Study of Respiratory models

Vraj Thakkar Prof. Tanmay Pal

July 2024

Abstract

Modeling the lungs has always been a part of active research due to its extremely complex structure and function. An accurate model would ease in the research of ventilation, CPAP machines as well as aiding in understanding lung diseases and their treatments. In this report, we explored mechanical models of lungs and analyzed the mechanics of breathing, focusing on the derivation of respiratory frequency. We looked at one of the most important models of lungs given by Otis. We understood the challenges and shortcomings of the model, primarily its assumptions, as pointed out by Mead. As we try to model the respiratory system with greater detail, models become quite complex and as a solution, we dive into the compartmental models of the respiratory system. These compartmental models add more detail to the previous mechanical models. We identified the factors affecting the frequency of breathing in these models. We are also exploring the evolutionary algorithms, being used to optimize the work done for calculating the frequency of breathing. We are also looking at one of the most important aspects of respiratory modeling, i.e. pattern of air flow while breathing. In the last part of the project, we delve into validating the discussed models in diseased conditions.

Contents

1 Mechanical Equivalent Models

This section looks at a dynamic model to study the interaction of forces that produce the chest wall motion during the resting phase. A mechanical equivalent of the model will also be shown to reproduce the motion of the chest wall. Hence, the model may well represent the chest wall motion and can be used to study the relative motion of the rib cage and abdomen.

1.1 Model Description

The chest wall is divided into two main components with regard to their elasticity, the rib cage, and the abdominal as elastic elements, and the active respiratory muscles (inelastic component). The rib cage and the abdominal elements are considered passive elements because no active energy(ATP) is used directly for their motion. These organs are stretched by the force produced due to the contraction of the respiratory muscles and they store energy in elastic form. Due to their elastic nature, they can be represented in a mechanical system with a spring of appropriate elastance. This stored energy is released while exhaling, in addition to the relaxation of respiratory muscles.

We want to model the movement of the chest wall using the information we described above. We would want to look at the change in the volume of the rib cage and abdomen per se. Also, a good description of the change in the volume component can be measured with the change in the cross-section area of the respective components. Hence, we come up with the following representation of the model. The passive elastic rib cage and abdominal compartments are represented by two springs characterized by their elasticity (respectively E_{RC} and E_A). We also know that there are certain resistances(viscous and turbulent forces encountered by friction between the smooth muscles and the moving air) innate in the respiratory system that oppose the flow of air, we represent all of them with a single dashpot. All three elements are attached to a rigid roof. The respiratory muscle force which is the actuator for the system is applied on the stiff non-intertial bar which is connected to the three components without any sliding inertia. A pictorial description of the system is shown in 1

Changes in the cross-sectional area of the abdominal component and rib cage are given by the change in the length of the springs representing those. The dashpot is attached to the bar at the point where the linear combination of A and RC corresponds to the one used for the estimation of breathing volume changes. The parameters of the system that can be tuned to accurately represent the movement of the chest wall are the distance (Horizontal) between the dashpot and the spring RC given by α and the distance between the dashpot and application of the respiratory muscles force (F_{mus}) represented as β. We can immediately also see from the model description that the range of α and β are $0 < \alpha < 1$ and $\alpha - 1 < \beta < \alpha$. This is after normalizing the distance between spring A and spring RC equal to 1, the following step has been done to

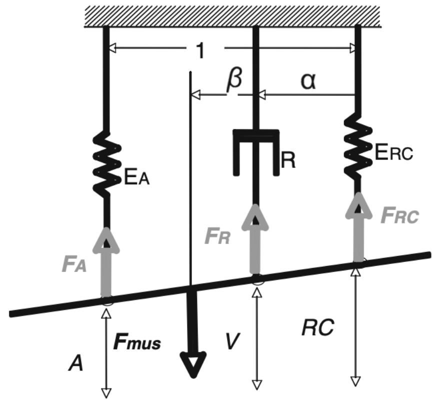

Figure 1: Model (References 5.)

reduce the number of variable parameters in the model. We can observe that in response to the respiratory muscles force, there are three opposing forces, the elastic forces of spring RC and A and the resistive force by the dashpot. The vertical displacement of the bottom end of the dashpot then represents the changes in volume V.

1.2 Formulating the equations of the model

The vertical displacement of the bottom end of the dashpot (V) is a linear combination of vertical displacements of the bottom end of the bar at Spring A and Spring RC as they are connected by a rigid rod.

$$V = \alpha A + (1 - \alpha)RC$$

where $0 < \alpha < 1$. We know that the force produced by the dashpot is proportional to the velocity of the point of connection of the dashpot and the bar. We also know that this force corresponds to the respiratory resistance force experienced by the air. So the force produced can be formulated as

$$F_R = R\frac{dV}{dt}$$

where R is viscous resistance of the dashpot. Also, we know that the force of the springs is given by

$$F_{RC} = -E_{RC}RC$$

$$F_A = -E_A A$$

Now using the principle of rotational dynamics on the non-intertial bar we can write the moment of all forces equal to the product of its angular acceleration and moment of inertia. Considering the point of application of F_{mus} as the origin we can write the relative distances and forces as

$$\beta \mathrm{R}\frac{\mathrm{d}V}{\mathrm{d}t} + (\alpha+\beta-1)\left(E_{\mathrm{A}}A\right) + (\alpha+\beta)\left(E_{\mathrm{RC}}\mathrm{RC}\right) = 0$$

we can also rewrite the equation as

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{(1-(\alpha+\beta))E_{\mathrm{A}}}{\beta R}A - \frac{(\alpha+\beta)E_{\mathrm{RC}}}{\beta R}\mathrm{RC}$$

which may be written

$$\frac{\mathrm{d}V}{\mathrm{d}t} = K_{\mathrm{A}}A + K_{\mathrm{RC}}\mathrm{RC}$$

with

$$K_{\mathrm{A}} = \frac{(1-(\alpha+\beta))E_{\mathrm{A}}}{\beta R}$$

$$K_{\mathrm{RC}} = -\frac{(\alpha+\beta)E_{\mathrm{RC}}}{\beta R}$$

We should note that given the correctness of the model, we expect the true respiratory system flow to be a linear combination of abdomen and ribcage cross-section areas.

