4 | Testing Framework Description

4.1 Cardiopulmonary interactions testing framework

Based on the requirements derived in <REQUIREMENTS SECTION>, a framework for testing the hypothesis described in <PROBLEM STATEMENT> was derived. The framework consists of a mathematical model of the cardiopulmonary interactions, combined with a testing and validation framework, which together allow for validation of the hypothesis. The architecture of this framework is presented in figure 4.1.

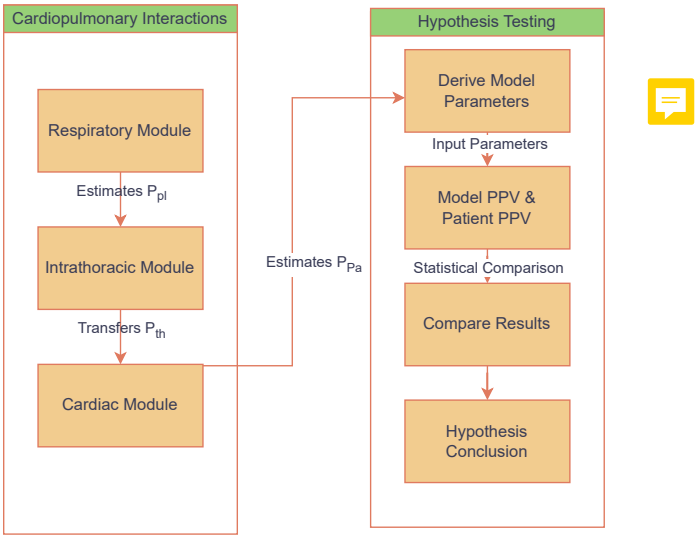


Figure 4.1: Architecture of the integrated mathematical model and hypothesis testing framework

4.1.1 Cardiopulmonary Interactions

Based on the cardiopulmonary interactions described in section 2.7, a mathematical model will be built, which simulates their underlying physiology. This model consists of three modules, each simulating a section of the cardiopulmonary interactions.

Respiratory Module

The respiratory module, aims to simulate the respiratory physiology of a patient undergoing PS MV. The mathematical modelling of the respiratory physiology, will be derived from the EOM.

The ventilator will be implemented as an extension module, integrated within the respiratory module.

Thus, the model will be able to simulate various aspects of the ventilator, such as rise time, cycle variables, PEEP etc.

The respiratory model will also be able to simulate the activation of the patient's respiratory muscles during spontaneous breathing activity.

Intrathoracic Pressure Module

The intrathoracic pressure module, will act as an intermediary module between the respiratory- and cardiovascular module. Thus, it simulates the effect that changes in P_{pl} have on P_{it}, thus enabling transducing of P_{pl} to transmural pressure in the cardiovascular system.

Cardiovascular Module

The cardiovscular module will model the patient's cardiovascular system during MV, allowing for PPV estimation. Thus, the main purpose of the cardiovascular module is to mathematically simulate pulmonary arterial pressure, which will be integrated with the intrathoracic pressure module in order to simulate the patient's PPV.

4.1.2 Hypothesis Testing

In order to test and conclude on the problem statement of chapter 3, a framework will be built to facilitate such testing. The framework will conduct several processes, each facilitating a function necessary to derive a conclusion.

Derive Model Parameters

In the first process of the hypothesis testing framework, parameters necessary for model simulation will be extracted from the patient's data. For a full list of parameters and their method of derivation, please refer to section 5.1.

Model PPV & Patient PPV

In this process, the patients PPV will be extracted from the data, and simultaneously the mathematical model will simulate PPV based on the extracted parameters. Thus, the hypothesis can be tested by comparing the extracted and simulated PPV values.

Compare Results

In this process, the simulated and extracted PPV values will compared via a coefficient of determination,

as well as Bland-Altmann plotting. Thus, it will be possible to conclude on the hypothesis.

Hypothesis Conclusion

Once the simulated and extracted PPV values are compared, it will be possible to draw a conclusion on whether or not it is possible to base P_{mus} estimations on C_{rs} at high PS levels. This conclusion will be made with respect to the assumptions and restrictions of the model.

