional hemodynamic simulations. These include the myogenic and metabolic responses.

The myogenic response involves the contraction of arterioles in response to increased intravascular pressure, serving as a key component of autoregulation to maintain consistent blood flow [7]. Similarly, metabolic responses adjust vascular tone based on the metabolic needs of tissues [6]. Traditional three dimensional models, while detailed, are often computationally intensive and impractical for extensive simulations. Thus, this research focuses on developing or modifying low-dimensional hemodynamic models that are computationally efficient yet sufficiently precise to capture the essential features of myogenic and metabolic responses and their effect on blood flow dynamics.

The main focuses of this thesis are threefold: first, to develop or refine mathematical models that accurately describe myogenic and metabolic responses under varying hemodynamic conditions; second, to implement these models within a solver tailored for low-dimensional simulations; and third, to analyze and discuss the results obtained from these simulations, providing insights whether the models can provide appropriate and precise results when compared to reality.

One of the potential applications of an accurate low-dimensional simulation is using its results as boundary conditions for higher-dimensional simulations, especially when precise direct measurements are difficult or clinical data is unavailable. An example can be the carotid artery, one of the main vessels supplying oxygenated blood to the head, making it a high-priority area of study. Prescribing appropriate boundary conditions is crucial, since it can effect the simulation results [8].

The relevance of this work extends beyond theoretical interest, potentially offering practical implications for medical research and clinical applications in the future. Enhanced understanding and simulation of these processes could lead to improved diagnostic tools, better therapeutic strategies, and more effective interventions for conditions related to vascular dysfunction and cardiovascular diseases. Furthermore, the low-dimensional approach promises access to complex simulations, allowing a broad range of researchers to engage with and benefit from advanced modeling techniques.

In summary, this thesis could not only contribute to the theoretical framework of biological modeling but also reduce the gap between haemodynamic simulations and blood flow in humans. By focusing on the integration of myogenic and metabolic models within low-dimensional hemodynamic simulations, this research could help us better understand these phenomena.

1.2 Overview

The content of the documentation essentially describes the work done regarding the simulation of myogenic and metabolic blood flow regulation. This includes a description of the biological process using literature research, the formulation of the mathematical models based on this research, its integration into the simulation, and finally, the evaluation of the results. Structure of the thesis:

- A brief literature review on autoregulation, the myogenic and metabolic mechanisms.
- Heavy modification of a myogenic response mathematical model already existing in the literature [9] [10].
- Presenting the virtual 1D transport model.
- Further development of the mathematical model of the O_2 transport to tissues and organs found in the literature [11].
- Modelling O_2 uptake in the pulmonary circulation.
- Formulation of the mathematical model of the metabolic mechanism.
- Results and discussion.
- Summary.

2 Literature review

2.1 General informations regarding first_blood and the arterial model

There are numerous ways to simulate the blood flow in the human vascular system. Three-dimensional simulations can be superior to others when studying local diseases of the arterial system, such as stenosis and aneurysms. In this case, the computational field is a three-dimensional geometry. Low-dimensional simulations have the advantage of being computationally less demanding, making it possible to simulate blood flow in almost the entire arterial system simultaneously. The latter approach considers each large vessel as an axisymmetric tube, which builds up a vascular tree.

Lumped zero dimensional models are usually applied as boundary conditions substituting the smaller arteries, veins and the organs. There are a few solvers documented in the literature using different numerical methods, coded in different environments such as MATLAB, Python or C++. An open source one- and zero-dimensional, modular hemodynamic solver called first_blood was developed by the Department of Hydrodynamic Sytems [1] [12]. The tasks documented in this thesis were performed with respect to first_blood.

Two governing equations of fluid dynamics, the equation of motion 2.2 and the continuity equation 2.1 are solved numerically for the vessels modelled in 1D. Since the vessel walls are not rigid, a third independent equation is required to establish the relationship between the time-dependent cross-section of the vessels and the transmural pressure. The vessels are not elastic but viscoelastic in reality. The viscous effect is small, by neglecting it the relationship can be written as 2.3. The Young's modulus E and wall thickness h would be hard to measure precisely, the applied material model gives an empirical exponential formula where only the radius r of the vessel is needed. The k_1 , k_2 and k_3 constants are obtained by curve fitting [13].

$$\frac{\partial A}{\partial t} + \frac{\partial (Av)}{\partial x} = 0 \quad (2.1)$$

$$\frac{\partial v}{\partial t} + v \frac{\partial v}{\partial x} + \frac{1}{\rho} \frac{\partial p}{\partial x} + \frac{8\pi\nu}{A} v = 0 \quad (2.2)$$

$$p(x, t) - p_0 = \frac{4Eh}{3r_0(x)} \left(1 - \frac{r_0(x)}{r(x, t)} \right) = \frac{4}{3} (k_1 e^{k_2 r_0} + k_3) \left(1 - \frac{r_0(x)}{r(x, t)} \right) \quad (2.3)$$

The system of partial differential equations is solved numerically using the MacCormack scheme and the method of characteristics. The MacCormack scheme is used for the inner grid points, while the method of characteristics is applied to the boundary conditions. The mathematical model has been recently updated and I had the pleasure of participating in

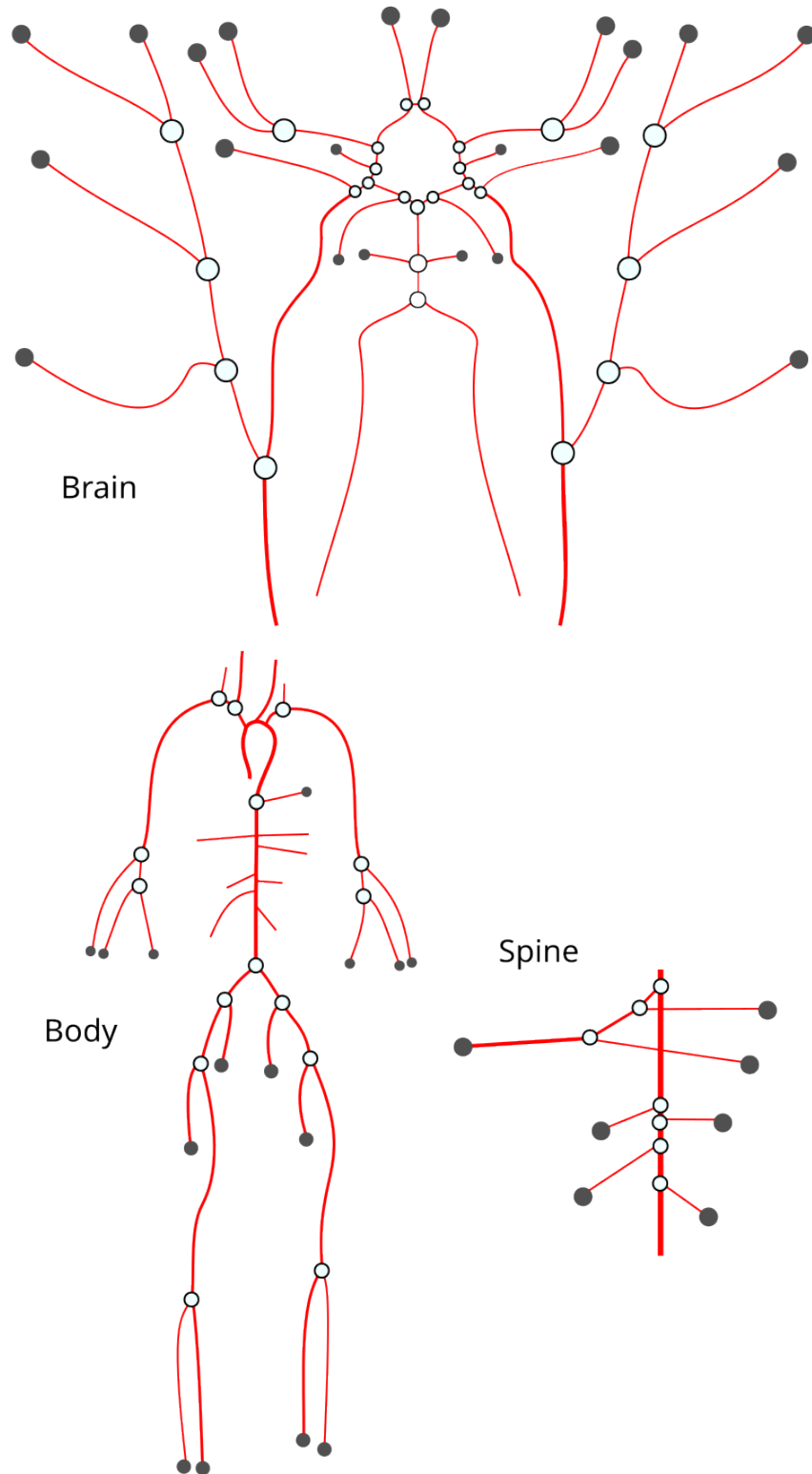


Figure 2.1: Arteries modelled in 1D. The detailed intracranial arteries with the circle of Willis are also included in the model [1].

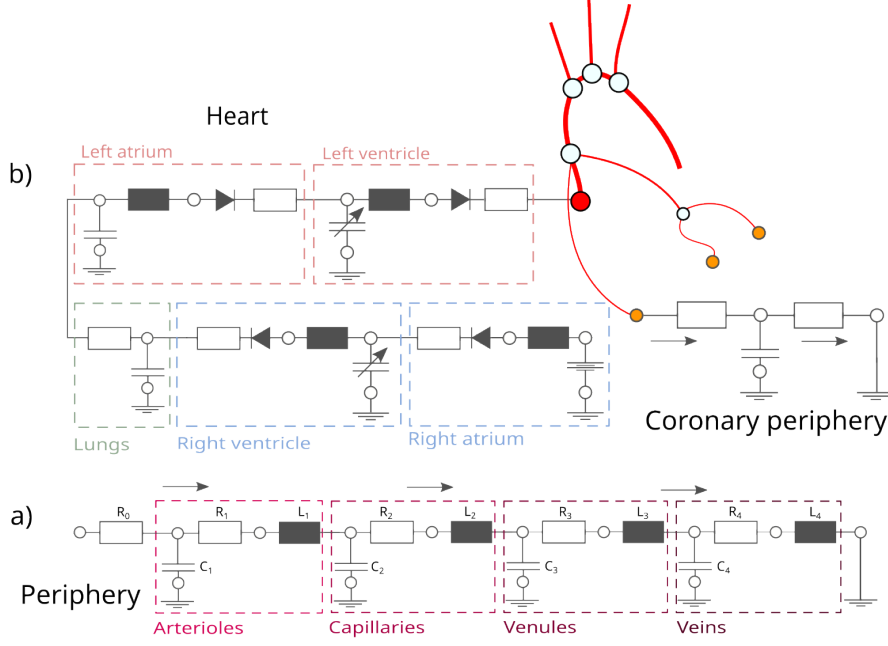


Figure 2.2: a) Lumped peripheral models of the smaller vessels and the veins. b) 0D model of the heart, the coronary arteries and the pulmonary circulation [1].

the process [14]. By running the simulation for any given 0 and 1D model, physiologically relevant velocity, PWV, pressure and volumetric flowrate values can be determined.

The vascular model used for this work is introduced here briefly. The arterial vessels modelled in 1D are the larger arteries and the cerebral arterial tree, 103 segments together 2.1. The detailed intracranial arteries are included in the model with the circle of Willis. Since the brain is one of the most important organs in the body, it is tightly connected to autoregulation, modelling it in detail is highly advantageous in terms of the current work.

Besides the one dimensional parts there are also zero dimensional models built with elements such as resistors, inductances, capacitors, diodes and elastances. Zero dimensional means that there is no space coordinate in the model. The smaller vessels (arterioles, capillaries and venules) and veins are modelled using lumped models, each compartment is taken into account with an RLC circuit at each periphery [15]. The heart and pulmonary circulation have a unique lumped model 2.2. For 0D simulations the volumetric flow rate and pressure values are determined by the solver in every time step for each edge element (resistors, inductances, compliances, etc...).

The model consists of numerous parameters, the measurable geometrical parameters of the model (for example lumen diameter and segment length) are based on [16]. The parameters that can not be measured (such as the parameters of the lumped model) are tuned to achieve realistic physiological values for a healthy patient.

2.2 Autoregulation

The purpose of autoregulation is to maintain consistent blood flow to tissues and organs, particularly vital ones like the brain to ensure adequate O_2 supply. Human cells need O_2 to produce ATP, which can be used or stored as energy.

