Université de Liège

GBIO0014-2 - In Silico Medicine Project 2023-2024

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Introduction

ARDS (Acute Respiratory Distress Syndrome) is a life-threatening lung injury that allows fluid to leak into the lungs, thus reducing the lungs' ability to take in oxygen and expel carbon dioxide, leading to severe respiratory failure [1]. Understanding such a severe condition is crucial for enabling better treatment and care.

In this project, we will use various numerical models to study different pulmonary processes in pigs. We will focus on the comparison between healthy pigs and pigs with ARDS. We will also use the term 'patients' to refer to pigs.

In practice, this document is organized as follows : the first part is dedicated to a description of the 'crude' observations - i.e. without the need for a particular model of lung mechanics - that can be made on both healthy and sick patients. These observations and statistical results, based solely on empirical data, provide a first approach to understanding the impact of ARDS on breathing. In the second part, we propose to use a single-compartment model of lung mechanics to study the impact of disease on the model's various parameters. By using a physiological interpretation of these parameters, we can establish an initial understanding of disease mechanisms. Finally, the third and last part introduces a two-compartment model, more complex than in the second part, to deepen and increase the complexity of our understanding.

1 Analysis of P-V and Q-V loops

The analysis of pressure-volume and flow-volume loops can provide multiple insights into a patient's condition. One can extract lung compliance, the work of breathing, as well as various lung volumes and flows. These parameters are significantly affected when the patient is ill, such as with ARDS. Hence, it is worthwhile to study them, as we will do in the following subsections.

It seems important to us to delve into how we extracted the different respiratory cycles from the raw data provided to us. Indeed, the pigs were volume-controlled throughout the duration of the experiment : the volume was therefore numerically reset to 0 at the beginning of each respiratory cycle recording.

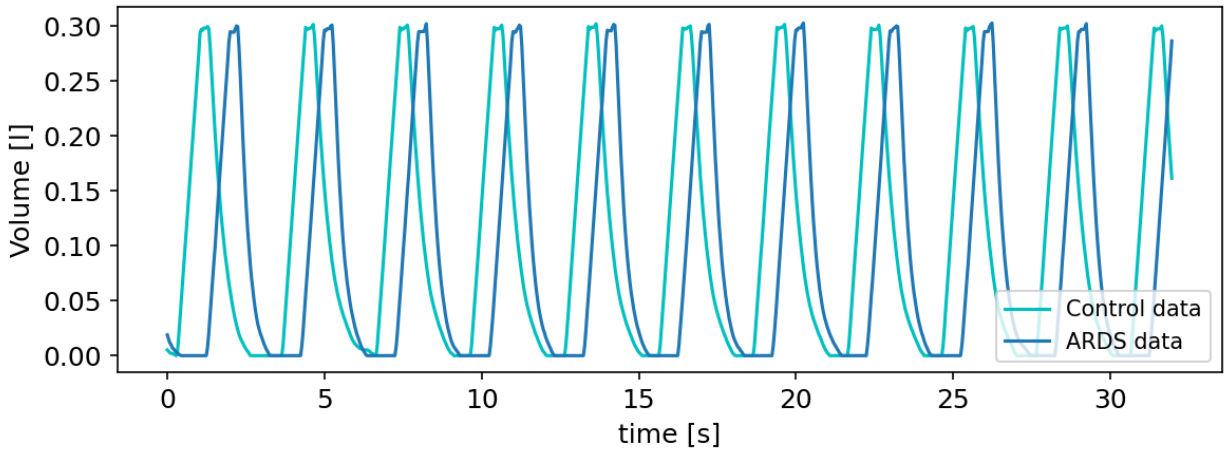


FIGURE 1 – Pulmonary volume over time for the two datasets. *10 complete cycles of breathing are identified.*

This is why we decided to delimit our cycles based on this initial volume reset in the lungs. Each cycle starts when the volume is zero and ends when it returns to a zero value, meaning that the respiratory cycle is complete. The pressure and flow values can be somewhat inaccurate and filled with digital artifacts during the time the volume is artificially forced to 0. This is also one of the reasons why we delimited our cycles based on volume.

1.1 Pressure-Volume Loops

You can see in Figure 2 that the inspiratory phase is separated from the expiratory phase by the blue y line drawn within the cycle : this separation was made according to the flow variation.

Indeed, it seemed obvious to separate inspiration from expiration based on flow rate (see the next section for a graphical visualization). Flow rate, theoretically, expresses nothing other than the variation in volume in the lungs over time. When the flow rate changes sign, it indicates a change in the respiratory phase. If the flow rate is positive, air enters the lungs, which solely defines the inspiration phase.

When the flow rate decreases to return to 0, the end of the inspiratory phase is reached : no more air enters the lungs. Then the flow rate becomes negative, and expiration begins as the volume decreases in the lungs : air is therefore exhaled.

A surprising observation is that the volume does not decrease as soon as the flow rate becomes negative. The underlying mechanism is not exactly clear, and further research could be carried out. Hypotheses that are possible explanations for this phenomenon are :

- Artifacts introduced by the hardware and the way in which quantities are measured. We can imagine that the sensors are not placed in the same place, which could introduce a phase difference that translates into a delay.
- The lungs' elastic properties and the inertia cause a lag in the system. When the flow rate turns negative (indicating the beginning of expiration), the lung tissues are still in the process of stretching and expanding due to the preceding positive flow. This results in a continued increase in volume for a short period.
- Non-elastic properties of the lungs could introduce complex phenomena such as the one observed.
- ...

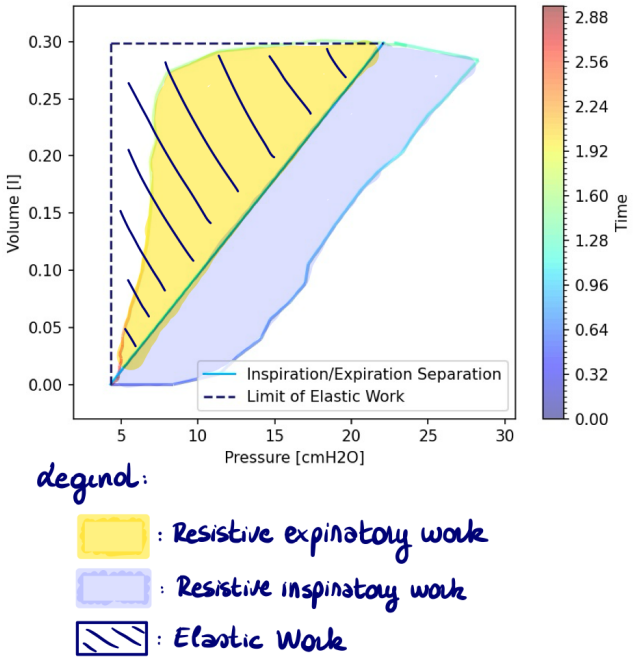


FIGURE 2 – Separation of the different works on the Pressure-Volume curve

The different components of the Work of breathing can be described as :

- The resistive inspiratory work, taking place during the inspiration phase, that refers to the work required to overcome the resistance of the airways during inspiration.
- The resistive expiratory work, representing the energy expenditure by the respiratory muscles to exhale air against resistance.
- The elastic work, deployed to overcome the elastic resistance of the lungs, thus including the resistive expiratory work ([10]) like described in Figure 2.
- Finally, the work of breathing is the sum of the elastic work and the resistive works, so Work Of breathing = Elastic work + Resistive Inspiratory Work ; Elastic Work already includes Resistive Expiratory Work.