5 | Methods

5.1 Respiratory Module

The purpose of the respiratory module, is to simulate the patients breathing mechanics during respiration. The module simulates the respirators interaction with the respiratory system, as well as the patient's own spontaneous breathing. The patient's respiratory physiology is thus modelled as a system of governing equations, as well as a set of parameters simulating various respiratory properties.

The respiratory modules parameters and their method of derivation are shown in table 5.1

The respiratory module also takes a number of inputs, which simulate MV settings, characteristica of the respiratory muscle activation, as well as global simulation parameters.

These inputs are shown in table 5.2

During the models simulation of the patient's respiratory mechanics, a number of state variables are logged. The state variables are shown in table 5.3

5.1.1 System of Equations

The underlying mechanics of the respiratory module, consist of a system of governing equations, derived from the respiratory equation of motion (EOM) described in section section 2.2

The system is governed by two time dependant driver functions, as well as a set of differential equations.

5.1.2 Driver Functions

Simulation of the ventilators effect on the patient's respiratory physiology, as well as respiratory muscle activity, are implemented through the use of driver functions.

The driver functions each have time varying pressure profiles, which are build based on assumptions

Parameters	Definition	*Derivation Method*
Mechanical Properties		
C_{rs}	Respiratory system compliance $[\frac{L}{cmH2O}]$	$\frac{\Delta V}{\Delta P}$ at $P_{mus} = 0$
C_{cw}	Chest wall compliance $[\frac{L}{cmH2O}]$	4% of vital capacity
Bulk Properties		
R_{aw}	Arway Resistance $[\frac{cmH2O}{\frac{L}{s}}]$	Least-Square fitting on five breaths at $Pmus$=0

Table 5.1: Parameters of the respiratory module of the cardiopulmonary model

Inputs	**Definition**	**Der**
Vent Settings		
PS	Pressure Support [cmH2O]	PS of timeframe which
PEEP	Positive end expiratory presure [cmH2O]	PEEP setti
PSTrigger	Threshold for ΔP_{pl} needed for activating PS [cmH2O]	Manual
TCT	Total cycle time -> Duration of respiratory cycle [s]	t_{ins}
t_{insp}	Inspiratory time [s]	Positive flow ti
t_{exp}	Expiratory time [s]	Negative flow t
Rise Time	Time from PSTrigger activating till PS level has been reached [s]	20% of t_{insp} (M
RR	Respiratory rate [breaths/minute]	Manually set d
P_{mus} Settings		
Ti P_{mus}	Inspiratory time for respiratory muscles [s]	Same
Te P_{mus}	Expiratory time for respiratory muscles [s]	Sam
P_{mus} Set	Max P_{mus} [cmH2O]	Surrogate P_{mus} calcula
P_{mus} Deflation time	Time from end-inspiratory P_{mus}, untill relaxed diaphragm	Man
P_{mus} Cycle	Threshold for P_{mus} cycling off [L/min]	Man
Simulation Parameters		
Δt	timestep at which model is simulated [s]	Synchronized with
Simulation length	Total length of simulation [s]	manually set d
Expiratory time constant	Time for respiratory system to empty 63% [s]	Man

Table 5.2: Table of the inputs needed to simulate patient breathing cycle

State Variables	Definition	Derivation Method
P_{ao}	Pressure at airway opening [cmH2O]	$\frac{\Delta V}{C_{rs}}$
$\dot{V}$	flow [L/min]	$\frac{P_{ao}-P_{pl}}{R_{aw}}$
V	Volume [L]	$\dot{v} * \Delta t$
P_{pl}	Pleural pressure [cmH2O]	$\frac{V}{C_{cw}} + P_{mus} + P_{ao}$

Table 5.3: State variables of the respiratory module of the cardiopulmonary model

derived from knowledge of human respiratory physiology, as well as knowledge of the inner workings of MV.

Pvent profile

The profile of the inspiratory driver function has two states.

The states relate to whether drop in P_{pl} has reached the threshold set in the PSTrigger input variable.

eq. (5.1) describes the time dependant relationship of P_{vent} if PSTrigger has not been reached.

$$P_{vent}(t) = PEEP \mid \ if P_{pl} > PSTrigger \tag{5.1}$$

Thus, if P_{pl} has not dropped below the PSTrigger threshold, the pressure delivered by the ventilator will equal PEEP.