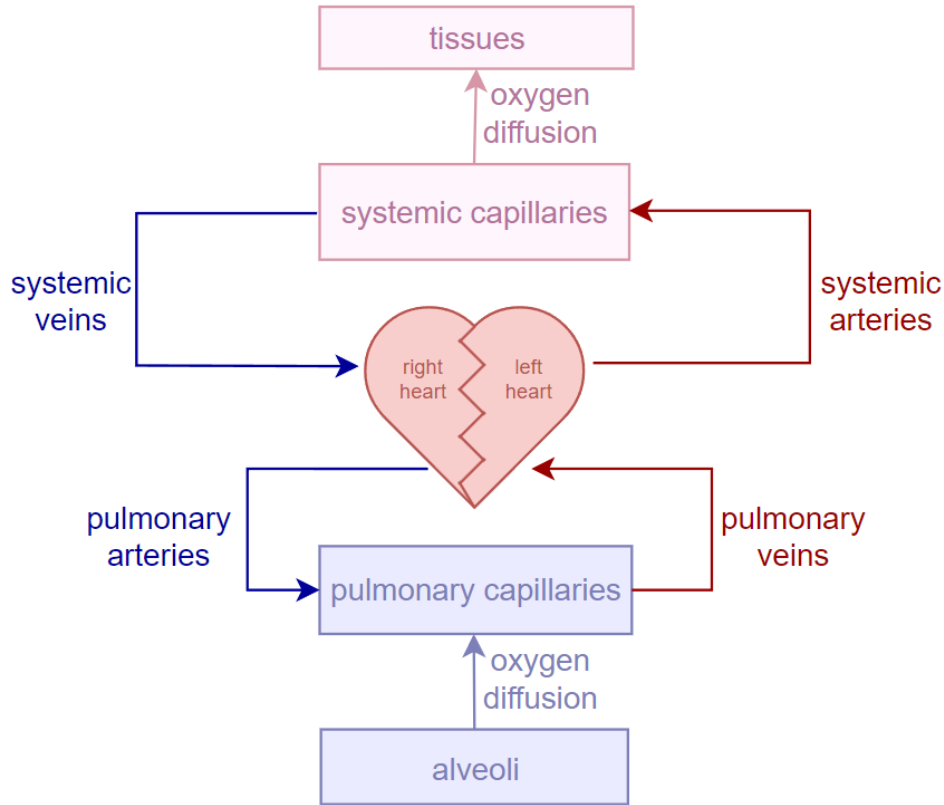


Figure 2.3: Cycle of blood flow carrying oxygen. Dark red arrows indicate oxygenated blood, while dark blue arrows indicate deoxygenated blood.

Inhaled O_2 diffuses from the alveoli into the pulmonary capillaries. The oxygenated blood from the lungs flows through the pulmonary veins, the left heart and systemic arteries before O_2 diffuses from the blood plasma into tissues via systemic capillaries. The deoxygenated blood is then carried by the systemic veins to the right heart and then by the pulmonary arteries to the lungs. Essentially, several advection-driven processes transport blood to and from two diffusion-driven processes. The heart maintains blood flow by providing energy to the system [17]. This cycle is presented in 2.3.

In suboptimal conditions (e.g., low blood pressure or low tissue O_2 levels), the system attempts to correct this through regulation mechanisms that control the amount of blood flowing through the capillaries. Local regulation consists of two main phenomena: myogenic and metabolic mechanisms that operate independently. The former responds to changes in blood pressure, while the latter responds to changes in O_2 levels [6]. This work aims to capture the known and accepted characteristics of these processes.

When considering autoregulation, the brain often comes to mind first, as it is one of the most vital organs in the body. The blood supply to the intracranial system is therefore a high priority, with a numerical value around $50 - 60 \left[\frac{ml}{min100g} \right]$, around 20% of the cardiac output when the body is at rest [2]. Cerebral autoregulation can be seen as the body's attempt to maintain this value under various conditions. The cerebral pre-capillary arterioles can dilate or contract in response to changes in pressure to achieve this, changing the vascular resistance and the blood flow. Physicians often use the MAP-CBF diagram to represent this phenomenon.

According to the original theoretical cerebral autoregulation curve, for a MAP value between 60 and 150 $[mmHg]$ (the lower and upper limit of autoregulation), cerebral blood flow remains almost constant. This theory was described by Lassen in 1959. The classic autoregulation curve was rejected because some of the observed patients were given vasoactive drugs, and some had vascular diseases.

The updated autoregulation curve has a similar shape, but its width is different. Recent studies suggest that the plateau is much narrower, around $5 - 10 [mmHg]$. It is also unclear whether the autoregulation curve is symmetric, as the brain might respond better to an increase in MAP than to a decrease. Obtaining the real curve is challenging, as measuring CBF has its own difficulties. Two common methods, Doppler ultrasound and magnetic resonance imaging, both have considerable measurement uncertainties [2], [18]. Consequently, the literature lacks a well-accepted cerebral autoregulation curve, complicating the validation of simulations. For this reason, it is advisable to emphasise examining fundamental and clearly expected phenomena when evaluating the results. 2.4 shows an autoregulation curve found in the literature.

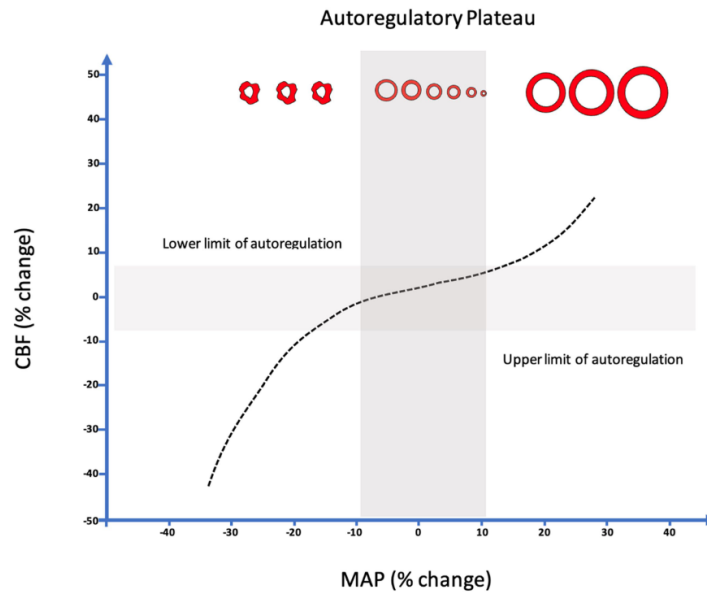


Figure 2.4: Current, updated autoregulation curve[2]. The diameter changes of arterioles can be observed, as altering vascular resistance is a way to control blood flow.

2.3 The myogenic response and myogenic tone

Arteries are responsible for delivering oxygenated blood to organs and tissues. These vessels vary in diameter and length, with each type serving a different purpose. Smaller arterial vessels include arterioles, terminal arterioles, and capillaries, with diameters of 20-200 μm , 8-20 μm , and 4-7 μm , respectively. Larger arteries have relatively low vascular resistance, contributing about 10% to the total vascular resistance, while small arteries and arterioles contribute 50-55%, capillaries 30-35%, and the rest comes from venules and veins [4].

The myogenic response is observed in arterioles that supply blood to the brain and heart, among other organs. It works as follows: when blood pressure increases, the vessel wall initially expands. If the pressure remains constant, the vessel then contracts, often to a diameter smaller than its original size [7]. This contraction increases blood flow velocity and decreases pressure.

The vascular resistance of vessels depends heavily on their diameter ($R \sim \frac{1}{d^4}$), so by adjusting the diameter based on pressure, the body can regulate blood flow distribution to tissues and capillary pressure. Increased and maintained pressure in resistance arteries and arterioles causes these vessels to contract, a phenomenon known as the myogenic response. The steady-state response of these vessels is called myogenic tone. These mechanisms contribute to the autoregulation of blood flow in the brain, heart, skeletal muscles, and other organs [7].

Despite their importance, not all aspects of these biological functions are fully understood due to their complexity. Processes involving G-protein coupled receptors and ion channels, among others, play a role in the development of myogenic tone and response. The mathematical model presented later does not encompass the entire process but focuses on establishing a direct relationship between pressure and peripheral resistance based on documented observations by physicians [7].

A model for myogenic autoregulation already exists in the literature [9]. This model assumes that myogenic autoregulation is driven by changes in blood flow and establishes a sigmoidal relationship between flow rate and peripheral capacitances. The peripheral resistances are also time-dependent, calculated based on the updated capacitances. However, this model has some inaccuracies. As previously mentioned, the myogenic response is primarily pressure-induced, and its main mechanism is to regulate pressure and flow by altering vascular resistances. Additionally, the article does not explain how the central slope and saturation values of the sigmoid curve are determined, or whether they are based on any measurement data. The original model presented in [10] has similar limitations.

The current work on modeling the myogenic response is only partially based on these cited models. The aspects adopted include two things, describing the independent variable of the sigmoid curve with a first-order low-pass filter and assuming that the body's

response to changes is bounded by a sigmoidal curve.

2.4 The metabolic response

Cells use ATP as a source of energy. ATP is typically produced through either oxidative phosphorylation or glycolysis, with the body preferring the former, which requires O_2 . For that reason the body is in continuous need for O_2 . O_2 demand can change for various reasons, including the onset of exercise. If the O_2 supply is insufficient, meaning that it does not match the need of the tissues, adenosine is produced. Adenosine, along with other substances produced as metabolic waste, causes vasodilation. Therefore, if the O_2 concentration is lower than needed, the vessels dilate, reducing their vascular resistance and allowing a larger blood flow to the tissue, increasing the O_2 supply. Literature suggests that the surface area responsible for O_2 diffusion also increases during exercise, increasing the amount of O_2 that can diffuse from the plasma to the tissues. This process results in a balance between the new level of O_2 demand and supply [6] [4].

Blood is not homogeneous, it consists of four components: plasma, red blood cells (RBCs) that carry the majority of the O_2 , white blood cells, and platelets. Blood carries O_2 in two forms: bound to hemoglobin (HB) in RBCs and dissolved in plasma. Although the amount of O_2 dissolved in plasma is small (about 2%), it is crucial for O_2 transport, since the O_2 dissolved in plasma is in equilibrium with the O_2 bound to HB [6].

Oxygenated blood from the lungs is transported to organs through large and small arteries. O_2 diffusion occurs in the capillaries where the velocity is small and the surface/volume ratio is high. The difference in partial pressure of dissolved O_2 between the plasma and the tissues ($P_{O_2,p} - P_{O_2,t}$) causes O_2 to diffuse from the plasma to the tissues. This diffusion allows the O_2 bound to HB to dissolve into the plasma to maintain equilibrium. This process continues while the blood is in the capillaries. Afterward, the deoxygenated blood is collected as it moves through venules and veins toward the right heart. In a healthy human under normal conditions, the blood entering the capillaries is characterized by $P_{O_2} = 95[mmHg]$ and $HB_{O_2} = 0.97[1]$. After passing through the capillaries, these values change to about $P_{O_2} = 40[mmHg]$ and $HB_{O_2} = 0.75[1]$ [4].

3 Modelling the myogenic response

3.1 Developing the mathematical model

The simulation models the behavior of arterioles by considering the parameters of the peripheral models time-dependent. For example, resistances vary with geometry, where a smaller diameter results in higher resistance. In this context, the goal is to establish a relationship between peripheral resistances and pressure, since the myogenic response reacts to changes in blood pressure.

A brief description of the derivation is provided. First, an idealized relationship between pressure and peripheral resistance is given, based on a few assumptions. However, the derived curve is not realistic, as it does not account for the body's limitations, such as the fact that vessels cannot stretch or contract without constraints. Therefore, a more realistic sigmoidal relationship will be provided, taking the derived theoretical curve into account.

The results of the base model with nominal parameters are realistic, including different pressure, flow rate, and velocity values. Therefore, the base simulation without any regulation mechanisms is used as the reference. We assume that the body aims to maintain this state under various conditions. The notations used for the derivation can be seen in 3.1.