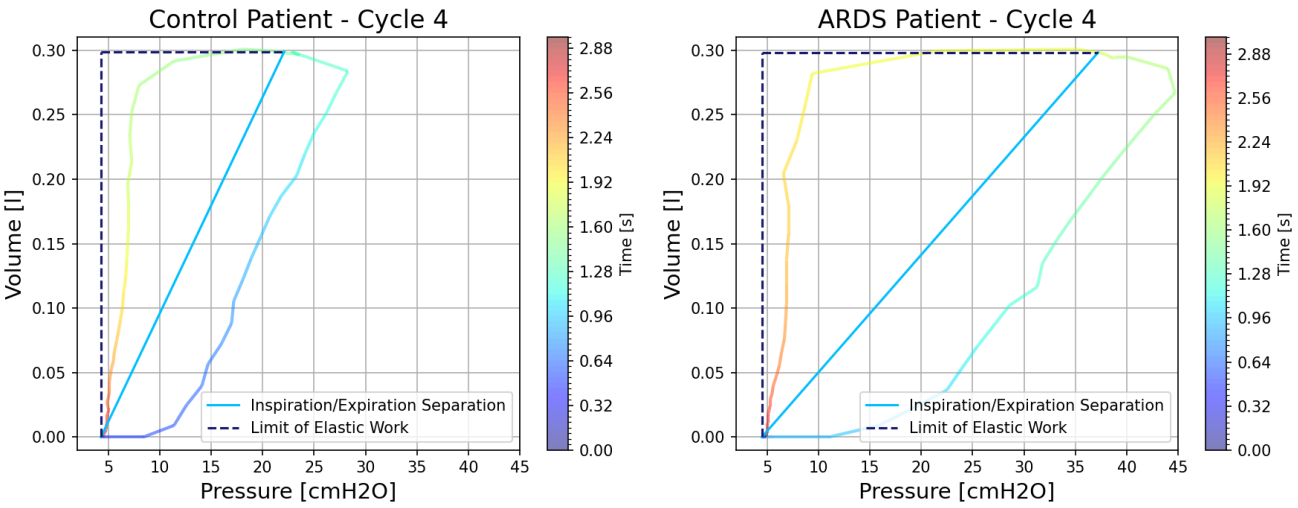


FIGURE 3 – fourth P-V loop for both Control and ARDS Patients

Here we extracted one Pressure-Volume cycle (the fourth one, arbitrarily) for both Control and ARDS patients. The values of the different works can be easily extracted from those specific curves, but knowing that the dataset that was provided to us contains 10 complete cycles of respiration 1, we preferred to analyze the different works statistically over the whole dataset, thanks to their different quantiles (minimum, Q25, median, Q75, maximum values) (see Table 1).

The works were obtained by numerical integration using the `trapz` function from `numpy`.

Control	min	Q25	Q50	Q75	max
Work Of Breathing $[l \cdot cmH_2O]$	4.48537203	4.54881432	4.60966463	4.66407152	4.71496607
Resistive Inspiratory Work $[l \cdot cmH_2O]$	1.83479703	1.88326432	1.93227213	1.94458027	1.97152607
Resistive Expiratory Work $[l \cdot cmH_2O]$	1.86822297	1.89293866	1.91724197	1.94575632	2.06650103
Elastic Work $[l \cdot cmH_2O]$	2.650575	2.66555	2.6773925	2.71949125	2.74344

Control patient

ARDS	min	Q25	Q50	Q75	max
Work Of Breathing $[l \cdot cmH_2O]$	8.04864141	8.15505277	8.28437523	8.35130919	8.51115168
Resistive Inspiratory Work $[l \cdot cmH_2O]$	3.29569641	3.32812777	3.44001523	3.49670919	3.55777668
Resistive Expiratory Work $[l \cdot cmH_2O]$	3.977945	4.04747091	4.05916954	4.07246382	4.13525971
Elastic Work $[l \cdot cmH_2O]$	4.752945	4.826925	4.84436	4.8546	4.953375

ARDS patient

TABLE 1 – Work of breathing and its three components derived from the Pressure-Volume loops - Results are estimated over 10 cycles.

On a more practical note, we can say that these are the works that the lungs must perform to ensure ventilation. In practice, this are also the works the ventilator must provide if the patient is completely under control. There are intermediate modes in which ventilators are used solely as aids to maintain the patient's respiratory muscular system, while assisting with the effort involved. A knowledge of these values may therefore also be of interest when designing a ventilator.

1.2 Flow-Volume Loops

The separation of inspiration/expiration on the flow-volume curves was carried out in the same manner as in the previous section. The separating line is located at Q = 0 : the inspiratory phase occurs when the flow is positive, above this line, and the expiratory phase occurs below it.

Below are the graphs representing the Q-V curves for the ARDS and Control patients, during their fourth cycle.

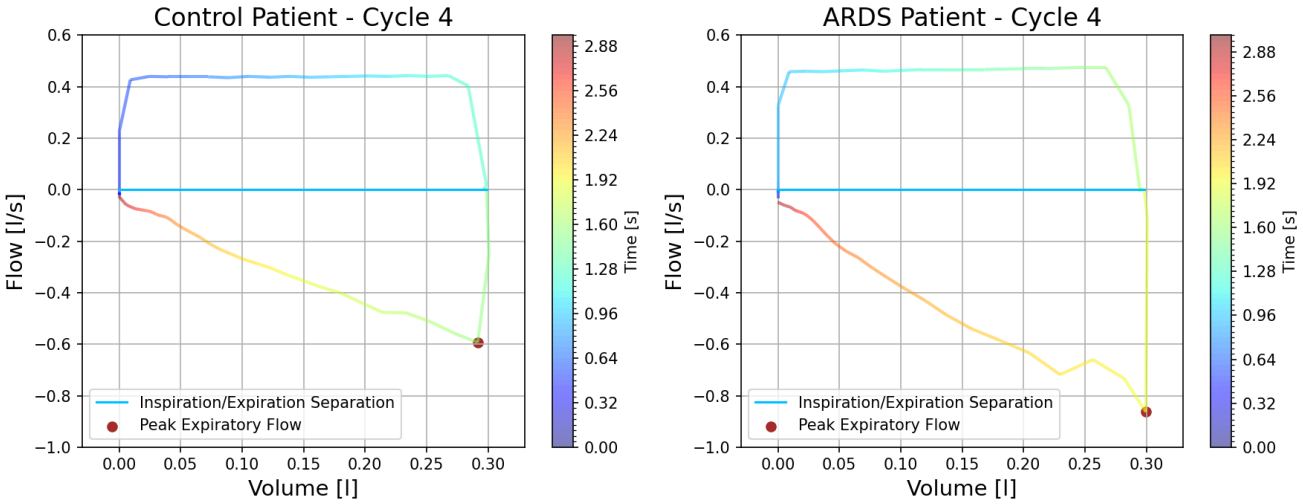


FIGURE 4 – Fourth Q-V loop for both Control and ARDS Patients. *Inspiration phase is above the separation line. Expiration phase is under the separation line. The tidal volume corresponds to the length of the separation line.*

From this curves, one could extract different interesting values :

- The peak expiratory flow (PEF) is a measure of the maximum flow rate of air that is exhaled from the lungs during expiration. In other words, it represents the maximum velocity at which the air is being expelled from the lungs during expiration.
- The tidal volume, refers to the volume of air inspired or expired with each normal breath cycle. In other words, it is the amount of air that is moved into and out of the lungs during a typical breath.

Once again, to reduce potential inaccuracies and errors associated with the use of a single cycle, we opted to study these values over the 10 respiratory cycles provided to draw robust conclusions.

Control	min	Q25	Q50	Q75	max
Peak Expiratory Flow $[l/s]$	-0.605	-0.6	-0.595	-0.59083333	-0.57166667
Tidal Volume $[l]$	0.2975	0.2982	0.2988	0.2995	0.2995

Control patient

ARDS	min	Q25	Q50	Q75	max
Peak Expiratory Flow $[l/s]$	-0.866667	-0.84875	-0.8375	-0.822083	-0.813333
Tidal Volume $[l]$	0.2943	0.29705	0.29785	0.29865	0.2995

ARDS patient

TABLE 2 – Peak Expiratory Flow and Tidal Volume derived from the Flow-Volume curves - Results are estimated over 10 cycles.