Eq 5.2 describes the time dependant relationship of P_{vent}, if the PSTrigger threshold has been reached during the respiratory cycle.

$$P_{vent} = \begin{cases} PS * \frac{t}{t_{rise}} + PEEP & \text{if } 0 < t \leq t_{rise}(1) \\ PS + PEEP & \text{if } t_{rise} < t \leq t_{insp}(2) \\ PS - (PS * (\frac{t}{t_{deflate}} + PEEP) & \text{if } t_{insp} < t \leq t_{insp} + t_{deflate}(3) \\ PEEP & \text{if } t_{insp} + t_{deflate} \leq TCT(4) \end{cases} \tag{5.2}$$

Eq 5.2 consists of 4 phases.

1. When PSTrigger is activated, the vent starts delivering pressure.This pressure rises from PEEP to PS over the course of t_{rise} [Hess R., 2014].
2. When P_{vent} reaches PS, it remains there for the remainder of inspiration.
3. At the end of inspiration, pressure delivery decreases, reaching PEEP after $t_{deflate}$ has passed.
4. Until start of next inspiration, PEEP remains 0.

Pmus profile

The profile of the P_{mus} driver function simulates the pressure exerted by the patient's respiratory muscles.

For a patient undergoing MV, P_{mus} is mainly exerted by contraction of the diaphragm, but if forced breathing occurs, the external- and internal intercostals would aid in P_{mus} generation.

The P_{mus} profile is infused with physiological knowledge regarding the nature of P_{mus} generation, which constitutes that P_{mus} rises monotonously during inspiration, decrements monotonously during expiration, and remains 0 between expiration and inspiration [Vicario et al., 2015].

Due to the monotonic and cyclical nature of SB at rest, the P_{mus} profile is implemented as a sine wave, with varying periods and phase shifts.

The P_{mus} profile has two states. The first state simulates a full inspiratory and expiratory cycle. The second state ends the inspiratory phase and begins expiration, once the flow threshold for the P_{mus} cycle variable is reached. The two states enable simulation of a full spontaneous breathing (SB) cycle, as well as prematurely ending the cycle if P_{mus} cycle variable is reached due flow caused by increase in P_{vent}.

$$P_{mus} = \begin{cases} P_{musSet} * sin(\frac{\pi}{2*Pmus_{ti}} * t) & \text{if } 0 < t \leq t_{P_{musti}}(1) \\ P_{musset} * sin(\frac{\pi(t+t_{deflate}-2*t_{insp})}{2*(t_{deflate}-t_{insp})} & \text{if } t_{insp} < t \leq t_{deflate}(2) \\ 0 & \text{if } t_{deflate} < t \leq TCT(3) \end{cases} \tag{5.3}$$

Eq 5.3 is derived from [Vicario et al., 2015], and consists of 3 phases.

1. The inspiratory phase has a period of $\frac{\pi}{2}$. When t = P_{musti}, P_{mus} reaches the set level.
2. The expiratory phase has a period of $\frac{\pi}{2}$. $t_{deflate}$ is assumed to always be shorter than t_{insp} - thus, P_{mus} will decrease as it reaches 0.
3. In the third phase, P_{mus} is 0 until the beginning of the next respiratory cycle

5.1.3 Differential Equations

The governing equations of the respiratory module, are implemented as a set of differential equations derived from the EOM

As depicted in figure A.0.1, the part of the respiratory module comprising the system of equations, can be described in the following pseudocode:

for Δt *in* TCT

1. $P_{mus} = P_{musdriver}$

2. Calc ΔP_{mus}
3. $P_{vent} = P_{ventdriver}(t)$
4. Calc flow(t)
5. Calc ΔV
6. Calc ΔP_{ao}
7. Calc ΔP_{pl}

End

Eq 5.4 describes how change in P_{mus} is calculated

$$\Delta P_{mus} = P_{mus}(t) -_{Pmus} (t-1) \tag{5.4}$$

In eq. (5.4), ΔP_{mus} is calculated by the output of the P_{mus} driver function at t-1 subtracted from the output at t.

The change in flow at Δt is described in eq. (5.5)

$$flow = \frac{P_{ao}(t) - P_{pl}(t)}{R_{aw}} \tag{5.5}$$

Similar to electron flow in an electrical circuit, eq. (5.5) describes how airflow is calculated as the pressure difference between two nodes over a resistance. In the case of the airways, the first node is P_{ao}, the second node is P_{pl}, and resistance is R_{aw}.