Notation	Dimension	Description
$\sigma_{\theta,0}$	Pa	Circumferential wall tension at the inner diameter
R_{fact}	1	Ratio of the current and nominal resistance
R_{max}	1	Parameter of the sigmoid curve
R_{min}	1	Parameter of the sigmoid curve
d_0	1	Nominal normalised diameter
d_{min}	1	Minimum of the normalised diameter
d_{max}	1	Maximum of the normalised diameter
p_{ref}	mmHg	Reference pressure
a	m	Inner radius
b	m	Outer radius
h	m	Wall thickness
x_{myo}	mmHg	Independent variable of the sigmoid curve
f	$\frac{1}{\text{mmHg}}$	Constant parameter of the sigmoid curve
sat_{min}	1	Smaller saturation value of the sigmoid curve
sat_{max}	1	Larger saturation value of the sigmoid curve

Table 3.1: Notations of parameters.

This section presents the derivation of the constructed mathematical model. The following assumptions are made:

- The arterioles are modeled as thick-walled tubes, since the ratio of the inner radius and the wall thickness is around $\frac{3}{4}$ [19].
- The poisson coefficient of the vessel walls is close to 0.5 [1], meaning that it can be considered incompressible with good approximation.
- The shortening of the vessels as a response to increased pressure is neglected. This together with incompressibility means that the area of the annulus is constant.
- Theoretically the vessels response to stretch, trying to maintain constant circumferential wall tension despite changes in pressure [6]. Without further information we assume that the body strives to keep the circumferential wall tension constant at the inner diameter of the vessel.
- The pressure outside the arterioles is atmospheric.

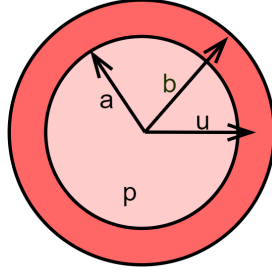


Figure 3.1: Cross section of an arteriole.

The circumferential wall tension for a thick walled-tube can be written as:

$$\sigma_{\theta}(u) = \frac{pa^2}{b^2 - a^2} \left(1 + \frac{b^2}{u^2} \right), \quad (3.1)$$

where a and b are the inner and outer radius of the tube, p is the internal pressure and u is the radial coordinate ($a \leq u \leq b$) 3.1. The third assumption above can be written in mathematical form:

$$(r + h)^2 - r^2 = c, \quad (3.2)$$

where c is a constant parameter, h is the wall thickness and r is the inner radius of the annulus. h can be determined as a function of r as $h = -r \pm \sqrt{r^2 + c}$ from 3.2. Since h , r and c are all positive, $h = -r + \sqrt{r^2 + c}$.

From the fourth assumption 3.1 should be evaluated at $u = r$. The inner radius of the tube is naturally $a = r$. We obtain:

$$\sigma_{\theta,0} = \frac{pr^2}{b^2 - r^2} \left(1 + \frac{b^2}{r^2} \right), \quad (3.3)$$

where $\sigma_{\theta,0}$ is constant. Substituting $b = r + h$ and $h = -r + \sqrt{r^2 + c}$ to 3.3 we get (details of the simplification are in Appendix A):

$$\sigma_{\theta,0} = p \left(1 + \frac{2r^2}{c} \right). \quad (3.4)$$

As previously mentioned a relationship between the peripheral resistances (R) and the pressure is needed, making the peripheral parameters time-dependent. The resistances are inversely proportional to r^4 , so

$$R = \frac{\left(\frac{\sigma_{\theta,0}}{p} - 1 \right)^{-2}}{k}. \quad (3.5)$$

Note that k is a constant parameter. After dividing both sides with the nominal resistance we obtain:

$$R_{fact} = \frac{\left(\frac{\sigma_{\theta,0}}{p} - 1 \right)^{-2}}{k^*}, \quad (3.6)$$

where k^* is also a constant parameter, and R_{fact} is a scaling factor of the nominal resistance. To determine the two constants ($\sigma_{\theta,0}$ and k^*) two equations are needed. $\sigma_{\theta,0}$ can be calculated by substituting $b = r + h$ to 3.3, rearranging and using the first assumption ($\frac{h}{r} \approx \frac{4}{3}$ if $p = p_{ref}$).

$$\sigma_{\theta,0} = p \left(1 + \frac{2}{2\frac{h}{r} + (\frac{h}{r})^2} \right) = \frac{29}{20} p_{ref} \quad (3.7)$$

This provides a value for $\sigma_{\theta,0}$, since p_{ref} is a given parameter from the reference model. k^* can be calculated by substituting the value of $\sigma_{\theta,0}$ to 3.6, since R_{fact} is 1 if $p = p_{ref}$. This gives $k^* = \left(\frac{29}{20} - 1 \right)^{-2} = \frac{400}{81} [1]$. At this stage the theoretical idealised curve is given with all its parameters and constants.

In reality the vessels can not expand or contract without limitations, meaning that function given by 3.6 is not realistic. Instead, we assume that the system aims to follow the derived curve but fails. A more realistic sigmoidal connection is assumed between the pressure and the scaling factor of R :

$$R_{fact} = \frac{R_{max} + R_{min} e^{-f \cdot x_{myo}}}{1 + e^{-f \cdot x_{myo}}}, \quad (3.8)$$

3.6 and 3.8 are obviously really different functions. So the next step is to determine the parameters (R_{max} , R_{min} and f) of the sigmoid curve considering the derived curve given by 3.6. There are many ways to do that, here we mention two. The first matches the slope of 3.8 to 3.6 at the nominal point. The second sets the parameters so that 3.8 approximates the saturation values at roughly the same points as 3.6.

For the slope fitting we have to give the value of f . By matching the derivatives of 3.8 and 3.6 at p_{ref} we get: $f = \frac{8}{R_{max}-R_{min}} \frac{\sigma_{\theta,0}}{p_{ref}^2 k^*} \left(\frac{\sigma_{\theta,0}}{p_{ref}} - 1 \right)^{-3}$. The derivation of f can be seen in Appendix B.

The second can be done by plotting the curves on the same diagram and adjusting the value of f so that the desired outcome is obtained. Either one of the methods could be implemented, we chose the second one. 3.2 presents the curve given by 3.6 and both methods.

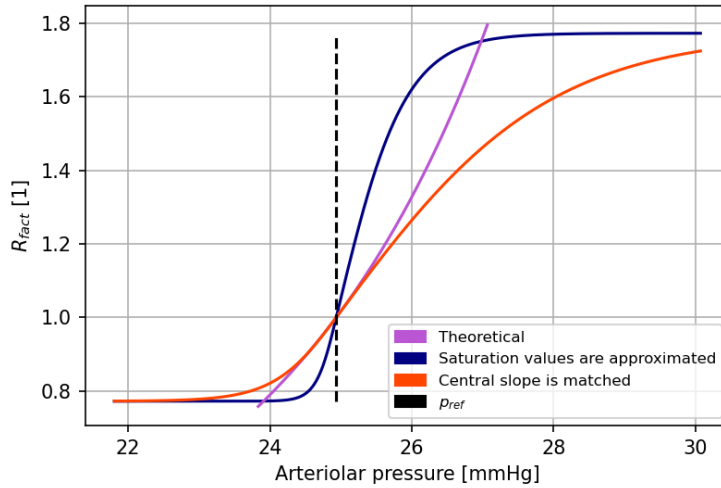


Figure 3.2: The theoretical curve given by 3.6 and the two sigmoidal curves. The first matches the central slope of 3.6, the second approximates the saturation values at the same pressure values as the theoretical curve. In this work, the last was applied.

The saturation values of the curve (sat_{max} and sat_{min}) should also be determined. Since the vascular resistance is a function of the diameter, this can be given with the normalized diameters obtained from [3] shown by 3.3. The derivation is presented in Appendix C. With sat_{max} and sat_{min} R_{min} and R_{max} can be determined as:

$$R_{min} = \begin{cases} sat_{min}, & \text{if } x_{myo} < 0 \\ 2 - sat_{max}, & \text{otherwise.} \end{cases} \quad (3.9)$$

$$R_{max} = \begin{cases} 2 - sat_{min}, & \text{if } x_{myo} > 0 \\ sat_{max}, & \text{otherwise.} \end{cases} \quad (3.10)$$

x_{myo} , the independent variable of the myogenic control can be calculated from p with a low-pass filter. Without that the high frequency noises would effect the simulation in an unrealistic way. The differential equation for the filter is [9]:

$$\tau_{myo} \frac{dx_{myo}}{dt} = -x_{myo} + G_{myo}(\bar{p} - p_{ref}) \quad (3.11)$$

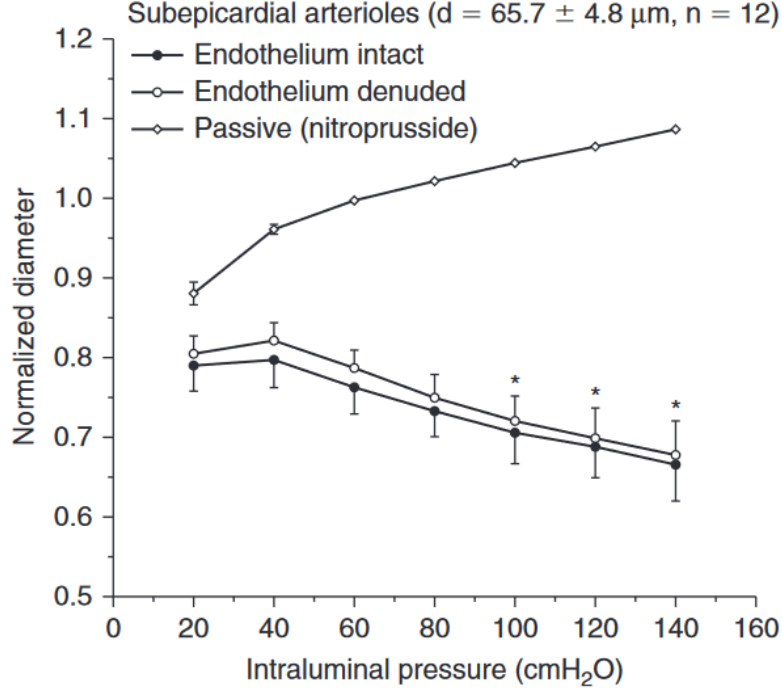


Figure 3.3: Pressure diameter relations of subepicardial arterioles [3].

$G_{myo} = 0.9[1]$ is the static gain, $\tau_{myo} = 40[s]$ is the time constant of the low-pass filter, $\bar{p}$ is the time average of the last cardiac cycle and p_{ref} is the reference pressure. For each periphery p_{ref} is determined as the time average of the arteriolar pressure of the last cardiac cycle from a previous simulation (without any autoregulation).

The running simulation can calculate the scaling factor of resistances (R_{fact}) from the reference and the actual pressure with the given model, the arteriolar resistances are given for the next time step.

4 Modelling the metabolic response

4.1 Virtual one dimensional transport model

For the vessels modelled in one dimension the 4.1 transport equation is solved, where C_x is a general transport variable. The effect of diffusion is small compared to the advection, the minimum of the Péclet number is around $P_{e_{O_2}} = \frac{v_{cap} L_{cap}}{D_{O_2}} = \frac{0.001[\frac{m}{s}] \cdot 0.00315[m]}{1.66 \cdot 10^{-9}[\frac{m^2}{s}]} \approx 1897[1]$ for O_2 dissolved in plasma. Red blood cells are much larger than O_2 molecules, the effect of diffusion is even smaller. For the simulation of the metabolic response only these two transport variables are considered, so the diffusion can be neglected.

The velocity field is calculated by the solver in every timestep for all vessels, thus the concentration values can also be determined. At the intersections of the vessels there are nodes, the concentration is determined by assuming perfect mixing, providing boundary conditions. The concentration of the nodes is calculated as the weighed average of concentrations flowing towards the node and the weights are the volumetric flowrates.

$$\frac{\partial C_x}{\partial t} = -v \frac{\partial C_x}{\partial x} \quad (4.1)$$

Besides the vessels modelled in 1D there are also lumped models. For example the peripherals are modelling the small vessels, the veins and organs. For these zero dimensional models the solver determines the volumetric flowrate and pressure values in each time step. The solution of the transport equation only with these parameters is not possible, since at least one translational coordinate and a velocity value is needed. The next description gives the steps of how the simulation of transport is implemented for a zero dimensional model.

- The time-average of the volumetric flowrate corresponding to the resistance at the given peripheral model is calculated from a previous simulation for a cardiac cycle. For example the R1 resistance is the arteriolar resistance, therefore the arteriolar volumetric flowrate corresponds to that edge. (The structure of a peripheral model can be seen in 2.2)
- Suggested and measured values for the average velocity corresponding to each compartment can be found in the literature. For the simulation the average in time and in space is needed for the arterioles, capillaries, venules and veins. Since the literature does not have one well accepted value for these, they are tuned to achieve realistic results. 4.1 presents the values considered in this work.
- With the two values above a cross-section can be assigned for each periphery for every compartment in a given peripheral model. This way in every time step with the previously calculated volumetric flowrate a realistic velocity value can be obtained as a ratio.

