Cardiopulmonary model

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# Purpose of Cardiopulmonary model

The model consists of three modules, each simulating various physiological mechanisms within the cardiopulmonary system. The output of the model is a simulated PPV signal, which will be validated against clinically measured PPV signals.

Fig 1 shows the high level architecture of the model, as the integration of all individual modules and their input-output relationships.

A diagram of a model

Description automatically generated

*Fig 1 The high level architecture of the cardiopulmonary model. The model consists of 3 modules which combined simulate the cardiopulmonary interactions, as well as a validation module providing quantifiable metrics of the models performance.*

# Respiratory Module

## Underlying models

The mathematical model of the respiratory system is derived from the linear single order compartment model of the lungs (LSOCML), depicted in fig 1.

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*Fig 1 The linear first-order single-compartment model of respiratory mechanics. It depicts the lungs as a compartment with mechanical properties Raw and C. Pressure is delivered as a combination of the ventilator (Pvent) and respiratory muscles (Pmus).V corresponds to the volume expansion and deflation from* ΔP *.*

From LSOCML, what is known as the respiratory equation of motion (EOM) can be derived, described in eq 1

The LSOCML can be expanded to describe further details of the respiratory system and transcribed into its electrical analogue, as seen in fig 2

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*Fig 2 The expanded LSOCML, comprised of two compartments - the lung and the chest wall.*

*The lung is described by pressure at airway opening (Pao), airway resistance Raw, alveolar pressure (Pal) and lung elastance (EL).*

*The chest wall is described by pleural pressure (Ppl), chest wall resistance RCW, chest wall elastance ECW and pressure exerted by the respiratory muscles (Pmus)*

The expanded LSOCML serves as the base model for the model of the respiratory system. It thus contains all the variables and parameters of interest necessary in order to simulate the intrathoracic pressure (Pth) affecting the patient’s PPV.

## Respiratory Module Implementation

Table 1 shows which parameters govern the behavior of the model. They are delineated by parameter types and are shown alongside the methods by which they are derived.

|  |  |
| --- | --- |
| **Parameters** | **Derivation method** |
| ***Mechanical Properties*** |  |
| CL | at Pmus=0 |
| CW | Model fitting |
| ***Bulk Properties*** |  |
| RW | Model fitting |
| RL | Model fitting of patients Pao |
| ***Vent Settings*** |  |
| Pvent | Extracted from patient’s data |
| PEEP | Extracted from patient’s data |
| Respiratory Rate | Set by clinician |
| ***Patient/Conditional Parameters*** |  |
| Pmus | Customizable |
| Ppl | Patient’s Ppl at Pmus = 0, customizable |
| Inspiratory/Expiratory ratio | Customizable |

*Table 1 An overview of the models parameters, delineated by their parameter type*

Table 2 shows the models state variables, alongside their method of derivation.

|  |  |
| --- | --- |
| **State Variables** | **Derivation method** |
| Pao | R\*Q+E\*V+PEEP |
| Palv | ΔPalv = ΔV/C  Palv = Palv + Δpalv |
| Flow (Q) | Q = (Pao-Palv)/R |
| V | ΔV = Δt |

*Table 2 The state variables of the model, alongside the method by which they are derived*

## Algorithm

The state variables of the model are calculated as a system of ordinary differential equations (ODE). This means that they have an initial condition, and a solving algorithm estimates the next output of the function at a given timestep. An example of such an ODE solving algorithm is the 4th order Runge-Kutta method (implemented via Matlabs ode45())

1. **Calibrate parameters**

In this step, CL, CW, RW and RL are calibrated.

**CL calibration**

Calibrating CL assumes that patient respiratory effort is negligible at high levels of PS, and thus Pmus=0. At this setting, CL is calibrated as the average CL over five stable breaths.

Calibration requires the patient to be ventilated at high PS levels (≥18cmH2O). Once the patient’s breathing patterns have stabilized, CL is calculated as in eq 2

Eq 2 requires Vt. Vt is derived from the inspiratory flow signal, as shown in eq 3:

By convention, inspiratory flow is positive and expiratory flow negative, and thus inspiratory flow is calculated by integrating all positive values of flow for each breath.

**RL Calibration**

RL is calibrated in a manner similar to CL, by using patient data from five breaths, to optimize the RL value.

Pao is calculated according to eq 4:

Thus, by having the patients Pao and flow data, as well as the calibrated CL, RL can be calculated as the average RL over five breaths.

**Ccw and RCW calibration**

Ccw and Rcw are calibrated over five stable breaths

1. **Input settings**

The model requires a number of input settings, which set the parameters governing the respiratory pattern to be investigated.