The change in V at Δt is described in eq. (5.6).

$$\Delta V = flow * \Delta t \tag{5.6}$$

The relationship described in eq. (5.6), is derived from the knowledge that volume is the definite integral over flow duration, as described in eq. (5.7).

$$V_t = \int_{start\dot{V}}^{end\dot{V}} \dot{V}\, dt \tag{5.7}$$

Thus, flow can be expressed as the derivative of V as described in eq. (5.8), from which eq. (5.6) is derived.

$$\dot{V} = \frac{\Delta V}{\Delta T} => \Delta V = \dot{V} * \Delta t \tag{5.8}$$

Change in P_{ao} at Δt is described in eq. (5.10).

$$\Delta P_{ao} = \frac{\Delta V}{C_{rs}} \tag{5.9}$$

This relationship is derived from the fact that $C = \frac{\Delta V}{\Delta P}$. Since C_{rs} has been estimated from the patient data prior to model simulation, and V has been calculated, P_{ao} can be calculated as described in eq. (5.10).

Change in P_{pl} at Δt is described by eq. (5.10)

$$\Delta P_{pl} = \frac{\Delta V}{C_w} + \Delta P_{mus} + \Delta P_{ao} \tag{5.10}$$

This relationship derived from the EOM, and originally described as eq. (5.11) in Mauri et al. [2017].

$$P_{mus} = \frac{\Delta V}{C_w} - \Delta P_{es} \tag{5.11}$$

Eq 5.10 has been rearranged from eq. (5.11) to output P_{mus}, and assumes that P_{es} can be substituted for P_{pl}.

5.2 Intrathoracic Pressure Module

The purpose of the intrathoracic pressure module, is to simulate the effect of P_{pl} on P_{it}.

As described in section section 2.7, changes in P_{pl} are transduced to changes in P_{it}, which enact changes in the transmural pressures affecting the cardiovascular system.

5.2.1 Equations

The equation underlying the intrathoracic pressure module is described in

$$P_{it} = P_{pl} * \alpha \tag{5.12}$$

It is derived from Cushway et al. [2022] The physiology underlying eq. (5.12), assumes that during transduction from P_{pl} to P_{it}, there will be a pressure loss due to factors such as elasticity of intrathoracic tissue and differing volumes between the pleural cavity and intrathoracic cavity. This pressure loss is described by the factor α.

5.3 Cardiovascular Module

The base model for the system of equations governing the CVS is based on the CircAdapt model. CircAdapt is a full heart model, build as a hierarchy of components, simulating the physiology of various anatomical structures of the heart. Four types of structural components exist, as well as a global component governing the timing of the heart.

Fig 4 shows examples of how each component relates to the CVS.