1.3 Results Analysis : Influence of ARDS on these loops

1.3.1 Pressure-Volume Loop

It is evident from Figure 3 and Table 1 that the lungs affected by ARDS behave differently from healthy lungs. Indeed, as the pigs were volume-controlled, the pressure-volume curve is only intended to study the influence of ARDS on pressure in the airways, as the same amount of volume is mobilized in both groups.

The first observation that stands out is the maximum pressure deployed in both cases : a lung affected by ARDS requires a higher peak airway pressure (about 45 $[cmH_2O]$ compared to 28 $[cmH_2O]$, median [1] values) to mobilize the same volume as a healthy lung. In other words, an individual with ARDS will have much lower pulmonary compliance than a healthy individual [10, 8]. The compliance is the ratio of a change in lung volume to the corresponding change in air pressure.

From Table 1, it is evident that ARDS affects the work of breathing and its various components. Specifically, the median values for a pig with ARDS are twice as large as those for healthy pigs. This result is anticipated, as the different works are correlated with the area under the P-V curve. Consequently, a substantial increase in pressure exerted in the case of ARDS will naturally elevate the respiratory workload.

We can also observe that in the case of a healthy individual, the resistive inspiratory work is practically equal to the resistive expiratory work, (which is expected because the airways traversed during inspiration and expiration are symmetrical and typically have similar resistance to airflow), while in an individual with ARDS, greater work is required during expiration compared to inspiration. This might be explained by the obstruction of the airways by the fluids encountered in ARDS. Thick pulmonary secretions and collapsed (or filled) alveoli might increase the resistance to exhalation, increasing the work required to exhale air against resistance.

All of this can be elucidated by the observation made earlier : a lung affected by ARDS is much less compliant as it is filled with fluids and therefore much stiffer. Consequently, the respiratory muscles must provide additional effort to allow adequate ventilation. Elastic work is also impacted by the pulmonary stiffness associated with ARDS : with reduced compliance, more energy is required to overcome the elastic resistance of stiffer lungs.

1.3.2 Flow-Volume Loop

Results from Table 2 and Figure 4 allow us to analyse the influence of ARDS on the flow rate. Because pigs are volume-controlled during the whole experiment, it is obvious that the tidal volume is nearly constant between healthy and ARDS pigs, with really small variations between the different quantiles : it has been predetermined constant for both groups.

A parameter that is strongly influenced by ARDS is the peak expiratory flow : as can be seen in Table 2, pigs affected by ARDS have a median PEF (Peak Expiratory Flow) that is 41% greater in absolute value than healthy pigs. In ARDS pigs, inspiratory flows are also a little above the ones associated with healthy pigs.

This result can be explained by the nature of the volume-controlled experiment. Indeed, the volume delivered to the pigs is predefined, greatly affecting the dynamics of flow and pressure in the system. As a lung affected by ARDS is much less compliant than a healthy lung, the pressure in its airways must be much higher to deliver the same volume as in a healthy lung.

Therefore, even though the resistance of the diseased lungs is increased due to fluids in the alveoli, and this same resistance impedes the airflow deployed by the diseased patient, the significant increase in pressure allows for the emergence of a higher peak expiratory airflow in the case of lungs affected by ARDS.

2 Single compartment model

A common model when it comes to lung modeling is the "single compartment model", which represents the pulmonary system as a single compartment defined by 3 parameters and 3 quantities that evolve over time.

The 3 parameters are respectively respiratory elastance Ers $[cmH2O/l]$, respiratory resistance Rrs $[cmH2O.s/l]$ and offset pressure P_0 $[cmH_2O]$. These are considered to be constant in the model, but here we consider them to be constant during a single respiratory cycle, and will study their distribution from one cycle to the next, for both control and sick patients.

The physiological interpretation of these quantities is important for analyzing the results :

- Ers represents the stiffness or rigidity of the respiratory system. It reflects how much pressure is required to produce a given change in lung volume. Higher elastance means the respiratory system has to work harder to ensure proper breathing. It can be viewed as the inverse of the compliance.

1. Focusing on median values in our results analysis enables us to mitigate the influence of any potential outliers

- Rrs represents the obstruction or hindrance to airflow within the respiratory system. Higher resistance means it requires more pressure to maintain airflow through the airways. Elevated Rrs indicates increased difficulty in moving air in and out of the lungs, resulting in increased work of breathing.
- P_0 represents the baseline pressure within the respiratory system at the onset of inspiration. In a positive pressure ventilation setting, such as mechanical ventilation, positive P_0 values are maintained to keep the airways open and facilitate gas exchange.

The 3 variables describing the state of the compartment over time are respectively lung volume $V(t)$ $[l]$, flow rate $Q(t)$ $[l/s]$ and airway pressure Paw(t) $[cmH2O]$. These variables change over time. The law describing the model is a linear relationship written as :

$$\text{Paw}(t) = \text{Ers}.V(t) + \text{Rrs}.Q(t) + P_0 \tag{1}$$

2.1 Methods

We can use the experimental data from each cycle - i.e. the point-measured values of Paw, V and Q - to determine an estimate of lung properties. A linear regression is performed for each cycle and for each of the two patients to determine the parameter values that minimize the residual sum of squares between model predictions and experimental data (for further details, please refer to 'LinearRegression' from [6]). The results are presented in Table 3 and can be interpreted with good confidence, since the regression scores R^2 are all close to 1 (best is 1), indicating a regression close to the experimental data.

Control	$Q25$	$Q50$	$Q75$
Ers $[cmH2O/l]$	54.583235	55.178957	55.324919
Rrs $[cmH2O.s/l]$	16.676792	16.821022	16.989591
P_0 $[cmH2O]$	4.734757	4.779001	4.784016

Control patient - Results are estimated over 10 cycles - *R^2 regression scores are all in the interval* $[0.9828; 0.9872]$

ARDS	$Q25$	$Q50$	$Q75$
Ers $[cmH2O/l]$	104.142661	104.745358	104.892127
Rrs $[cmH2O.s/l]$	26.021115	26.198070	26.600102
P_0 $[cmH2O]$	5.166231	5.219899	5.345834

ARDS patient - Results are estimated over 10 cycles - *R^2 regression scores are all in the interval* $[0.9828; 0.9875]$

Table 3 – Mechanical characteristics estimated by linear regression for each respiratory cycle on both the control and ARDS patients.

2.2 Results analysis

A first glance at the results presented in Table 3 already reveals an effect of ARDS on model parameters - and therefore, by extension, on lungs and lung mechanics.

It can be seen that offset pressure is not greatly influenced by pathology. In practice, this is not surprising, since this variable corresponds to the PEEP set by the ventilator, and therefore not by lung mechanics, in order to avoid lung collapse.

Elastance Ers and resistance Rrs, on the other hand, are clearly affected by pathology, and in a homogeneous way for all quantiles, i.e. the $Q75 - Q25$ gap is not significantly modified from one patient to another.

The elastance value is almost doubled for the ARDS patient compared to the control patient. This indicates that a greater pressure difference is required to achieve the same change in lung volume. This increases the lung work required for ARDS patients. Given that elastance is the inverse of compliance, we can confirm the results of the previous section, indicating that pulmonary compliance is greatly reduced when the patient is affected by ARDS.

For the respiratory resistance (Rrs), a rise from 16 to 26 indicates an increase of approximately 62.5%. This suggests that for ARDS patients, there's an increased resistance to airflow compared to the control patients.