- The length of each compartment is also required for the calculations, these values can be estimated. 4.1 gives the values that provided acceptable results for the simulation. The venous vessel lengths are assumed to be equal to the length of the arterial path from the heart to the considered periphery.

	v [$\frac{m}{s}$]	L [m]
arterioles	0.02	0.0225
capillaries	0.001	0.00315
venulares	0.033	0.00515
veins	0.133	*

Table 4.1: Velocity and length values for each compartment. * indicates that for each peripheral model the sum of the venous vessel lengths were uniquely determined based on the arterial model. The venous vessel lengths are assumed to be equal to the length of the arterial path from the heart to the considered periphery.

Providing that all compartments at each periphery have every necessary additional parameter (a cross section and length), the transport of substances can be simulated the same way as for the vessels modelled in one dimension. The parameters of this model were tuned based on the simulation results. Since the original parameters are from different sources, they are not necessarily free from contradictions. It should be clarified that the goal is to achieve realistic results with realistic parameters.

The presented simplified model basically considers the vessels as being pooled together. The cross section given to each compartment at every periphery is the total cross-section of all the vessels modelled by that compartment. The given length is ideally the expected value of the path a given particle travels there.

Each peripheral model has four compartments (arterioles capillaries, venulares and veins). Basically this way we simulate transport processes with four consecutive virtual 1D models at each periphery.

The transport model can include other terms if other effects should be taken into account besides advection. These include diffusion in space or reaction between different transport variables among other phenomena.

4.2 Modeling the oxygen transport to tissues

Mainly the haemoglobin (HB) in red blood cells (RBCs) is responsible for the delivery of oxygen. A HB molecule can bind a maximum of four O_2 molecules reversibly. Hemoglobin saturation (HB_{sat}) indicates the percentage of bound O_2 molecules relative to the maximum amount possible. If all HB molecules are bound to four O_2 molecules, the saturation is 100%. O_2 molecules stay attached to the HB molecules because of a balance between the $P_{O_2,p}$ and the HB saturation. This balance can be represented with a sigmoid curve.

The curve is obtained by fitting (with the method of least squares), the data points are taken from the relevant interval of $P_{O_2,p}$ ($40mmHg \leq P_{O_2,p} \leq 95mmHg$) 4.2. The function is given by 4.2, the curve is shown by 4.1. The shape of the curve can be explained by the fact that the first O_2 molecule bound to a HB molecule changes the O_2 -affinity, making the binding of the second and third O_2 molecule easier [4].

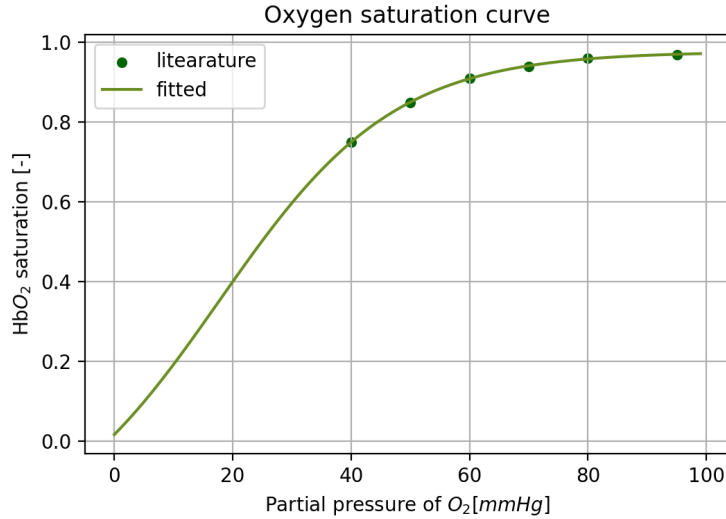


Figure 4.1: Fitted sigmoid curve. Data points are from the relevant interval of haemoglobin saturation [4].

P_{O_2} [mmHg]	40	50	60	70	80	95
HB_{O_2} [1]	0.75	0.85	0.91	0.94	0.96	0.97

Table 4.2: Corresponding values of P_{O_2} and HB_{O_2} in normal physiological conditions in the relevant interval ($40mmHg \leq P_{O_2} \leq 95mmHg$) [4].

O_2 is transferred by flow to organs from the pulmonary circulation. In the larger arteries, arterioles, venules and veins O_2 is not absorbed or only in small amounts. For this reason the 4.1 equation is solved for these parts of the vascular model for the HB_{O_2} , plasma O_2 and RBC concentration. The O_2 diffusion takes place in the capillaries, where the velocity of plasma is $\approx 0.5 - 1[\frac{mm}{s}]$ [20], leaving enough time for the O_2 diffusion from the plasma to tissues and dissolution from HB to plasma. The differential equations describing the three calculated transport variables are not independent there.

Capillaries can be found in the peripherals and also in the pulmonary circulation. First we discuss the former, but the two models are quite similar. The mathematical model describing the tissue oxygenation is a heavily modified version of the one presented in [11]. The main differences are the following. In case of our model:

- The model is one dimensional instead of three.
- O_2 and RBC diffusion is neglected due to its small effect.

- The process of O_2 dissolution from HB to plasma is considered with a separate equation instead of linearization. Linearization would be a large deviation from reality, since the balance between HB_{O_2} and the plasma O_2 can be given by a sigmoidal relationship 4.2 and the relevant interval is large ($40 < P_{O_2} < 95$ [mmHg]).
- The inter-compartment advection term is not considered. This means that the partial pressure difference of O_2 between the compartments does not inflict a change in O_2 concentration.

$$HB_{O_2} = \frac{L}{1 + e^{-k(P_{O_2}-m)}} + b \quad (4.2)$$

Where $L = 1.251[-]$, $k = 0.0676[1/mmHg]$, $m = 17.71[mmHg]$ and $b = -0.274[-]$.

Notation	Name, Dimension	Value
κ_c	Permeability of the capillary wall $[\frac{m^3(O_2)}{mmHg \cdot m \cdot s}]$	$4.2 \cdot 10^{-14}$
h_c	Wall thickness of capillary vessels $[m]$	$1.0 \cdot 10^{-6}$
$\frac{S_c}{V_c}$	Capillary vessel surface area to capillary volume $[\frac{1}{m}]$	$4.74 \cdot 10^5$
α_b	O_2 solubility in plasma $[\frac{m^3(O_2)}{mmHg \cdot m^3(plasma)}]$	$3.11 \cdot 10^{-5}$
α_t	O_2 solubility in tissue $[\frac{m^3(O_2)}{mmHg \cdot m^3(tissue)}]$	$3.95 \cdot 10^{-5}$
τ	Time constant of O_2 dissolution $[s]^*$	$8.0 \cdot 10^{-2}$
ϕ_c	Capillary volume fraction [%]	1.1303
ϕ_t	Tissue volume fraction [%]	98.8697
M_{max}	Maximum consumption rate of oxygen $[\frac{m^3(O_2)}{s \cdot m^3(plasma)}]$	$2.4 \cdot 10^{-4}$
C_{50}	C_t at the half maximum consumption rate $[\frac{m^3(O_2)}{mmHg \cdot m^3(plasma)}]$	$2.6 \cdot 10^{-5}$

Table 4.3: Parameters of tissue oxygenation. [21] provided an interval for each parameter, and the applied values fall within that range. The exceptions are ϕ_c and $\frac{S_c}{V_c}$, which come from synthetic geometries suggesting different values: $\phi_c = 1.42[\%]$ and $\frac{S_c}{V_c} = 6.1638 \cdot 10^5[\frac{1}{m}]$. ϕ_t is then calculated as $1-\phi_c$. The cited article specifically models the human brain, so the parameters determined are not necessarily valid for all body parts. The adopted mathematical model used for the synthetic geometries is given by [22], which focuses solely on the cerebral microvasculature. Therefore, deviating from the values suggested by these references in case of these geometrical parameters is acceptable.

The equations describing the process, where C_c and C_t is the plasma and tissue O_2 concentration:

$$\frac{\partial C_c}{\partial t} = - \underbrace{v \frac{\partial C_c}{\partial x}}_{\text{advection}} - \underbrace{\frac{\kappa_c S_c}{h_c V_c} \left(\frac{C_c}{\alpha_b} - \frac{C_t}{\alpha_t} \right)}_{\text{diffusion from plasma to tissue}} + \underbrace{\frac{1}{\tau} \Delta C_{O_2, plasma}}_{O_2 \text{ dissolving from HB to plasma}} ; \quad (4.3)$$

$$\frac{\partial C_t}{\partial t} = \underbrace{\frac{\kappa_c S_c \phi_c}{h_c V_c \phi_t} \left(\frac{C_c}{\alpha_b} - \frac{C_t}{\alpha_t} \right)}_{\text{diffusion from plasma to tissue}} + \underbrace{\frac{M_{max} C_t}{C_t + C_{50}}}_{O_2 \text{ consumption}} ; \quad (4.4)$$

$$\frac{\partial HB_{O_2}}{\partial t} = - \underbrace{v \frac{\partial HB_{O_2}}{\partial x}}_{\text{advection}} - \underbrace{\frac{1}{\tau} \Delta HB_{O_2}}_{O_2 \text{ dissolving from HB to plasma}} \quad (4.5)$$

The diffusion of O_2 into tissue is driven by the partial pressure difference of dissolved O_2 between the plasma and the tissue, expressed as $P_{O_2,p} - P_{O_2,t} = \frac{C_c}{\alpha_b} - \frac{C_t}{\alpha_t}$. The term $\frac{\kappa_c S_c}{h_c V_c}$ represents the rate of change in C_c due to a unit difference in partial pressure. The dissolution of O_2 to plasma from O_2 bound to hemoglobin (HB) into plasma is modeled as follows:

- At each timestep there is a given HB_{O_2} and C_c value. These are not necessarily in perfect balance (if the sigmoidal relationship given by 4.2 is not met they are not in balance). ΔHB_{O_2} gives the difference between HB_{O_2} and the ideal value where it would be in balance with the current C_c .
- The difference dissolves into the plasma described by the differential equation of a first-order lag. The time constant was tuned to achieve realistic results.
- The dissolved value also appears in the 4.5 equation, so that the the mass balance is fulfilled.

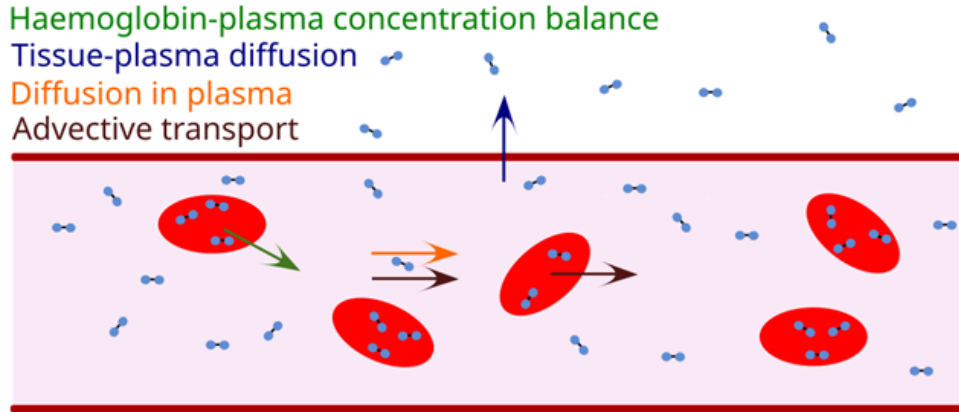


Figure 4.2: The transport of O_2 in capillaries.

$\Delta C_{O_2,plasma}$ is the concentration difference corresponding to ΔHB_{O_2} . It can be calculated as $\Delta HB_{O_2} \cdot C_{RBC} \cdot N_{O_2/RBC} \frac{M}{N_A \cdot \rho}$. C_{RBC} is the concentration of RBC in plasma, $N_{O_2/RBC} = 10^9 \left[\frac{1}{1} \right]$ is the maximal number of O_2 molecules in a RBC in case of maximal saturation, $M = 0.032 \left[\frac{kg}{mol} \right]$ is the molar mass of O_2 , $N_A = 6 \cdot 10^{23} \left[\frac{1}{mol} \right]$ is the avogadro constant, $\rho = 1.43 \left[\frac{kg}{m^3} \right]$ is the density of O_2 in standard conditions.