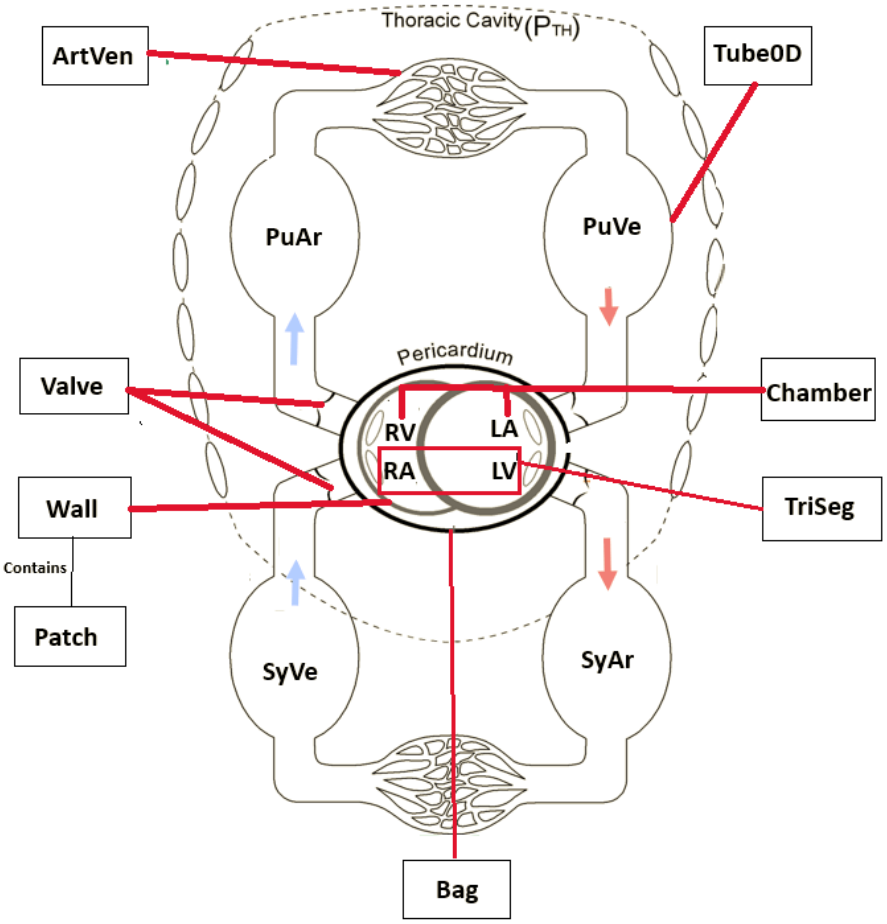


Fig 4 examples of how the components of the CircAdapt framework relate to the CVS. ArtVen models the bloodflow between arteries and veins. Tube0D models the pressure/volume relationships of vessels. Valve models bloodflow between compartments of the CVS. Wall contains the Patch module, and combined they model surface area and myocardial contraction of each compartment. Chamber models the atria. TriSeg models the ventricles, and lastly Bag models the pericardium.

The four component types will be presented individually.

5.3.1 Node Component Hierarchy

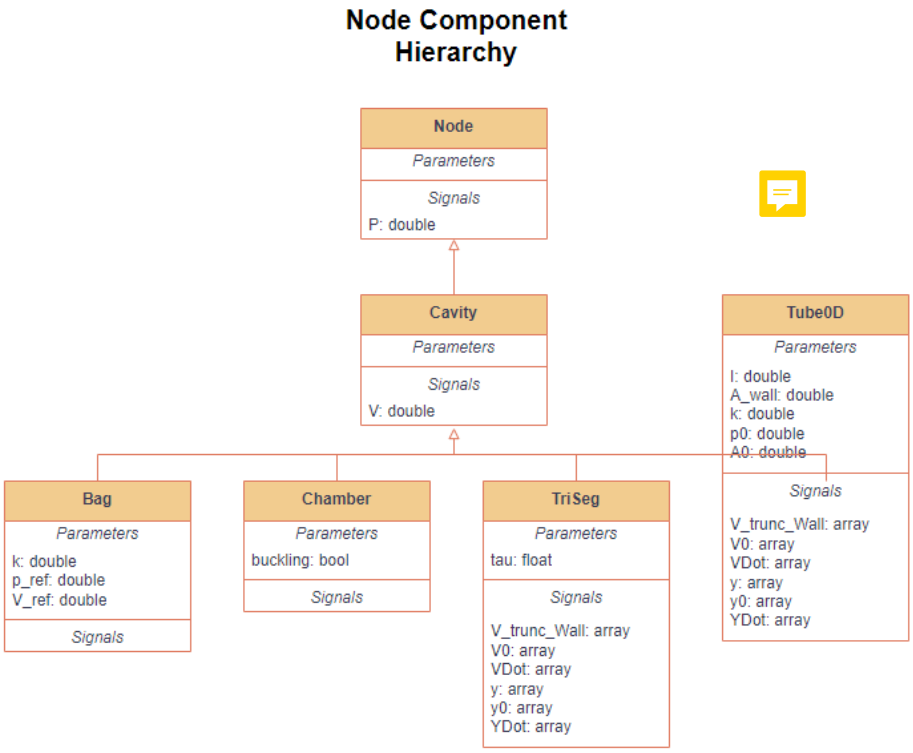


Figure 5.1: Caption

Node

Node is the parent object of all node-type components, is an object with pressure as a state variable.

Cavity

A cavity component Is a child object of the node component, with the volume state variable, related to the pressure inside the cavity.

Four child objects are derived from the cavity component.