Just like with elastance, this increased resistance would necessitate a greater pressure gradient to maintain airflow, which can add to the overall work of breathing for ARDS patients.

ARDS therefore appears to increase the lung work required by increasing both elastance and pulmonary resistance. From a physiological point of view, ARDS patients therefore find it harder to breathe, as the energy required to breathe is greatly increased.

From the point of view of doctors and medical staff, linear regression and modelling tools - even with a relatively simple model - can be used to quantify the burden felt by a patient. We can imagine a diagnostic system based on Ers and Rrs quantities or adaptative respirator based on empiricaly estimated parameters like in [4, 5].

3 Linear two-compartment model

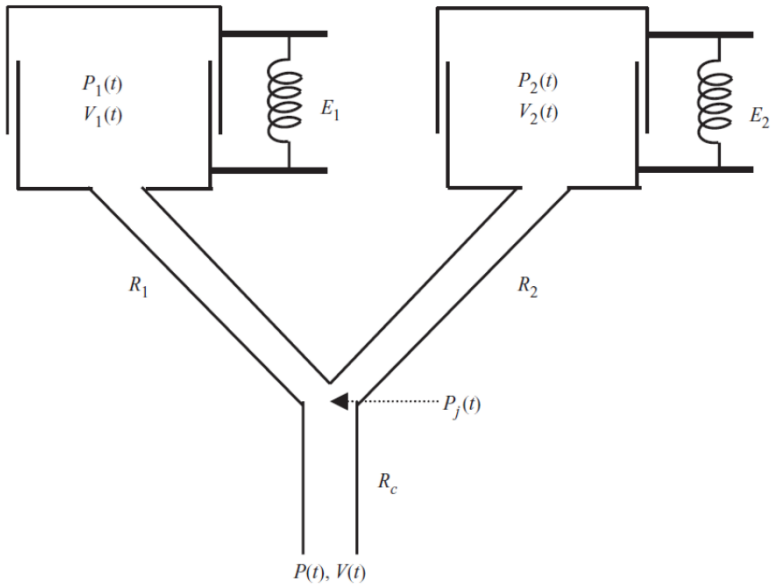


FIGURE 5 – Linear two-compartment model

In contrast to the simplistic single compartment model, the two compartment model offers a more nuanced understanding of the pulmonary system by accounting for the unique characteristics of each lung and their shared airway dynamics. In this model, we consider the respiratory system as comprised of two distinct compartments, each representing a lung, along with a common airway, typically the trachea, connecting them.

Within this framework, we introduce additional parameters to capture the complexity of the system. The respiratory elastance (Ers) and resistance (Rrs), previously attributed to the entire respiratory system in the single compartment model, are now individually assigned to each lung, denoted as E_1, E_2, R_1, and R_2, representing the stiffness and resistance of the left and right lungs, respectively. Additionally, the common airway is characterized by its own resistance, denoted as R_c, reflecting the hindrance to airflow through the shared trachea.

The distribution of air volume between the lungs is governed by specific mechanical parameters, influencing how air is partitioned between the left and right lungs during breathing cycles. This partitioning is vital as it determines the contribution of each lung to overall ventilation and gas exchange.

The physiological interpretation of these parameters remains consistent with the single compartment model. E_1 and E_2 represent the respective stiffness or rigidity of each lung, indicating the pressure required to induce volume changes. Higher E values signify increased resistance to expansion, necessitating greater effort in breathing. Similarly, R_1 and R_2 denote the obstruction or hindrance to airflow within each lung, with elevated values suggesting difficulties in ventilation and increased work of breathing.

Throughout the respiratory cycles, the dynamics of lung volumes (V_1, V_2), flow rates (Q_1, Q_2) and pressures in the lungs (P_1, P_2) are governed by a set of linear relationships, reflecting the interplay between the

individual lung compartments and the shared airway. This two compartment model provides a more comprehensive framework for understanding respiratory physiology, enabling insights into the unique contributions of each lung to overall pulmonary function and ventilation efficiency.

In practice, we only model gas exchanges between the lungs and the outside world. Thus, the states of the compartments P_i and V_i, $i \in 1, 2$ are relative quantities. In practice, this means that a pressure of zero indicates that the intrapulmonary pressure corresponds to the PEEP, and a volume of zero corresponds to the dead volume of the compartment (which we know to be non-zero, since the PEEP is there for that purpose).

3.1 Ventilator modeling

In pressure control mode, the ventilator imposes a pressure on the pulmonary system. A simple model for this type of ventilator is a square-wave signal with a p_{max} and p_{min} value during inspiration and expiration phases respectively - in addition to the PEEP to prevent lung collapse. It is therefore assumed that the ventilator is capable of instantaneously changing from one pressure to the other. Figure 6 shows the pressure pattern applied to our model, with the red crosses representing signal sampling at a frequency of 25 Hz - corresponding to the frequency of signal sampling on patients. The blue dotted line simply helps to visualize the square shape.

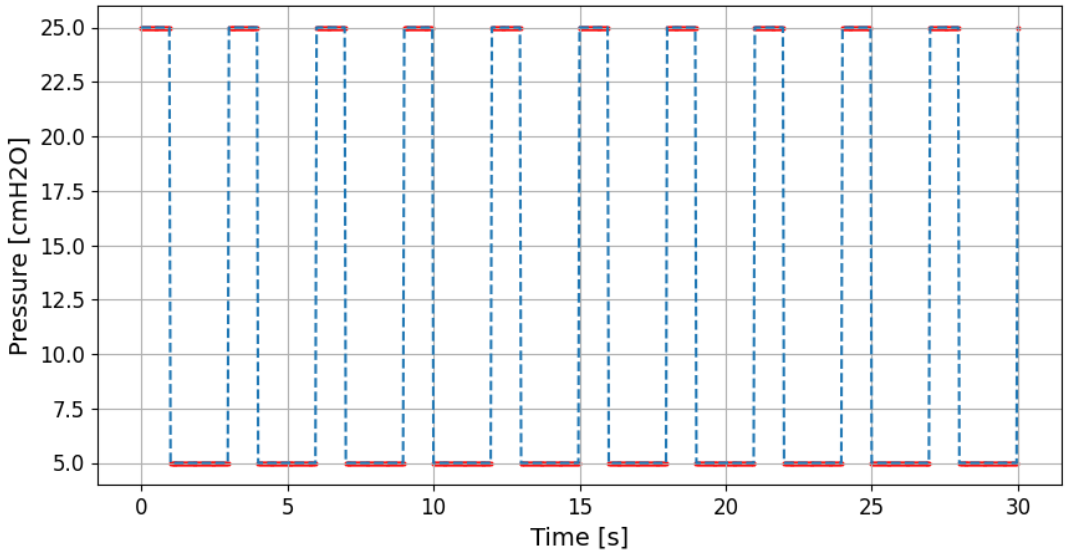


FIGURE 6 – Square pressure signal applied by the ventilator. *Sampling frequency* $f = 25\ Hz$ *;* $p_{max} = 20\ cmH2O$ *;* $p_{min} = 0\ cmH2O$ *and* $PEEP = 5\ cmH2O$*. The red crosses represent the values sampled, the blue dotted line is present only at the end of the visualization help.*