4.4 describes the O_2 concentration of tissues. The term corresponding to the O_2 diffusion from plasma to tissue is the same as in 4.3 but multiplied with $\frac{\phi_c}{\phi_t}$ (the ratio of capillary to tissue volume) and with a different sign to satisfy the law of conservation of mass. The multiplication by $\frac{\phi_c}{\phi_t}$ is necessary since the variables in the equations represent concentration, and the volumes of tissue and blood are different. The parameters and their values can be seen in 4.3.

The term corresponding to O_2 consumption in 4.4 is modelled by the Michaelis–Menten kinetics [11]. This model is often applied to describe nutrient uptake by cells. [23]

4.3 Modeling the oxygen transport in the pulmonary circulation

Gas exchange in the pulmonary circulation occurs with the help of alveoli, which are small air sacs in the lungs that allow gases to enter the blood. The difference between the partial pressure of O_2 in the alveoli and in the capillaries drives the diffusion of O_2 . The partial pressure of O_2 in the alveoli is about $P_{O_2,a} = 100[mmHg]$, with minimal fluctuations over time 4.3.

Developing a parameter-wise similar model to the one describing tissue O_2 consumption is not ideal since its parameters (like the surface of the alveoli and the thickness of the layer between the alveoli and the capillary) cannot be accurately estimated or measured. Therefore, in respiratory physiology the pulmonary diffusion constant is usually applied. This parameter represents the volume of gas that diffuses from the alveoli to the capillaries per second per unit partial pressure difference. The main advantage of this parameter is that it characterizes the entire lung. For O_2 , this value is approximately $3.33 \cdot 10^{-7} \left[\frac{m^3(O_2)}{s \cdot mmHg} \right]$ [4].

The O_2 diffusion is modelled with a short virtual one dimensional transport element corresponding to the pulmonary capillaries, so the pulmonary diffusion constant can not be applied. One reason is that there is no single partial pressure difference. The applied mathematical method is quite similar to the one described by equations 4.3, 4.4, and 4.5, which model the process in the systemic capillaries. This is because the processes are alike, with the main difference being the direction of O_2 diffusion. Since there are only small fluctuations in the partial pressure of O_2 in the alveoli, it is assumed to be constant, eliminating the need for a differential equation to model that variable.

$$\frac{\partial C_{p,c}}{\partial t} = - \underbrace{v \frac{\partial C_{p,c}}{\partial x}}_{\text{advection}} - \underbrace{K_{max} \sin^2\left(\frac{j\pi}{n}\right) \left(\frac{C_{p,c}}{\alpha_b} - P_{O_2,a}\right)}_{\text{diffusion from alveoli to tissue}} + \underbrace{\frac{1}{\tau} \Delta C_{O_2,plasma}}_{O_2 \text{ dissolving from HB to plasma}}, \quad (4.6)$$

$j \in \{1; 2 \dots n\};$

$$\frac{\partial HB_{O_2}}{\partial t} = - \underbrace{v \frac{\partial HB_{O_2}}{\partial x}}_{\text{advection}} - \underbrace{\frac{1}{\tau} \Delta HB_{O_2}}_{O_2 \text{ dissolving from HB to plasma}} \quad (4.7)$$

The term $K_{max} \sin^2\left(\frac{j\pi}{n}\right) \left(\frac{C_{p,c}}{\alpha_b} - P_{O_2,a}\right)$ describes the diffusion of O_2 from the alveoli. K_{max} is a constant parameter representing the maximum concentration change caused by a unit partial pressure difference in one second, $K_{max} = 6.479 \cdot 10^{-4} \left[\frac{m^3(O_2)}{m^3(plasma) \cdot mmHg \cdot s} \right]$. The $\sin^2\left(\frac{j\pi}{n}\right)$ factor models the gradual change of the vessels rather than a sudden shift, so there is no O_2 diffusion in the start and end of the pulmonary capillaries. In the peripheral model this was not applied, since the small arteries and veins are modeled separately from the capillaries contrary to the pulmonary circulation. $\left(\frac{C_{p,c}}{\alpha_b} - P_{O_2,a}\right)$ is the partial pressure difference driving the diffusion of O_2 . Equation 4.7 is equivalent to 4.5 because the O_2 dissolution to plasma is the same process in the systemic and pulmonary capillaries. 4.4 give the parameters of 4.6 and 4.7.

Notation	Name, Dimension	(value)
$C_{p,c}$	O_2 concentration in the pulmonary capillaries $\left[\frac{m^3(O_2)}{m^3(blood)} \right]$	-
$P_{O_2,a}$	Partial pressure of O_2 in the alveoli $[mmHg]$	100
n	Number of division points [1]	-
j	Index of the given division point [1]	-
K_{max}	$-, \left[\frac{m^3(O_2)}{m^3(plasma) \cdot mmHg \cdot s} \right]$	$6.479 \cdot 10^{-4}$

Table 4.4: Notations used in 4.6 and 4.7 describing the O_2 uptake in the pulmonary capillaries

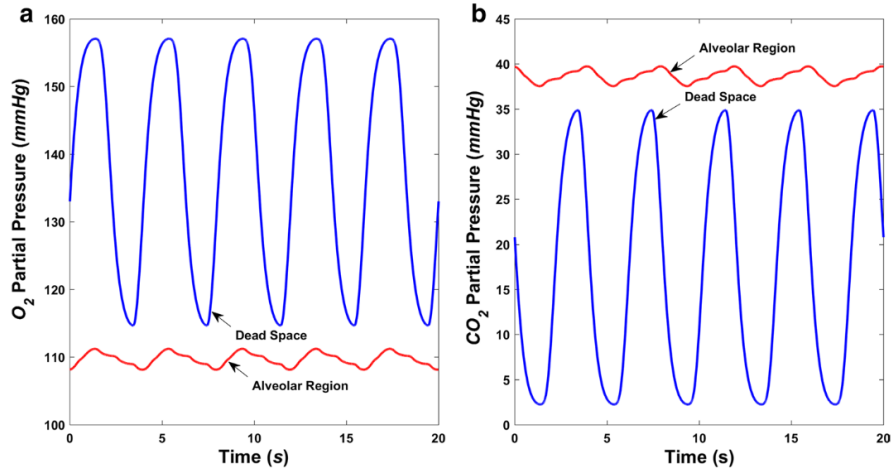


Figure 4.3: Simulated curve of $P_{O_2,a}$ in a) [5]. The fluctuation of the red curve is small, the average is around 110 $mmHg$. In our simulation $P_{O_2,a}$ was assumed to be constant 100 $mmHg$ in the alveolar region, the value given by [4].

4.4 Modelling the metabolic response

Using the above, the solver is suitable for simulating the transport of substances, as well as the O_2 consumption and uptake in the systemic and pulmonary circulation. These are

necessary for modeling metabolic regulation.

The body tries to maintain adequate O_2 supply. If the O_2 level is lower than needed, the vessels dilate. This reduces their vascular resistance and allows a larger blood flow to the tissue, increasing the O_2 supply. The following section provides a mathematical model describing the connection between C_t and R_{fact} , aiming to capture the body's vascular response.

Similar to the myogenic control a sigmoidal connection between tissue O_2 level and the peripheral resistances is assumed. The saturation levels of the sigmoid curve are the same as for the myogenic control since the same vessels are responsible for these mechanisms and there is no information in the literature to suggest otherwise according to the author's knowledge. Similarly to the modelling of the myogenic response, the base simulation without any regulation mechanisms is used as the reference.

Like 3.8, the time dependent peripheral resistances can be determined as:

$$R_{fact} = \frac{R_{max} + R_{min}e^{-f \cdot x_{met}}}{1 + e^{-f \cdot x_{met}}} \quad (4.8)$$

where f is scaled, so that the relative slope is the same as in 3.8. The independent variable of the metabolic control (x_{met}) is calculate from C_t with a low-pass filter:

$$\tau_{met} \frac{dx_{met}}{dt} = -x_{met} + G_{met}(\bar{C}_t - \bar{C}_{t,ref}) \quad (4.9)$$

$G_{met} = 0.9[1]$ is the static gain, $\tau_{met} = 40[s]$ is the time constant of the low-pass filter and $\bar{C}_t$ is the time average of C_t in the last cardiac cycle. For each periphery $\bar{C}_{t,ref}$ is calculated as the time average of the tissue O_2 concentration of the last cardiac cycle from a previous simulation (without any autoregulation).

Changes in vessel diameter does not only effect the peripheral resistances but also some of the parameters of 4.3 and 4.4, since the geometry depends on it. These coefficients are:

- $\frac{\phi_c}{\phi_t} \approx \frac{r^2 g}{1-r^2 g}$, where g is a constant. $\frac{\phi_c}{\phi_t}$ is the ratio of capillary and tissue volume. Initially ϕ_c is given, ϕ_t is calculated as $1 - \phi_c$ [21].
- We use the approximation $h = \frac{h_0 r_0}{r}$ based on the assumption that $rh \approx r_0 h_0$ holds for any vessel (r_0 and h_0 are the nominal radius and wall thickness). This assumption stems from the fact that the Poisson's ratio of the vessel wall is approximately 0.5, meaning the wall is nearly incompressible [1]. While this approximation is less accurate than $h = -r + \sqrt{r^2 + c}$ from 3.2, we still use $rh \approx r_0 h_0$ because it simplifies the relationship between r and h . Additionally, other parameters in the O_2 transport model, such as those mentioned in 4.3, have significant uncertainties as well as the mathematical model itself, so this simplification is acceptable.
- $\frac{S_c}{V_c} \sim \frac{1}{r}$. $\frac{S_c}{V_c}$ is the capillary surface area to volume ratio.

Based on these in 4.3 $\frac{1}{h} \frac{S_c}{V_c} \sim \frac{1}{r} r = 1$. Meaning that the coefficients in that equation do not depend on the changing radius. Also, in 4.4 $\frac{1}{h} \frac{S_c}{V_c} \frac{\phi_c}{\phi_t} \sim r \frac{1}{1-r^2g} \approx r^2$ where g is a constant parameter. The last approximation can be made because $\phi_c = r^2g$ is around $\approx 1.13\%$. So after changing the scale factor of the peripheral resistances (R_{fact}), the scale factor of the diffusion term in 4.4 is $R_{fact}^{-0.5}$, since $R \sim \frac{1}{r^4}$. The other parameters in the equations are considered independent of the vessel diameter.

5 Results and discussion

Haemodynamics, the study of blood flow in the vascular system, could help us better understand circulatory diseases and aid in medical decision-making. For this purpose, the models used must be accurate and realistic. Therefore, evaluating and discussing the results is arguably the most important part of this thesis.

The current documentation covers several related topics, focusing in particular on autoregulation. The myogenic and metabolic mechanisms, two local control processes in the body, are examined in greater detail. The main goal was to develop and implement these blood flow regulating processes within a haemodynamics solver.

5.1 Results of the myogenic mechanism

Different organs exhibit various levels of autoregulation. The brain and the heart are vital to the body, making their blood supply a high priority. Consequently, their regulation mechanisms are particularly well-developed. Since the CBF-MAP curve is the most well-known visualization of the phenomenon, the evaluation of the simulation is carried out in a similar manner.

Figure 5.1 shows the simulated CBF-MAP curves with and without the myogenic response for the cerebral peripheries (the myogenic response for other peripheries were turned off for all simulations). The MAP values were modified by changing the minimum of the elastance function of the left ventricle in the heart model that mimics the contraction of the heart 2.2. MAP was calculated as the time-average of the aortic pressure, CBF (the time-averaged volumetric flow rate of blood through the arteries supplying the intracranial system) is relative to the simulation computed with the base model.

A third-degree polynomial was fitted to the data points in both cases, since this type of function is recommended by physicians to describe autoregulation [24]. As expected, the myogenic response makes the CBF-MAP curve flatter over a certain range. However, the simulated curve is not as flat as the theoretical CBF-MAP curve, which is usually depicted with a more horizontal plateau. The simulation successfully mimics the body's behavior, meaning it attempts to maintain constant blood flow under varying conditions.

Deciding whether the results are sufficient is not straightforward. As mentioned earlier, the myogenic mechanism responds to changes in blood pressure, but the body has multiple mechanisms that regulate blood pressure, like the baroreflex. This means that the CBF-MAP curve observed by physicians is influenced by many factors [25]. Without accounting for these other processes, the simulated CBF-MAP curve won't match the one measured in humans. It's also impossible to measure the effect of only the myogenic response in humans, since the other responses can't be turned on or off independently.