Bag

The Bag component simulates the pericardium. It encapsulates all other components which constitute the heart. Thus, it adds a transmural pressure to the heart, related to the time-dependent volume of the components of the heart.

Eq 11 shows how the governing equation of transmural pressure within the Bag component:

$$p_{transmural(V)} = p_{ref} * \frac{V^k}{V_{ref}} \ (eq\ 11)$$

Chamber

The chamber component simulates atria of the heart. It has a volume and a pressure, as well as wall and patch components governing the behavior of the chamber.

Chamber has two governing equations. The first calculates wall tension, the second calculates pressure.

The equation governing wall tension is described in eq 12:

$$T = \frac{\Delta t}{\Delta Am} - (A_m - A_{m,0}) \ (eq\ 12)$$

Where T is wall tension, A_m is wall area, and A_{m0} is the zero-tension midwall area.

The equation governing pressure inside the chamber is described by eq 13:

$$p_c = \frac{T * \Delta A_m}{\Delta Vm}$$

Where V_m is the mid-wall volume.

TriSeg

The TriSeg component models the left and right ventricles of the heart, as a connected segment separated by a wall.

The volume encapsulated by the walls of the right- and left ventricles is defined by the governing equations

described in eq 14 and eq 15:

$$V_{Left} = V_{cLeft} + 0.5 * V_{wLeft} + 0.5V_{wSeptal} \ (eq\ 14)$$

$$V_{Right} = V_{cRight} + 0.5 * V_{wRight} + 0.5V_{wSeptal} \ (eq\ 15)$$

Where V_c is the volume of the cavity, V_w is the volume of the midwall, and $V_{wSeptal}$ is the volume of the septal wall.

Tube0D

The Tube0D component models the pressures and volumes inside the vessels of the CVS.

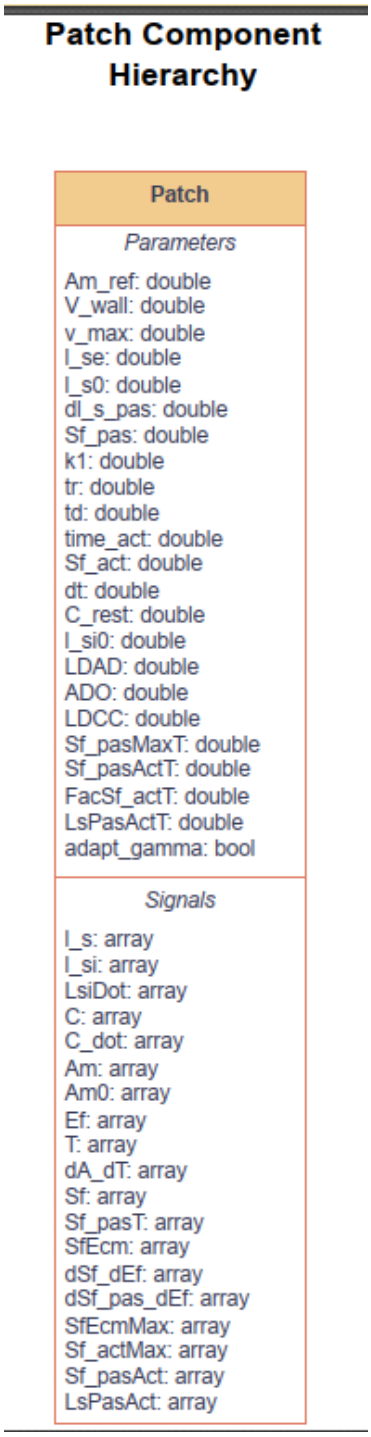
The governing equations for area of the tube is described in eq 16:

$$A = \frac{V}{Len}$$

Where A is the area, V is the volume and Len is the length of the vessel

Eq 17 describes the governing equation

5.3.2 Patch Component Hierarchy



The patch component models the contraction of the myocardial muscle tissue. It assumes that all sar-

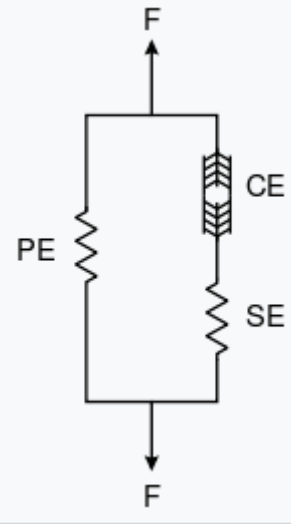


Figure 5.2: Caption

comeres are identical in size and force generation.