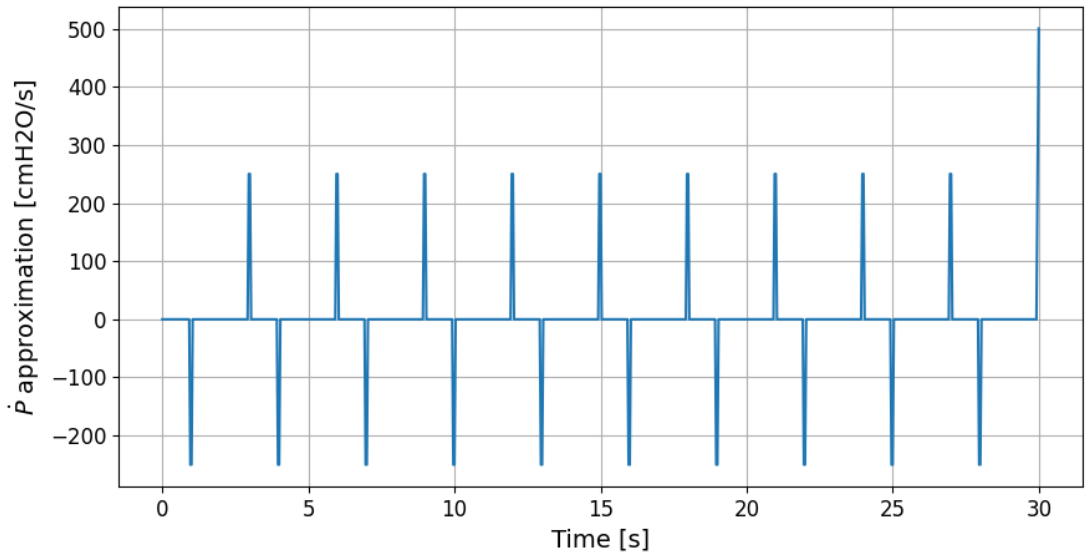


FIGURE 7 – Finite-difference approximation of $\dot{P}(t)$. The points used for the approximation are the sampled values of $P(t)$ - the red crosses in Figure 6.

3.2 Simulation of two healthy lungs

The two compartment model can be simulated under the pressure-control mode by integrating numerically the problem (2). V and Q refer respectively to the (relative) volume and flow of the complete model, i.e. the total volume exchanged of the two lungs ($V(t) = V_1(t) + V_2(t)$) and the flow in the duct common to both compartments. The initial condition Q_0, V_0 are assumed to start at an inspiration phase. In order to simulate healthy lungs, the values of R_1, R_2, E_1 and E_2 are set on the basis of the median values of the control patient presented in Table 3. The tracheal resistance value R_c is assumed to be known.

$$\begin{cases} \dfrac{dV}{dt} = Q \\ \dfrac{dQ}{dt} = \dfrac{(R_2 + R_1)\,\dot{P}(t) + (E_2 + E_1)\,\{P(t) - \text{PEEP}\} - [(R_2 + R_c)\,E_1 + (R_1 + R_c)\,E_2]\,Q(t) - E_1 E_2 V(t)}{R_1 R_2 + R_c\,(R_1 + R_2)} \\ [V(t=0), Q(t=0)] = [V_0, Q_0] = [0, 0] \\ R_1 = R_2 = \text{Rrs}_{Q50,\text{control}}, E_1 = E_2 = \text{Ers}_{Q50,\text{control}}, R_c = 5\ [cmH_2O.s/l] \end{cases} \tag{2}$$

In practice, we don't directly use the analytical expression of $P(t)$ or $\dot{P}(t)$, but rather sampled values. It is therefore necessary to approximate these functions in order to use numerical integration tools. A numerical approximation, based on finite differences, is used to estimate $\dot{P}$ and is shown in 7. We use the `numpy.gradient` [3] method, which employs a centered second-order approximation where possible, and a first- or second-order forward or backward approximation at the domain boundaries. The $P(t)$ function is approximated by linear interpolation. The approximation obtained corresponds well to very short (40 ms which is the sampling period) but intense variations in pressure.

The problem is solved numerically using the `RK45` method of integration implemented in the `scipy` library [9]. We set the sampling interval of the clinical data as the maximum step, and leave the other parameters of the method at their default values. In practice, this method of approximating the solution of ODEs is based on an adaptive time step with convergence criteria verified by the maximum relative and absolute error allowed, which are also parameters of the method.

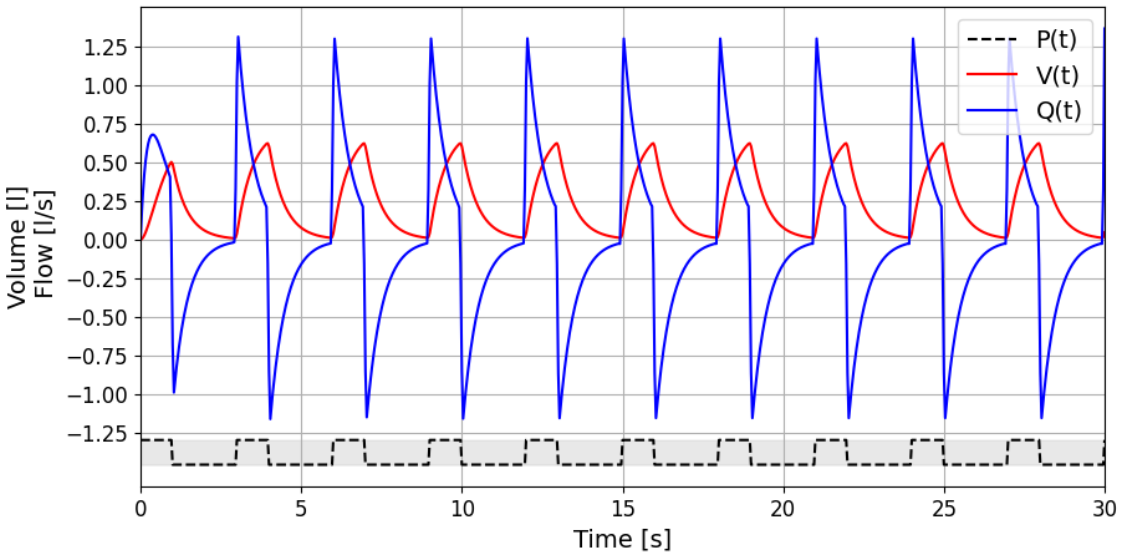


FIGURE 8 – Evolution of the two-compartment model, with parameters of healthy lungs, under a pressure control mode. *The problem is described as the problem (2).*

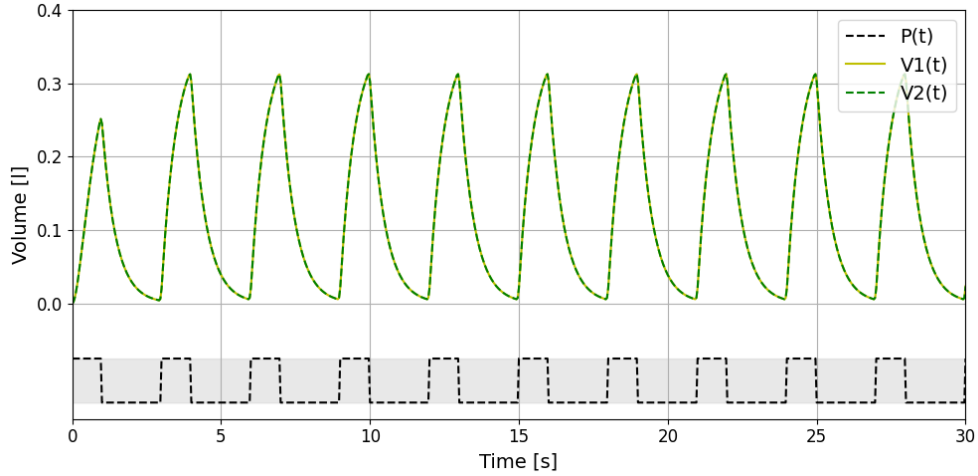
Figure 8 shows the evolution of model variables under the effect of the pressure control mode. We can see that the periodic behavior of imposed pressure translates well into a periodic behavior of respiratory volume and flow with the same frequency as the one of the ventilator. We also observe that the breathing cycles are all identical, with the exception of the first. This difference can be explained by the fact that the initial condition of the system is not a state which is part of the stable limit cycle solution, so it takes some time for the system to converge to its 'stable' periodic solution : the first cycle is the transient response of the model. The flow exhibits very sharp variations during rapid changes in pressure. Volume variations, on the other hand, are relatively smooth.