These settings are the patients Pmus, Inspiratory- and expiratory time, and the Ppl at end-expiration.

**Pmus setting**

The function of the Pmus setting, is to investigate how the patients PPV responds to different levels of patient effort. Thus, by combining the simulation of PS and Pmus over a respiratory cycle, it is possible to simulate how a given patient would respond in a variety of clinical situations.

**Inspiratory- and expiratory time**

In a clinical setting, the inspiratory- and expiratory time can possibly be calibrated from researching the patients respiratory pattern. The inspiratory- and expiratory times are assumed to be normally distributed, and thus the set values will differ over the simulated respiratory cycle.

**Ppl setting**

For simulation purposes, Ppl is assumed to be within -3cmH2O and -5cmH2O. However, since Ppl at end-expiration can vary both inter- and intra patiently, and Ppl is not uniform throughout the pleura, the model allows for a variation of this parameter in order to simulate the desired conditions.

1. **Calculate flow**

Flow is calculated as the pressure difference between Pao and Palv. This relationship is described in eq 5:

At end-expiration, Palv and Pao are equal to the set PEEP. As the ventilator reaches its PS setting, the Pao and Palv will gradually increase at every Δt, as the air enters through the inspiratory line and settles in the alveoli.

1. **Calculate Palv**

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As air flows from the ventilators inspiratory line to the patient’s alveoli, the pressure changes. This change in pressure can be is modelled by the flow at every timestep, over the patients CL, as described in eq 6:

The change in pressure is then added to the pressure at the previous timestep, as described in eq 7:

1. **Calculate Volume**

The patient’s flow curve is the derivative of the patient’s volume status. Change in lung volume is therefore the consequence of air flowing into the lungs over time, as described in eq 8:

1. **Calculate Pao**

Pressure at the patient’s airway opening (Pao), is a result of delivered flow and volume expansion. Thus, at the beginning of inspiration, Pao is equal to PEEP, and as the ventilator reaches its PS target, Pao subsequently increases. Pao at a given time can be described by eq 9:

1. **Calculate Ppl**

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Normally, baseline Ppl is assumed to be between -3cmH2O and -5cmH2O. In this model, baseline Ppl is adjustable to accommodate various patient conditions.

The patient’s Ppl vary based off two external factors. The first factor is ΔPpl as a result of ΔVL caused by ΔPalv. This relationship is assumed to be α\*ΔVL. The second factor is ΔPpl as a result of ΔVpl caused by respiratory muscle activation, Pmus.

Thus, ΔPpl can be described by eq 10:

# Intrathoracic Module

Fig 3 shows the abdominal and intrathoracic cavity, with the electrical analogues of the respiratory and cardiovascular system (CVS) depicted.

A diagram of a flowchart

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*Fig 3 The abdominal and intrathoracic cavity. The organs and anatomical structures of interests within these cavities have been modelled as electrical analogues. Furthermore, the pericardial sac is shown to contain the heart.*

Since the respiratory systems and the CVS are contained within the same cavity, pressure changes within the intrathoracic cavity affect them both.

The most significant of these are changes to pressure within the pleural cavity, Ppl. These changes have correlate with several corresponding significant physiological effects within the heart. All of these changes are directly associated with changes in transmural pressures.

Changes in Ppl correspond to changes in intrathoracic pressure (Pth) by a factor α. Thus, their relationship can be described by eq 11:

In the system of equations governing the model, Pth will be added as a transmural pressure factor on the CVS module.

# 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.

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*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.

## Node Component Hierarchy

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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:

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:

Where T is wall tension, Am is wall area, and Am0 is the zero-tension midwall area.

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

Where Vm 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:

Where Vc is the volume of the cavity, Vw is the volume of the midwall, and VwSeptal 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:

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

Eq 17 describes the governing equation

## Patch Component Hierarchy

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The patch component models the contraction of the myocardial muscle tissue. It assumes that all sarcomeres are identical in size and force generation.

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

A diagram of a circuit

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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:

Where vmax is the sarcomere shortening rate, ls the initial sarcomere length, lsi the current sarcomere length and lse the length of the SE.

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

Where , Frise(t) is the activation function, CL(lsi) 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 is thus defined, by the change in cross-bridge formations vs. cross-bridge decays.

## Connector component hierarchy

A diagram of components

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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:

Where q is flow, is change in pressure, q0 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

With being blood density, lvalve being length of the valve, Avalve is cross sectional area of the valve, Ap 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 Ekin = 0.5Lq2
* 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

## Wall Component Hierarchy

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# Model Validation