Each sarcormere is modelled as a three-element Hill contraction model, depicted in fig 5.

Fig 5 The Hill Contraction Model. Sarcomeres are modelled as a contractile element (CE), which pull on a series elastic element (SE). Examples of SE are tendons, apnoeurosis or the proteins of the extracellular matrix (ECM). In parallel with the SE, a parallel elastic element (PE) is passively pulled upon. Examples of PE's are cell membrane and connective tissues.

Eq 17 governs the rate of change of the length of the sarcomeres:

$$\frac{\Delta l_{si}}{\Delta t} = v_{\max} * \left(\frac{l_s - l_{si}}{l_{se}} - 1 \right) (eq\ 17)$$

Where v_{max} is the sarcomere shortening rate, l_s the initial sarcomere length, l_{si} the current sarcomere length and l_{se} the length of the SE.

The contractility curve, representing the density of cross-bridges in the sarcomere, is governed by eq 18:

$$\frac{\Delta C}{\Delta t} = \frac{C_L\,(l_{si})\,1}{\tau_{rise}} * F_{rise}(t) - \frac{C}{\tau_{decay}} * g(X)(eq\ 18)$$

Where $\tau = 0.33 * T_d * t_{duration}$, $F_{rise}(t)$ is the activation function, $C_L(l_{si})$ the crossbridge formation

function and g(X) the decay function.

Eq 18 has two function components. One describes the amount of cross bridges at a given time, the second component describes the decay of cross bridges at the given time. The ΔC is thus defined, by the change in cross-bridge formations vs. cross-bridge decays.

5.3.3 Connector component hierarchy

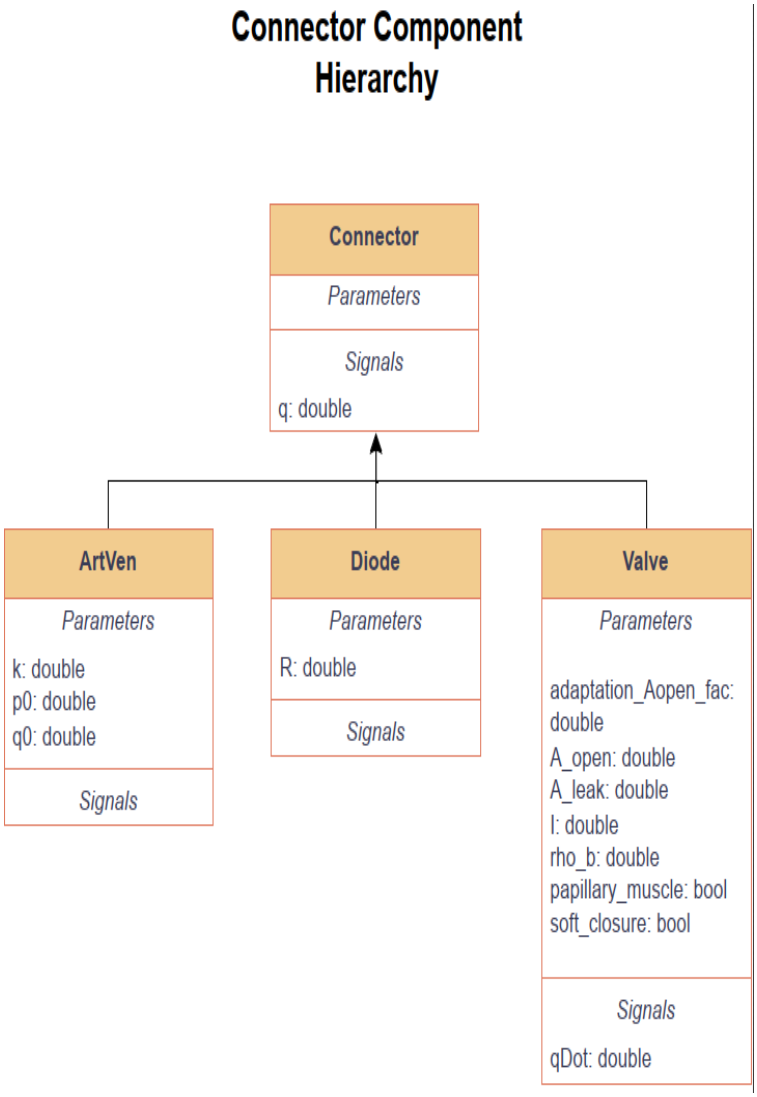


Figure 5.3: Caption

Connectors are components allowing bloodflow between nodes. CircAdapt actively uses two types of connectors, the ArtVen and Valve components.