Besides that there are fairly different CBF-MAP curves found in the literature. The uncertainties of the CBF measurement methods (for example magnetic resonance imaging

and transcranial Doppler ultrasound) are high [18], meaning that reliable numerical data is not expected in the near future regarding the MAP-CBF curve. Since the model gives qualitatively correct results the model is found to be acceptable. If more reliable numerical reference data becomes available for the effect of the myogenic response, the model parameters can be adjusted to better match it.

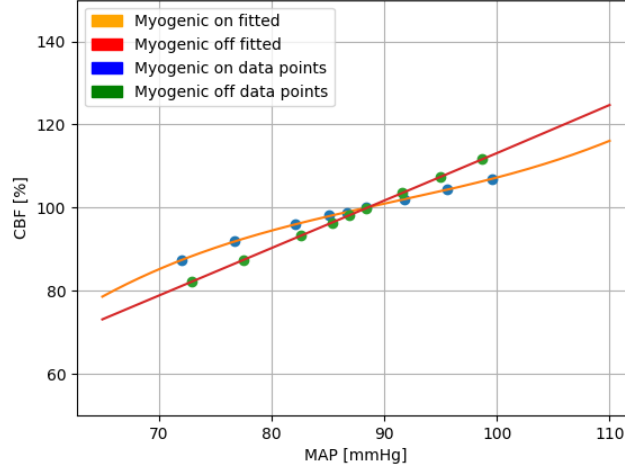


Figure 5.1: Evaluated CBF-MAP curves of the simulations. The myogenic response was only applied for the cerebral peripherals. The MAP values were modified by changing the minimum of the elastance function of the left ventricle in the heart model that mimics the contraction of the heart 2.2. MAP was calculated as the time-average of the aortic pressure, CBF is relative to the simulation computed with the base model.

5.2 Results of the metabolic response

The first task was to simulate O_2 uptake in the lungs and tissue oxygenation with a stable simulation. For that the transport of three variables, HB_{O_2} , C_c and C_{RBC} was simulated. The initial values are $HB_{O_2} = 0.97[1]$, $C_c = 2.955 \cdot 10^{-3} \left[\frac{m^3(O_2)}{m^3(plasma)} \right]$ and $C_{RBC} = 4.9 \cdot 10^{15} \left[\frac{1}{m^3} \right]$ everywhere. Providing that the parameter tuning and the mathematical model are correct, a circular process should be the result of the simulation after a transient period. Normally HB_{O_2} is around $0.75[1]$, $C_c = 1.244 \cdot 10^{-3} \left[\frac{m^3(O_2)}{m^3(plasma)} \right]$ and $C_{RBC} = 4.9 \cdot 10^{15} \left[\frac{1}{m^3} \right]$ in the venules, veins, left heart and pulmonary veins. In the systemic arteries and arterioles, the right heart and the pulmonary arteries, the HB_{O_2} , C_c and C_{RBC} values should be close to the initial conditions after the transient. D.2, D.1, D.3 and D.4 show the results of the transient simulation. The steady-state values of the transient simulation can be seen in 5.2 for C_c and HB_{sat} . As the evaluations show, the results represent the optimal outcomes since the steady-state values are close to the reference and within physiologically realistic ranges.

The mesh independence analysis of the simulation can be seen in 5.3 for the tissue

oxygenation and in 5.4 for the oxygen uptake. The nominal number of division points turned out to be sufficient, since in case of every parameter the deviation is well under 1% compared to the value corresponding to the finest mesh.

The results of the metabolic response need to be evaluated and discussed. In real life, this response can be observed when an organ's O_2 demand increases, such as during exercise. The body responds by dilating resistance vessels, which increases blood flow to that organ. The increased O_2 demand can be modeled by changing the O_2 consumption term in 4.4. To test whether the metabolic response model accurately mimics the body's behavior, four simulations were computed.

First, autoregulation is turned off, and all model parameters are set to their default values. In the second scenario, autoregulation is turned on, but the parameters remain the same. In the third scenario, the maximum oxygen consumption rate, M_{max} , is doubled, but the metabolic response is turned off. In the fourth scenario, M_{max} is still doubled, but this time, the metabolic response is turned on. The results of these simulations are shown in 5.5. In the first two scenarios, the tissue O_2 concentration, C_t , stabilizes at the same level, as expected. However, when O_2 consumption increases (in the third scenario), C_t decreases. When the metabolic response is activated (in the fourth scenario), C_t increases and stabilizes between the values from the first two and the third scenarios. These results are consistent with expectations. If accurate numerical data becomes available describing the metabolic response, the model parameters can be further refined to better match that data.

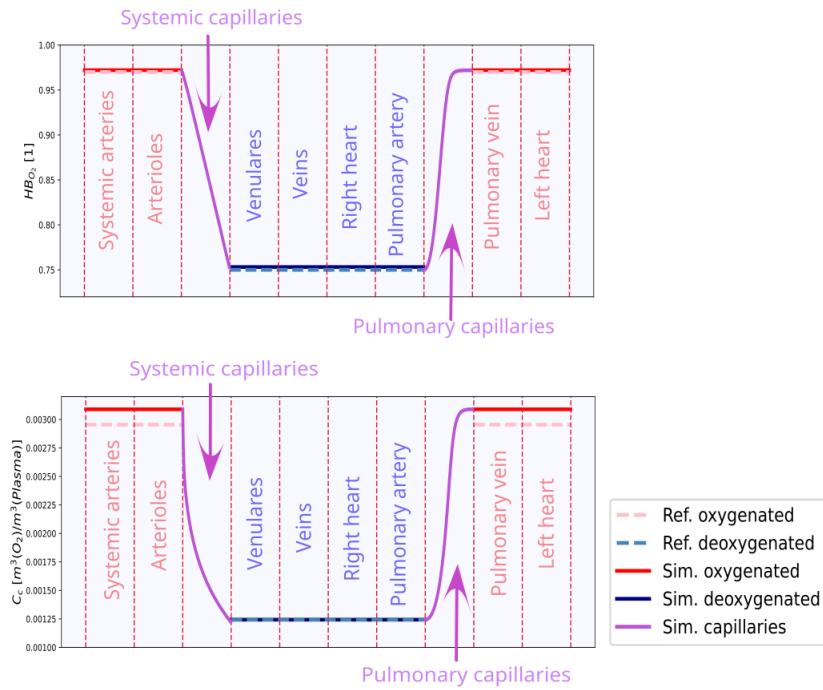


Figure 5.2: HB_{O_2} and C_c results of the transient simulation at each part of the vascular model. Ref.-reference, Sim.-simulated.

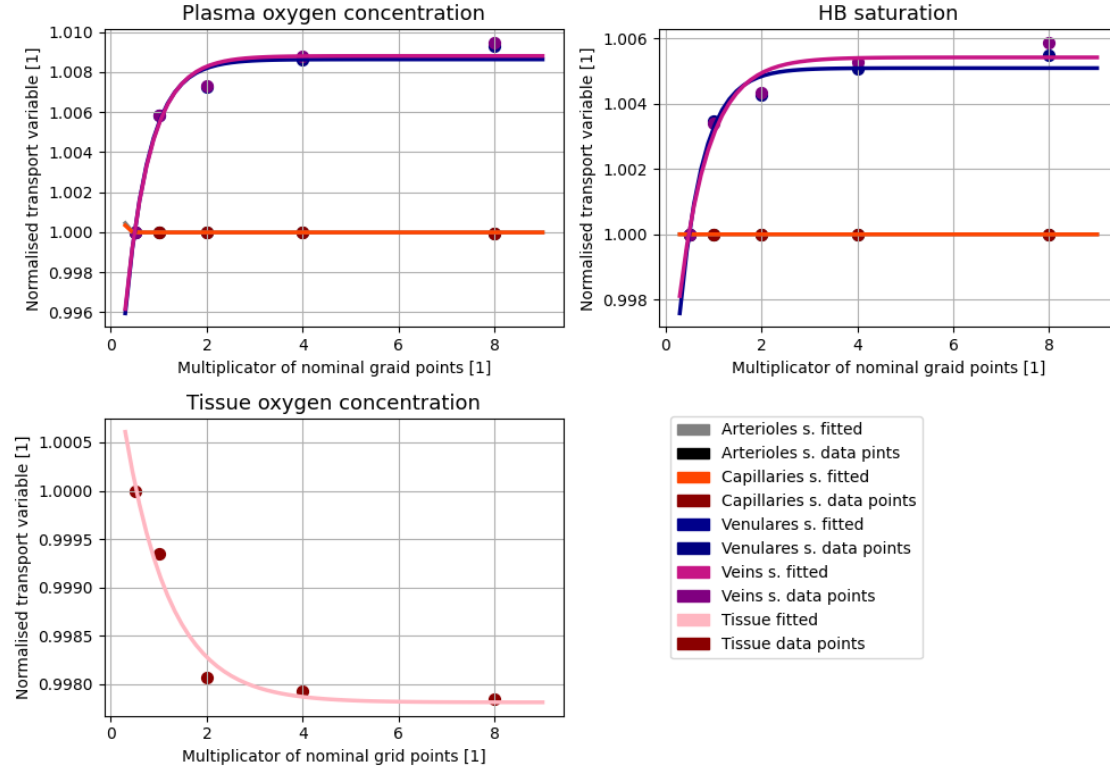


Figure 5.3: Mesh independence of the peripheral O_2 transport at the right posterior tibial. The plasma O_2 concentration, HB_{sat} and tissue O_2 concentration values are evaluated at $t = 75[s]$ simulation time after reaching the stationary state (the transient results can be seen in D.2, D.1, D.3 and D.4). The simulation was carried out for division points 0.5, 1, 2, 4 and 8 times the nominal. The values are divided by the corresponding value obtained with the sparsest mesh. s.-start.

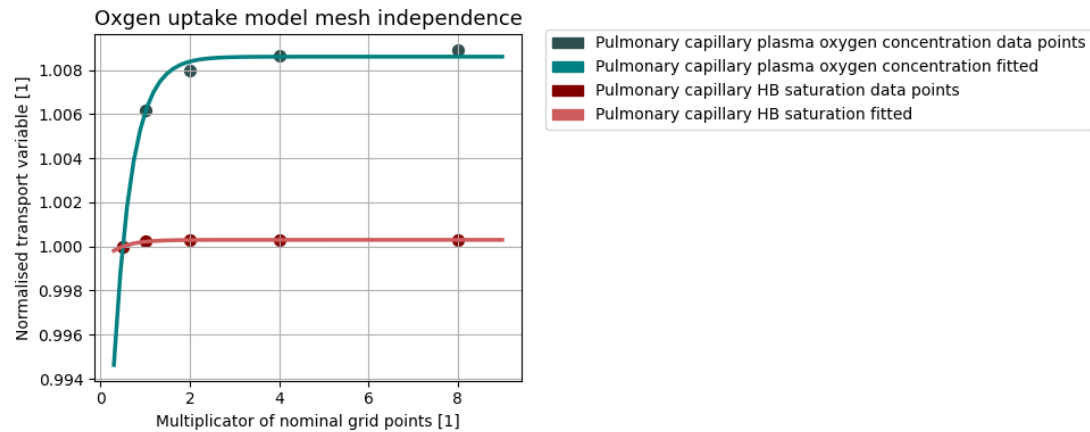


Figure 5.4: Mesh independence of the pulmonary O_2 transport. The plasma O_2 concentration and HB_{sat} values are evaluated at $t = 75[s]$ simulation time after reaching the stationary state. The simulation was carried out for division points 0.5, 1, 2, 4 and 8 times the nominal. The values are divided by the corresponding value obtained with the sparsest mesh.