From a physiological point of view, we can observe the effect of the controller on lung volume. When the controller is fully active (i.e. when the transient response has ended), the tidal volume (i.e. the total volume exchanged during a complete normal respiratory cycle) is around 613 mL. ($V_{min} \approx 11mL, V_{max} \approx 625mL$). Without more information on the pigs (weight, size, etc.) it is impossible to determine whether this value is consistent because literature refers to tidal volume as a specific value (in $\frac{mL}{kg}$). Note that in practice, in pressure-control mode, tidal volume is not always a straightforward quantity to impose [7] but it remains a relevent quantity that must be kept under control to avoid lung damage over the long term [2].

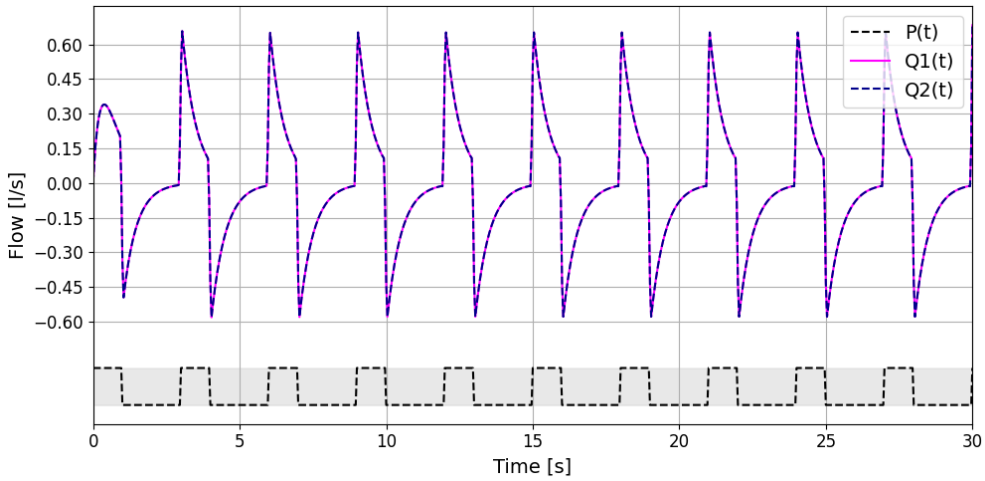
Although problem (2) simulates the complete system, it may be interesting to simulate the two compartments separately, in order to observe the evolution of pressure, flow and lung volume in the two lungs. Problem (3) allows us to simulate the two lungs separately.

$$\begin{cases} \textit{Equations for } Q_2 \textit{ and } V_2 \textit{ are obtained by interchanging subscripts 1 and 2.} \\ \dfrac{dV_1}{dt} = Q_1 \\ \dfrac{dQ_1}{dt} = \dfrac{R_2\dot{P}(t) + E_2\left\{P(t) - \text{PEEP}\right\} - \left[\left(R_2 + R_c\right)E_1 + \left(R_1 + R_c\right)E_2\right]Q_1(t) - E_1E_2V_1(t)}{R_1R_2 + R_c\left(R_1 + R_2\right)} \\ P_1(t) = E_1V_1(t) \\ \left[V_1(t=0), Q_1(t=0)\right] = \left[V_{1,0}, Q_{1,0}\right] = [0,0] \\ R_1 = R_2 = \text{Rrs}_{Q50,\text{control}}, E_1 = E_2 = \text{Ers}_{Q50,\text{control}}, R_c = 5\ [cmH_2O.s/l] \end{cases} \tag{3}$$

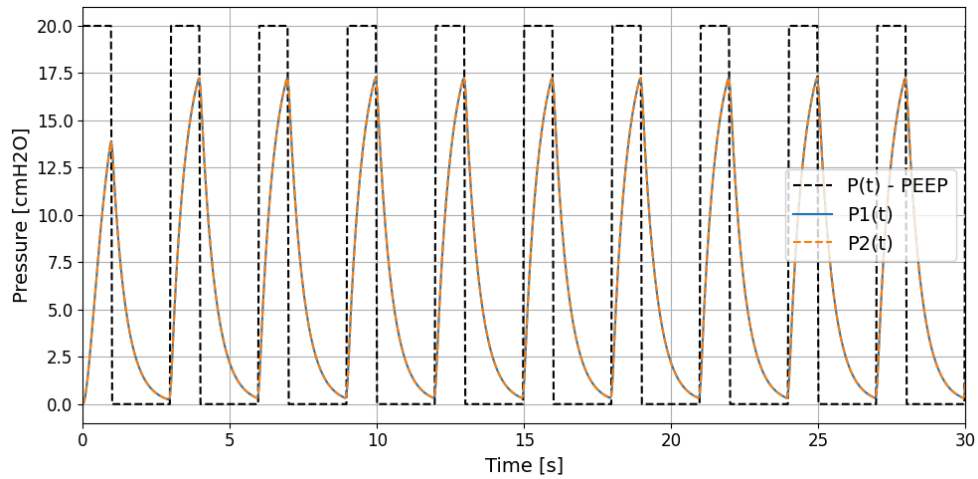
The problem is numerically solved in the same way as problem (2). Figures 9a, 9b, and 9c show the results obtained for each lung separately.



(a) Evolution of the exchanged volume of each lung. *A positive volume is a volume of air entering the lungs. The volume is relative to the dead volume imposed by the PEEP.*



(b) Evolution of flow in each lung. *A positive flow is an incoming flow corresponding to inspiration.*



(c) Evolution of the relative pressure of each lung. *Pressure is relative to PEEP.*

FIGURE 9 – Separate evolution of the two lungs of the two-compartment model, two healthy lungs, in pressure control mode. *The problem is described by as the problem (3).*

At first glance, we can see that the results are absolutely symmetrical for both lungs : this result is consistent with the symmetry of the deterministic problem (3). The volume exchanged is therefore distributed equally between the two lungs (Figure 9a) - each containing half the total volume. The flow is also split into two equal flows after the model's tracheal duct (Figure 9b). We also observe that the relationships $V(t) = V_1(t) + V_2(t)$ and $Q(t) = Q_1(t) + Q_2(t)$ are well respected, which lends credence to our simulations since the results in Figures 9 and 8 are consistent. Here, too, we observe the transient period before observing the perfectly periodic response in each lung.

Finally, we observe that the ventilator acting in pressure control mode does not directly impose on the lung to follow perfectly the shape of the P(t) signal, but rather indicates a reference that the lungs tend to reach. The p_{max} and p_{min} values are not reached exactly because the ventilator frequency is too fast for equilibrium to be reached - and because the values to be reached are asymptotic.

3.3 Simulation of one healthy lung, one diseased lung

The two-compartment model can be simulated by considering two lungs with different properties, thus allowing the study of the behavioral difference between a healthy lung and a lung affected by ARDS, in the same numerical simulation.

The system of equations remains strictly the same as that in Problem (3) of the previous section, except for the values of elastance and resistance of one of the two lungs, which are altered to express its impairment by the disease. We considered the median values of Rrs and Ers calculated previously for the 'ARDS' data in Table 3.

$$\begin{cases} \text{Same system of equations and initial conditions as (3).} \\ R_1 = \text{Rrs}_{Q50,\text{ARDS}}, R_2 = \text{Rrs}_{Q50,\text{control}}, \\ E_1 = \text{Ers}_{Q50,\text{ARDS}}, E_2 = \text{Ers}_{Q50,\text{control}}, \\ R_c = 5 \ [cmH_2O.s/l] \end{cases} \tag{4}$$

Figure 10 depicts the various graphs resulting from the simulation. It appears immediately that the behavior of the two lungs is not symmetrical, despite both being subjected to identical pressure control and sharing the same airways. Lung 1 is considered to be suffering from ARDS, while lung 2 is healthy.