ArtVen

ArtVen, short for arteriovenous, models the bloodflow at the pulmonary- and systemic capillaries between the arteries and veins.

The bloodflow is governed by eq 20:

$$q = \Delta p * q_0 \left(\frac{|\Delta p|}{p_0} \right)^k \quad (eq\ 20)$$

Where q is flow, Δp is change in pressure, q_0 is initial flow and k is an exponent constant

Valve

The valve component models flow between nodes. In the full CVS model, the valve component is responsible for simulating the flow between the atrioventricular valves (mitralvalve and tricuspid valve), as well as the ventriculoarterial valves (aortic valve and pulmonary valve).

Flow through the valve is governed by the unsteady Bernoulli equation, described in eq 21

$$\frac{\Delta q}{\Delta t} = \frac{A_{valve}}{l_{valve}} \left(\frac{\Delta p}{\rho} - \frac{1q * |q|}{2} * \left(\frac{1}{{A_{valve}}^2} - \frac{1}{{A_p}^2} \right) \right)$$

With ρ being blood density, l_{valve} being length of the valve, A_{valve} is cross sectional area of the valve, A_p is cross sectional area proximal to valve.

For the unsteady Bernoulli equation to be applicable, the valve component assumes that:

- Gravity can be ignored
- Inertia is estimated through $E_{kin} = 0.5Lq^2$
- Velocity is estimated through flow divided by area
- Flow entering the valve has all pressure-flow energy converted to kinetic energy
- Flow out of the valve does not regain pressure, due to loss of energy from turbulence

5.3.4

5.3.5 Wall Component Hierarchy

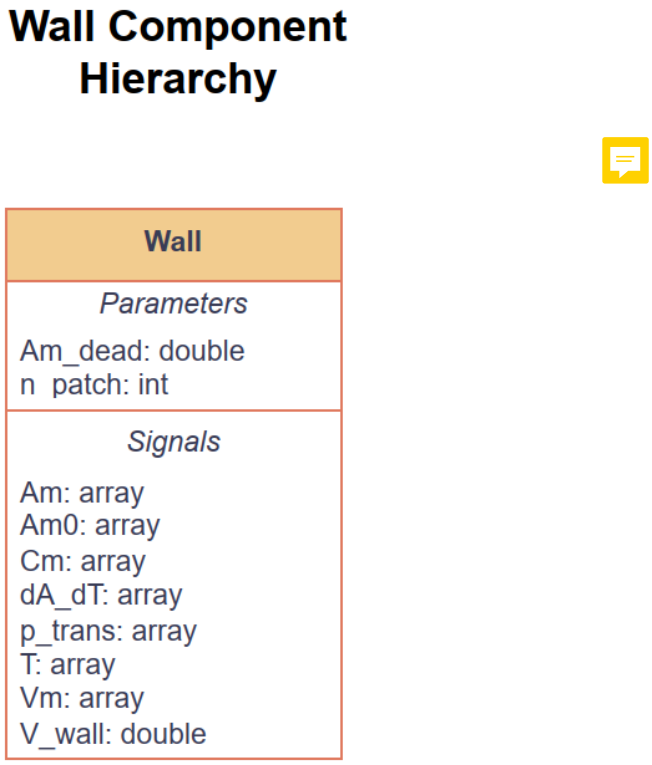


Figure 5.4: Caption

5.4

5.5 Hypothesis Testing

The following section describes the purpose and contents of the framework described in section 4.1 which was build in order to test and conclude on the hypothesis.

5.5.1 Derive Model Parameters and Inputs

The first process in the testing framework, is an extraction of the parameters necessary to model the patient's breathing mechanics.