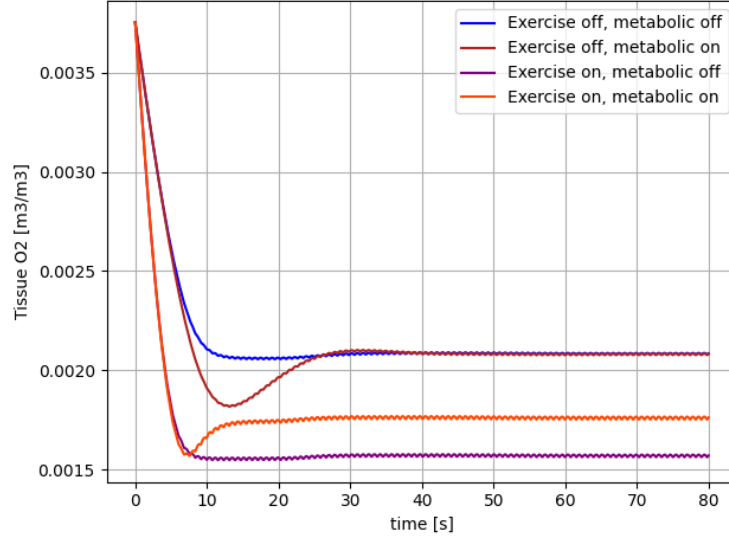


Figure 5.5: Evaluation of the metabolic response. The onset of exercise is modelled by doubling M_{max} , the maximum oxygen consumption rate in 4.4. The four cases include the combinations of exercise and metabolic response turned on and off.

6 Limitations

6.1 General limitations

The origin of the potential inaccuracies is diverse. There are zero and one dimensional parts of the model requiring different numerical mathematical methods for the simulation and numerous parameters. The small vessels, veins and organs including the heart have zero dimensional models, making the simulation of blood flow in the vascular system much simpler and computationally effective but in some way less precise. All parts of the model contain omissions. The results can only be used with consideration of the limitations.

The vascular model does not model the whole circulatory flow of blood in the vascular system, since the veins are not connected to the heart. For making the simulation more precise further development of this part of the model is inevitable. Since current work heavily relies on the velocity and pressure field determined by the solver and the model, any imprecision that shows up in them will carry over to the autoregulation simulations.

6.2 The myogenic response

The derivation of the mathematical model can be considered complex in a way. There are many assumptions made and some of the required parameters are hard to measure or estimate. The limits of the myogenic response in arterioles was estimated based on a measurement performed on swines that were given vasoactive substances before the measurement [3].

In conclusion the mathematical model is itself correct considering the assumptions made during its derivation, but some parameter adjustment is certainly needed that require further measurements.

6.3 The metabolic response

The simulation of the metabolic response is complex and can be divided into individual parts such as the modeling of transport processes, tissue oxygenation at the peripherals and O_2 uptake in the pulmonary capillaries. These phenomena are much more complex in reality than we can ever dream of, even most of the parameters can not be measured, only estimated. The metabolic response itself is not validated yet, since quantitative data is not presented in the literature to the author's knowledge. The results are accepted based only on qualitative evaluations.

Future plans include the validation of the model, and measurements performed on humans will be carried out to provide the necessary data. My supervisor, Dr. Richárd Wéber submitted an NNKP application in medical collaboration the details of which cover this.

7 Summary

The thesis presents a comprehensive approach to simulating myogenic and metabolic blood flow regulation, integrating insights from both literature research and mathematical modeling. It begins with a brief literature review that outlines the concept of autoregulation and the roles of myogenic and metabolic mechanisms in blood flow regulation. Also, a short description of the solver and the applied vascular model is given. The main objective of this work was to contribute to the further development of `first_blood`, a zero- and one-dimensional hemodynamic solver. Researches regarding the control mechanisms could have real-world impact on medical research and clinical practice in the future. By advancing our ability to simulate these processes, it may pave the way for better diagnostic methods, targeted therapies, and new treatments for vascular disorders, as well as cardiovascular diseases.

A substantial portion of the research involved modifying an existing mathematical model of the myogenic response based on established studies. First, a theoretical, idealized relationship between peripheral resistance and pressure was derived modelling the arteriolar vessels as thick walled tubes. Then, a more realistic sigmoidal relationship was developed, accounting for the body's limitations. The latter relationship builds on the former, with parameters selected to match specific properties of the idealized curve, such as the central slope or the saturation values. The limits of the myogenic response were estimated based on data from the literature considering arteriolar diameter changes as a response to intraluminal pressure.

The commonly used representation of autoregulation by physicians is the CBF-MAP curve. This was considered during the evaluation of the myogenic response. CBF-MAP curves were computed with the myogenic response model both activated and deactivated in the simulation. Different MAP values were obtained by adjusting the minimum elastance of the left ventricle in the heart model. This approach provided insight into the realism of the simulation.

The simulation of advective transport processes was also implemented within the solver for both one- and zero-dimensional models. The thesis introduces a virtual 1D transport model, enabling the simulation of substance transport even in lumped 0D models. The presented simplified model basically considers the vessels as being pooled together. Building on this, an O_2 transport cycle was formulated, which includes modeling O_2 uptake in the pulmonary capillaries and tissue oxygenation. Since the metabolic response depends on changes in O_2 levels, the goal was to establish a mathematical relationship between O_2 levels and peripheral resistance. The verification of the O_2 transport model was also conducted for lumped models.

The results of the simulations were thoroughly evaluated and discussed in the context of existing knowledge, highlighting the known possible limitations. The findings suggest that the simulations can mimic the behavior of the control mechanisms discussed, the myogenic and metabolic response models provide qualitatively correct results. Future plans include validating the models once suitable measurement data becomes available.

8 The tasks performed

The documentation contains descriptions of the processes, methods, and information closely related to the work done regarding the myogenic and metabolic responses. These include the development of the mathematical models, brief description of the implementations and validations. Of the parts described in the document, the author's work is:

- Further development and modification of the myogenic response model from [10][9].
- Further development of the tissue oxygenation model found in [11].
- Development of
 - the mathematical model for the transport in zero dimension.
 - pulmonary tissue oxygenation model.
 - metabolic response model.
- Implementation of the models above within `first_blood`.
- Evaluation of the results.

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A More detailed steps of the simplification of $\sigma_{\theta,0}$

After we substitute $b = r + h$ and $h = -r + \sqrt{r^2 + c}$ to 3.3:

$$\begin{aligned}\sigma_{\theta,0} &= \frac{pr^2}{b^2 - r^2} \left(1 + \frac{b^2}{r^2}\right) = \frac{pr^2}{(\sqrt{r^2 + c})^2 - r^2} \left(1 + \frac{(\sqrt{r^2 + c})^2}{r^2}\right) \\ &= p \left(\frac{2r^2 + c}{c}\right) = p \left(1 + \frac{2r^2}{c}\right).\end{aligned}\tag{A.1}$$

B Fitting the slope of the sigmoid curve to the derived theoretical function

Two curves are given, 3.6 and 3.8. The former is a theoretical idealised function that gives a relationship between blood pressure and peripheral resistance. Since the vessels can not contract or expand without limitations the real connection is assumed to be sigmoidal given by 3.8. The central slope of the sigmoidal curve can be set by determining f so that the slopes match at the nominal point. The derivatives are:

$$\frac{R_{fact}}{dx_{myo}} = \frac{-f R_{min} e^{-fx_{myo}} (1 + e^{-fx_{myo}}) - (R_{max} + R_{min} e^{-fx_{myo}}) (-f) e^{-fx_{myo}}}{(1 + e^{-fx_{myo}})^2}\tag{B.1}$$

and

$$\frac{R_{fact}}{p} = \frac{1}{k^*} \left(\frac{\sigma_{\theta,0}}{p} - 1\right)^{-3} (-2)(-1) \frac{\sigma_{\theta,0}}{p^2}\tag{B.2}$$

At the nominal point $p = p_{ref}$ and $x_{myo} \approx 0$, so the derivatives should be equal evaluated there.

$$\frac{2\sigma_{\theta,0}}{p_{ref}^2 k^*} \left(\frac{\sigma_{\theta,0}}{p_{ref}} - 1\right)^{-3} = \frac{f(R_{max} - R_{min})}{4}\tag{B.3}$$

From this, $f = \frac{8}{R_{max} - R_{min}} \frac{\sigma_{\theta,0}}{p_{ref}^2 k^*} \left(\frac{\sigma_{\theta,0}}{p_{ref}} - 1\right)^{-3}$.

C Determining sat_{min} and sat_{max}

The normalised diameters can be seen in 3.3. The values are $d_{max} = 0.80[-]$ at $p = 40[cmH_2O]$, $d_0 = 0.75[-]$ at $p = 60[cmH_2O]$, $d_{min} = 0.65[-]$ at $p = 140[cmH_2O]$ obtained from [3]. The minimal and maximal scaling factors of the resistances are therefore $sat_{max} = \left(\frac{0.65}{0.75}\right)^{-4} \approx 1.773[-]$ and $sat_{min} = \left(\frac{0.80}{0.75}\right)^{-4} \approx 0.772[-]$, since $R_{fact} = 1$ in case of the nominal diameter and $R \sim \frac{1}{d^4}$.

D Transient simulation results of tissue oxygenation and O_2 uptake in the pulmonary capillaries

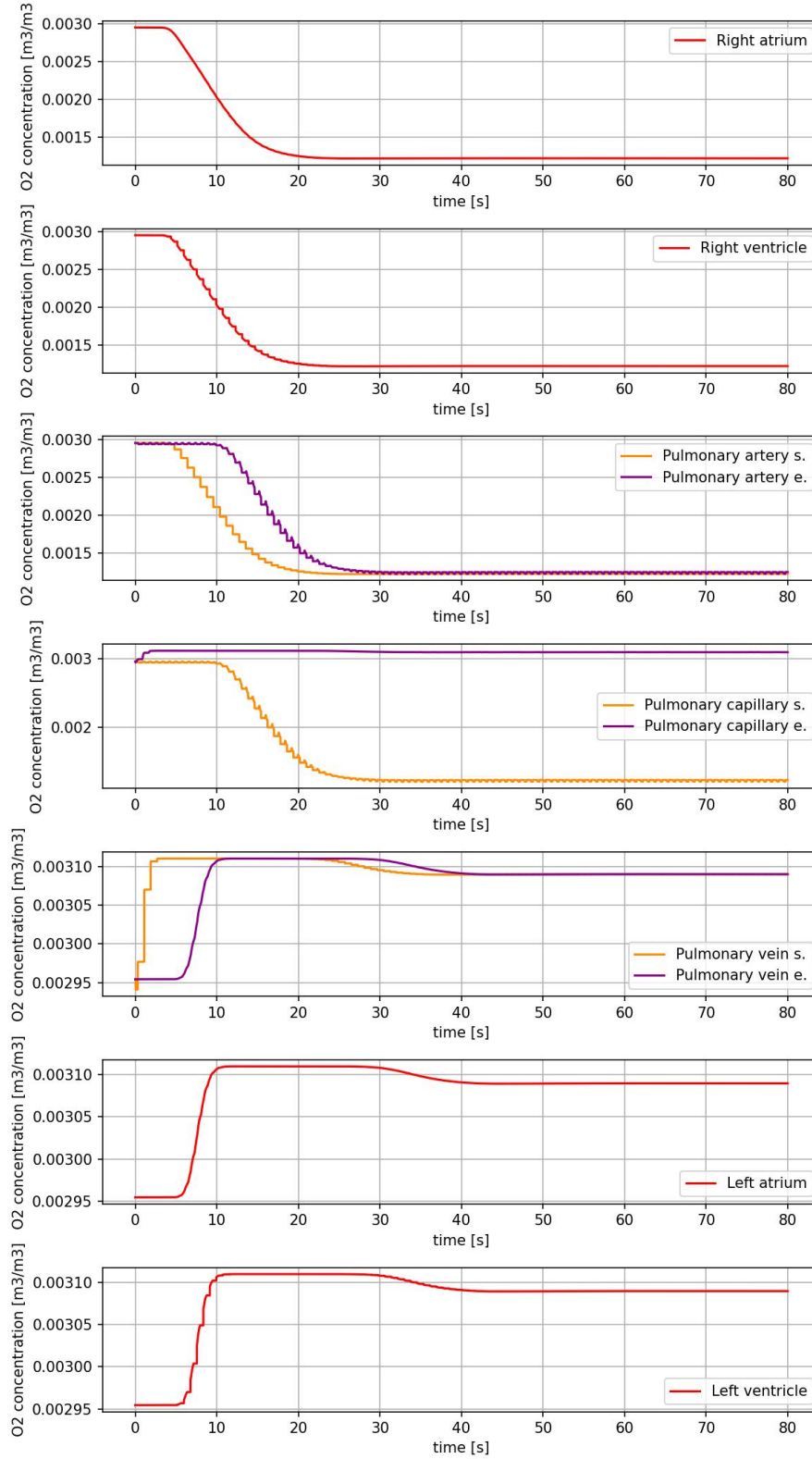


Figure D.1: Plasma O_2 concentration in time in the heart and pulmonary circulation. As expected, from the initial values the steady-state value significantly decreases before the pulmonary capillaries. The steady-state value after the capillaries is close to the initial values that characterise oxygenated blood. s.-start, e.-end.