For all three subplots, it can be observed that the system is periodically driven by the pressure provided by the controller, and that the various cycles are identical, except for the first one, which is simply the transient representation of the system awaiting stabilization

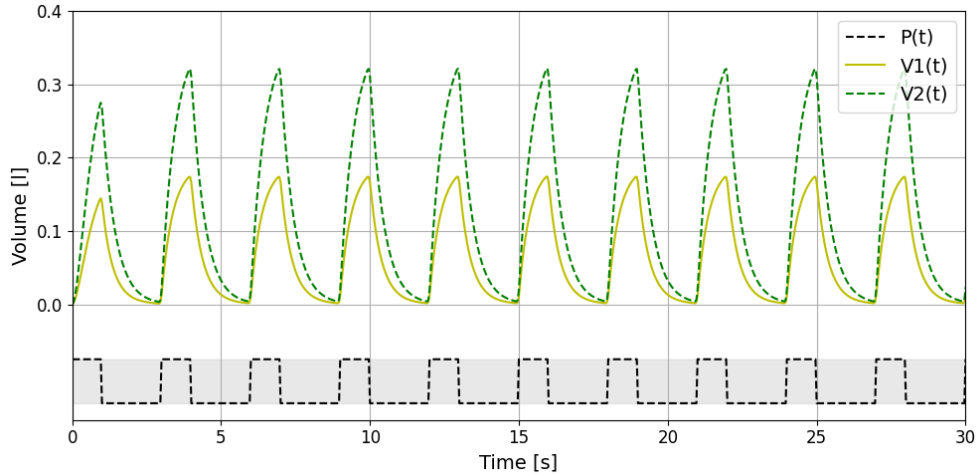
In Figure 10a, it can be observed that the volumes mobilized by each lung are not the same : during each breathing cycle, the healthy lung recruits nearly twice the volume mobilized by the lung with ARDS. The total volume deployed in both lungs ($V(t) = V_1(t) + V_2(t)$) is obviously affected : it amounts 75% of the volume mobilized when both lungs are healthy. This observation suggests that each compartment operates independently : despite the ARDS affecting the first lung, the second healthy lung behaves independently of the first, with a behavior identical to that of the previous subsection, as shown in Figure 9. There is no singinficant compensatory mechanism between the two lungs.

The relative flows for each lung are also different, as can be seen in Figure 10b. Indeed, unlike the case of two lungs sharing the same properties, the airflow brought in from the trachea is not symmetrically distributed between the two lungs : the flow entering the lung affected by ARDS is smaller than that entering the healthy lung.

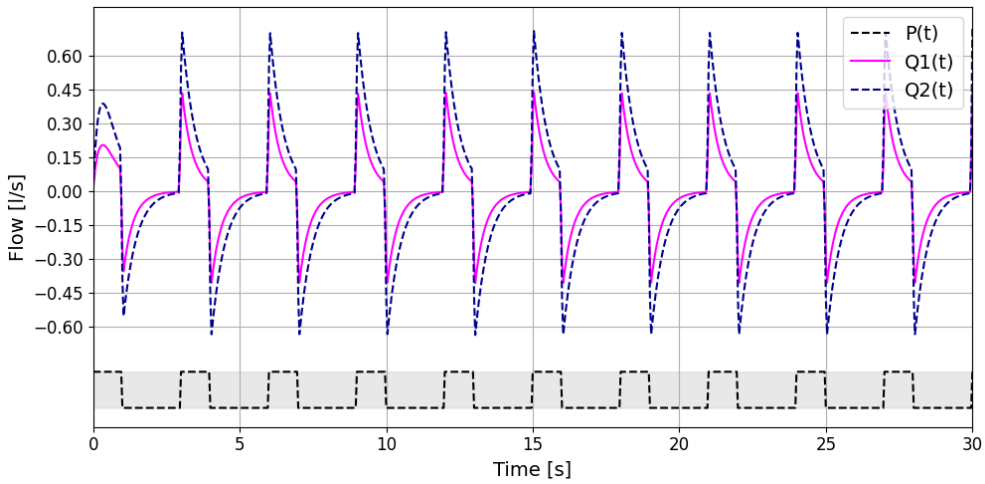
The fact that both volume and flow are reduced in the case of the lung with ARDS is entirely physiological : based on the elastance and resistance values considered in Table 3, we know that the healthy lung is much more compliant and less rigid (resistive) than the diseased lung. Since the compliance (inverse of elastance) of a lung with ARDS is greatly reduced, the variation in lung volume will be much smaller than that of a healthy lung, for the same imposed pressure variation (which is the same for both lungs in pressure-controlled mode, see Figure 10c). Since flow is the derivative of volume with respect to time, it is evident that we also observe a decrease in this case.

From Figure 10c, one can observe that the relative pressure variation in each lung is symmetrical. This comes from the expression of the relative pressure in each lungs in (3), so $P_1(t) = E_1 V_1(t)$, same for lung 2. This is entirely expected in the case of a pressure-controlled system : the input pressure is imposed, and it's up to both compartments to adjust their relative volumes and flows according to the elastance and resistance parameters imposed on them.

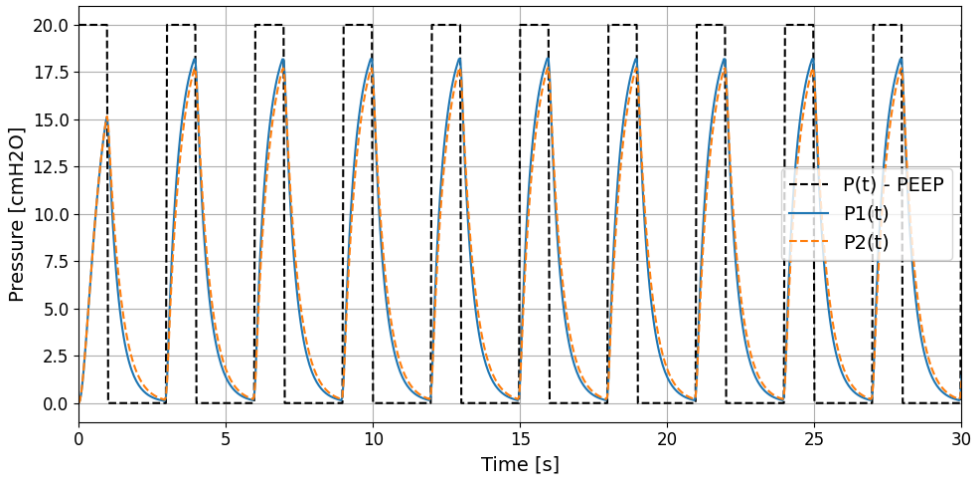
Moreover, even if the volume mobilized in both lungs is not the same, pressure is symmetrical because of the different elastance values in both cases. Indeed, one can see that even if the volume in healthy lung is twice as big as the one from ARDS lung, the elastance for healthy lung is half of the elastance for ARDS lung, thus, these two values balance out in the expression of relative pressure, which explains why it is the same in both lungs.



(a) Evolution of the exchanged volume of each lung. *A positive volume is a volume of air entering the lungs. The volume is relative to the dead volume imposed by the PEEP.*



(b) Evolution of flow in each lung. *A positive flow is an incoming flow corresponding to inspiration.*



(c) Evolution of the relative pressure of each lung. *Pressure is relative to PEEP.*

FIGURE 10 – Separate evolution of the two lungs of the two-compartment model, one lung is healthy and the other suffers from ARDS, in pressure control mode. Lung 1 suffers from ARDS and lung 2 is healthy. *The problem is described by as the problem (4).*

3.4 Simulation of both lungs affected by ARDS

In this subsection, we will simulate the two-compartment model with each compartment having the same properties, namely those of two lungs affected by ARDS.