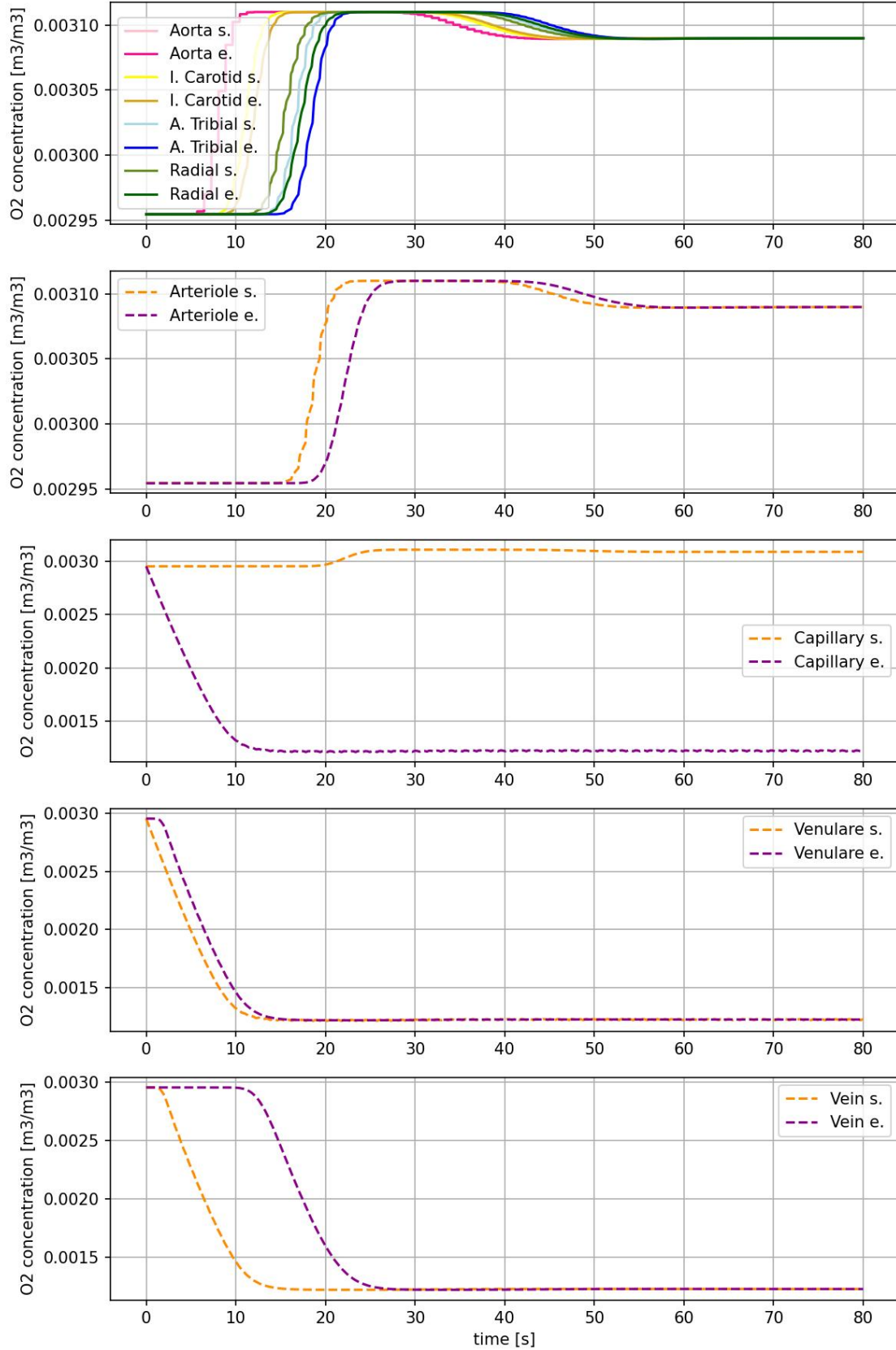


Figure D.2: Plasma O_2 concentration in time. The plot on the top visualizes the concentration for some of the larger systemic arteries modelled in one dimension. The other four plots show the simulation results for the peripheral model corresponding to the posterior tibial. The O_2 uptake in the capillaries can be observed in the middle. s.-start, e.-end.

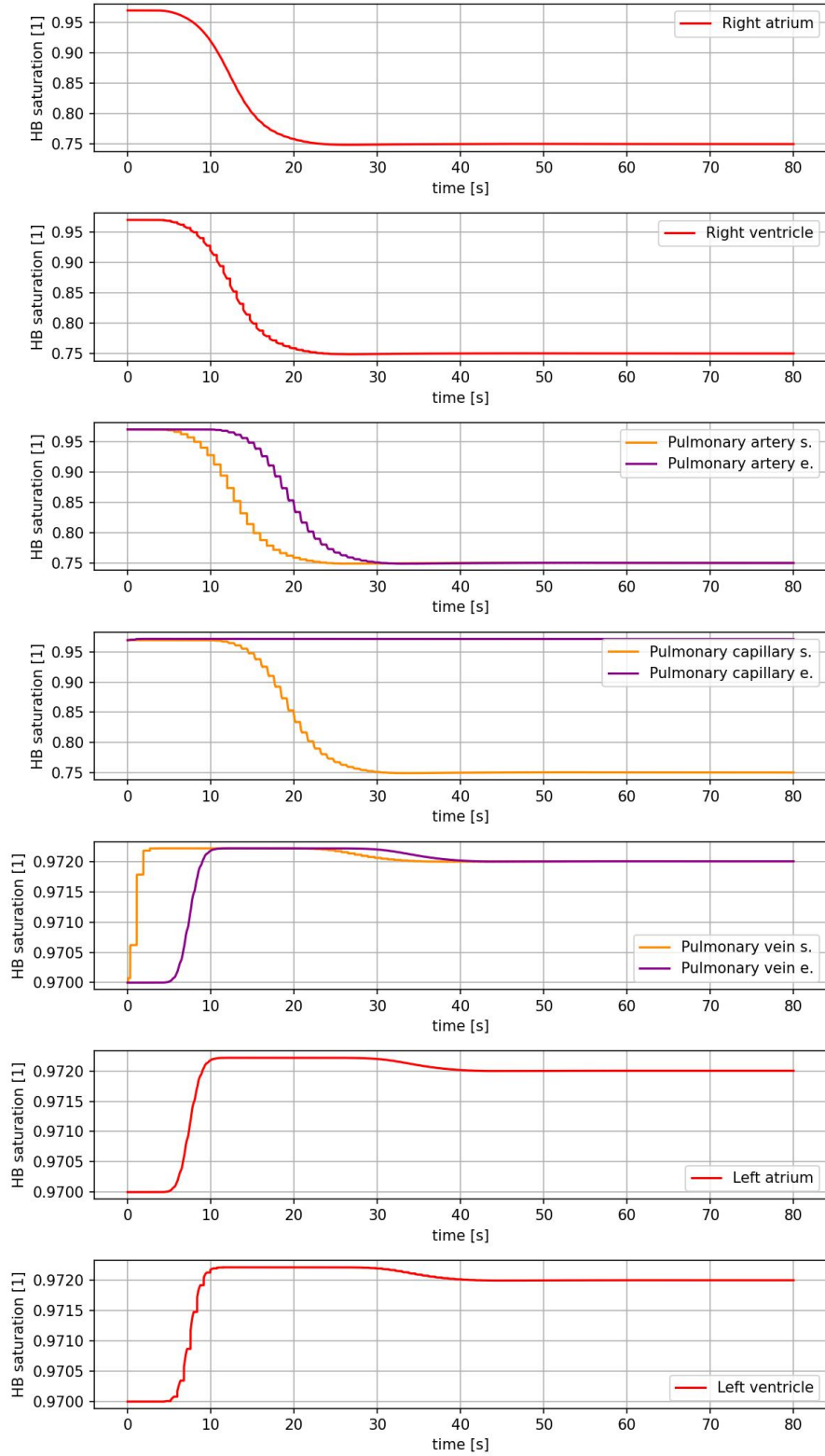


Figure D.3: HB_{sat} concentration in the heart and pulmonary circulation. Similarly to D.1 before and after the pulmonary capillaries the steady-state values correspond to the deoxygenated and oxygenated blood respectively. s.-start, e.-end.

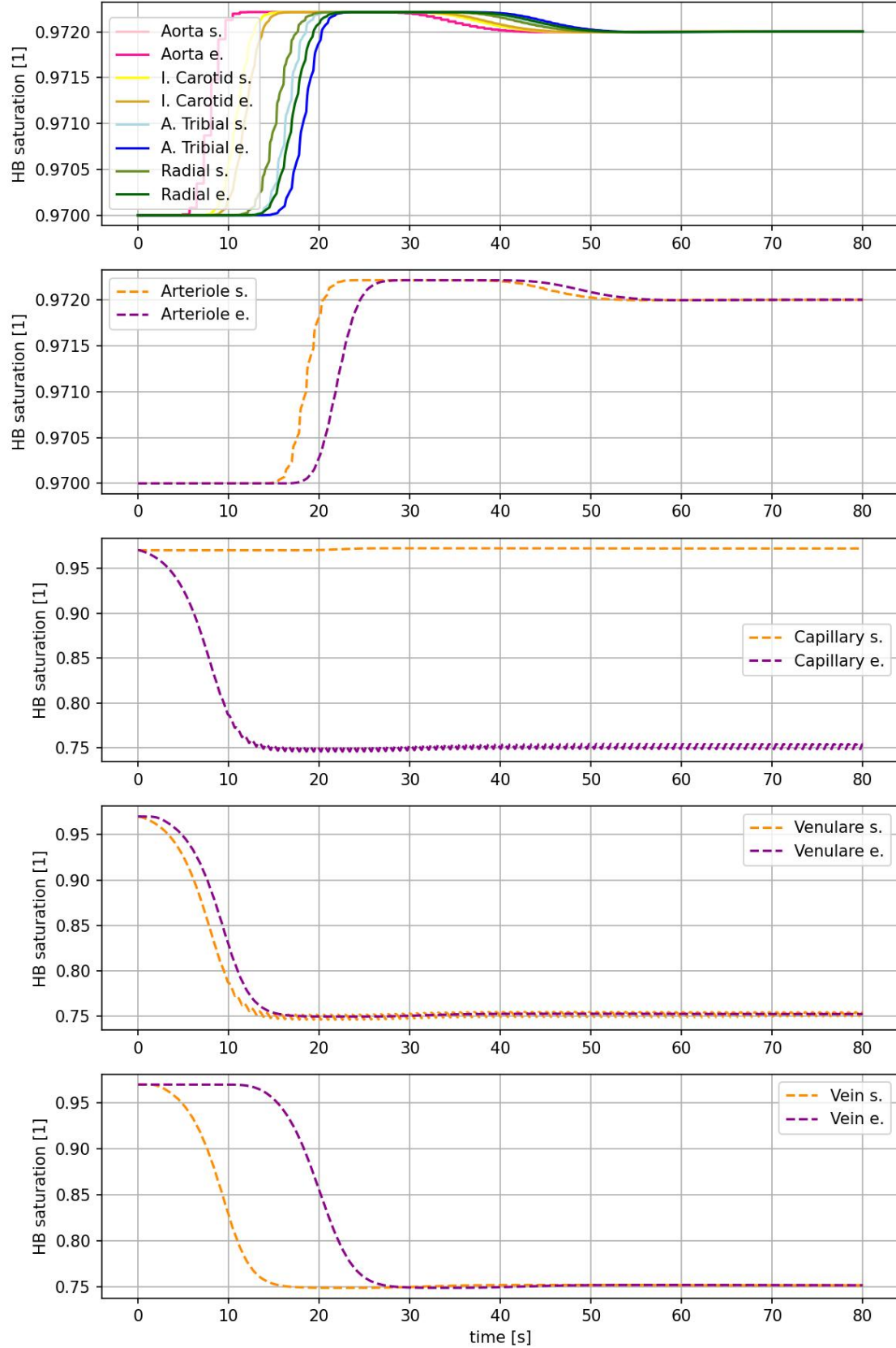


Figure D.4: HB_{sat} concentration in time. Similarly to D.2, the concentration of some arteries modelled in one dimension above the results of the same model corresponding to the posterior tibial. The O_2 uptake in the capillaries can also be observed here as well. s.-start, e.-end.