The equations governing our model remain identical, but the elastance and resistance values for each lung will be those medians described in Table 3 for lungs affected by ARDS.

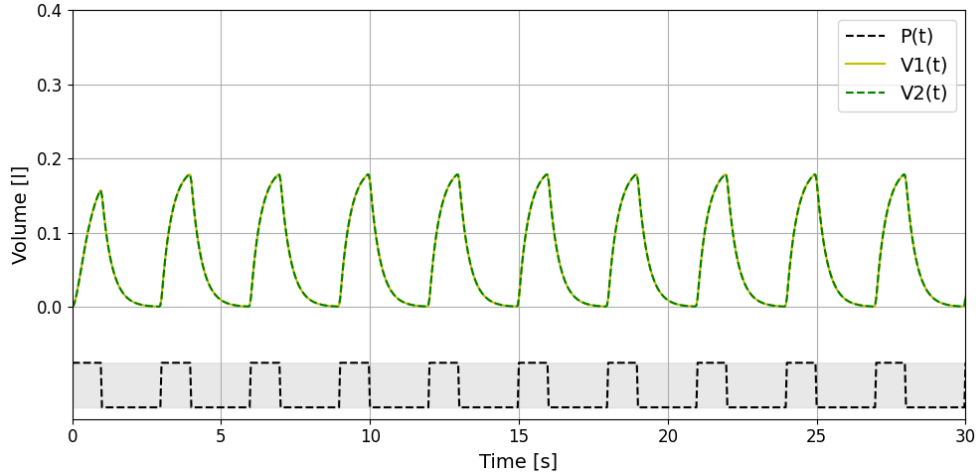
$$\begin{cases} \text{Same system of equations and initial conditions as 3.} \\ R_1 = R_2 = \text{Rrs}_{Q50,\text{ARDS}}, E_1 = E_2 = \text{Ers}_{Q50,\text{ARDS}}, R_c = 5\ [cmH_2O.s/l] \end{cases} \tag{5}$$

Figure 11 illustrates the evolution of volume, flow, and pressure over time in the case of this particular numerical simulation.

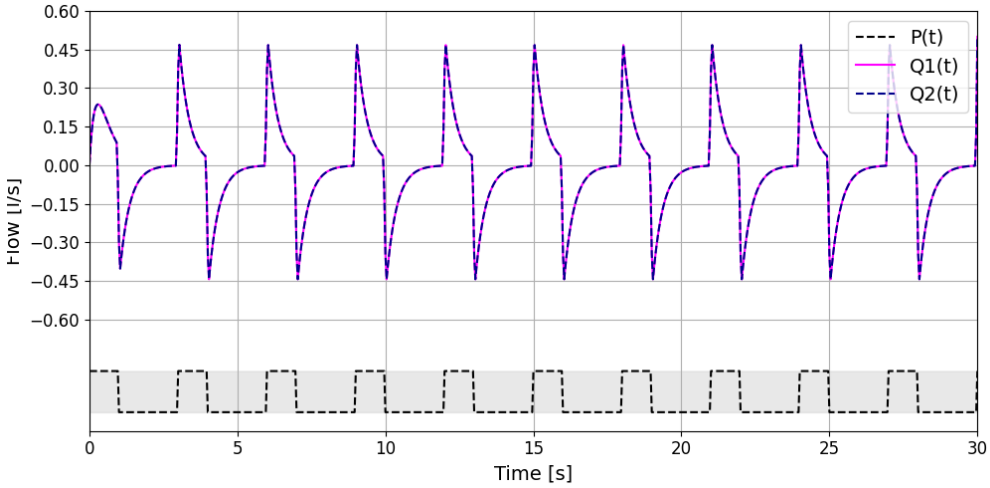
We can directly identify that, as in the previous simulations, the model is periodically governed by pressure variations induced by the controller, with identical cycles once the system has stabilized.

Just as in the previous case where both lungs were healthy and had the same properties, the results between the two lungs with ARDS are entirely symmetrical : the exchanged volume (Figure 11a) is the same for both lungs, as is the exchanged flow (Figure 11b).

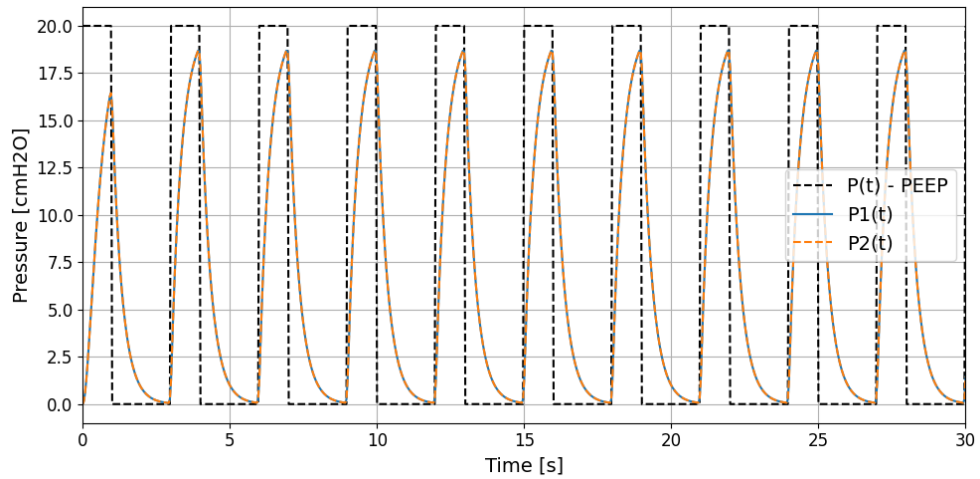
It's noticeable that each lung behaves in the same manner as the single lung affected by ARDS in the previous subsection (Figure 10), which again demonstrates the independence between the compartments.



(a) Evolution of the exchanged volume of each lung. *A positive volume is a volume of air entering the lungs. The volume is relative to the dead volume imposed by the PEEP.*



(b) Evolution of flow in each lung. *A positive flow is an incoming flow corresponding to inspiration.*



(c) Evolution of the relative pressure of each lung. *Pressure is relative to PEEP.*

FIGURE 11 – Separate evolution of the two lungs of the two-compartment model, both lungs suffer from ARDS, in pressure control mode. *The problem is described by as the problem (5).*

3.5 Conclusion on ARDS based on the two compartments model

In conclusion, the utilization of a modeling framework incorporating parameters derived from empirical data offers a robust approach to understanding the intricate dynamics of breath mechanics in patients with Acute Respiratory Distress Syndrome. By grounding our simulations in real-world observations, we can effectively capture the nuanced physiological variations observed in ARDS patients, leading to more accurate representations of lung function and gas exchange.

This approach not only enhances our comprehension of ARDS pathophysiology but also holds promise for guiding clinical decision-making and therapeutic interventions. By accurately modeling the impact of ARDS on breath mechanics, clinicians can gain valuable insights into patient-specific responses to treatment modalities, facilitating the development of tailored therapeutic strategies.

Furthermore, the integration of empirical data-derived parameters into our modeling framework enhances the translational potential of our findings to clinical practice. By aligning our simulations with real-world patient data, we can more effectively bridge the gap between theoretical research and clinical application, ultimately improving patient outcomes in ARDS management.

In essence, the incorporation of empirical data-driven models offers a valuable avenue for advancing our understanding of ARDS and optimizing clinical care for affected patients. By leveraging the wealth of information gleaned from empirical observations, we can continue to refine our models and develop more effective strategies for managing this complex and challenging clinical syndrome.

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