1.3 Model results and limitations

Data from pneumotachograph and respiratory inductive plethysmography (RIP) were taken for different people. Pnuemotachograph measures the rate of airflow ($\frac{dV}{dt}$) whereas RIP measures the cross-sectional area changes of the abdomen (A) and rib cage (RC). Measurements were taken, varying the resistive load in the pneumotachograph, the values of K_A and K_{RC} were then calculated breath by breath in the least square sense. The model performs well with $R^2 > 0.70$ for 1193 out of 2971 total breaths analyzed ((Reference 5)). The primary limitations, of the model are related to the assumption that the geometric and mechanical properties (values of $\alpha, \beta, F_{mus}, etc.$) of the respiratory system remain constant over the breathing cycle. Though certain breaths validate this assumption, it may be possible that the values change during the breath as well as during each consequent breath.

2 Mechanics of breathing

In this section, we present a more detailed model of the breathing. It is worthwhile to understand what happens during a breathing cycle. During inspiration, the diaphragm contracts and moves downwards creating space in the chest cavity for it to expand. The respiratory muscles then help the lungs to expand to fill in the cavity. They contract to pull the rib cage upward and outward when we inhale. While breathing out the diaphragm and respiratory muscles relax resulting in an inward force that causes the lungs to deflate. Hence we know that the chest and lungs both are elastic in nature as they adjust the airflow by inflating and deflating (springs A and RC). We also realize that the air flowing through the respiratory tract encounters viscous and turbulent resistance (Dashpot with resistance R). We also presume that there is some non-elastic resistance associated with the sliding of organs when they are displaced. Inertia should also be considered as we see that the system is continuously accelerating or decelerating however this and the kinetic energy imparted to air are considered negligible due to their comparatively small quantity. Let's describe each of these three major phenomena in greater detail.

2.1 Elastic Forces

When a person completely relaxes his lungs, say after expiration, then the volume of the lungs is closed to the normal volume which is also known as the relaxation volume. At this point, the elastic forces acting on the lungs equal the air pressure inside the lungs. When the volume change occurs from this volume, elastic forces are developed proportional to the change in volume. These elastic forces are typically measured in terms of relaxation pressures. This is achieved by first asking the person to inhale up to the total lung capacity (TLC) and then relax the respiratory muscles completely, allowing the lungs to passively return to the functional residual capacity (FRC). Pressure and volume are measured using a specific instrumental set-up which will be described soon in greater detail. We should ideally then get $\Delta P_{el} = k\Delta V$ where K is the elastance of the lung mechanical system and $\Delta P_{el}, \Delta V$ are the changes in pressure and volume measured. The equation is usually represented as $P_{el} = kV$ where P_{el} is the pressure developed when the displacement from the relaxation volume is V.

2.2 Air Viscous and Turbulent Forces

Previous research in the area has led to the formation of air viscance and turbulent forces as follows.

$$P_{alv} = k_1(\frac{dV}{dt}) + k_2(\frac{dV}{dt})^2$$

Where P_{alv} is the pressure gradient between alveoli and mouth that is required to move the air with velocity $\frac{dV}{dt}$. The constants k_1 and K_2 are the air viscance

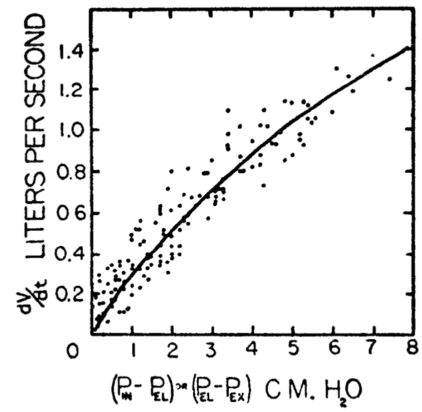

Figure 2: Data obtained from the experiment Reference 3.

and the turbulent resistance, respectively. There has been enough evidence and data to assert this equation as presented by other authors.

2.3 Resistance associated with tissue deformation

There are no direct methods to measure this quantity as of now. An experiment has been proposed to calculate its value which will be described now. A trained subject is placed in a Drinker respirator and is instructed to relax as completely as possible so that his breathing movements are produced by alternating the pressure within the respiratory chamber instead of by the action of his respiratory muscles, readings for $\frac{dV}{dt}, P$ are obtained in discrete time intervals and interpolated to present a continuous pressure-volume graph as in Fig 3 .This experimental setup eliminates any active work done by the body while breathing. So the pressure and volume readings we get correspond to the ones required for a normal breathing cycle. We get the following equation from the experiment (Reference 3.).

$$P_{exp} = k_3\left(\frac{dV}{dt}\right) + k_4\left(\frac{dV}{dt}\right)^2$$

We can break these into P_{el}, P_{avl}, P_{td}. We know that we can get the values for P_{el}, P_{avl}. Let's analyze the Fig. 3 and understand how we can use these pre-known values to calculate the resistance associated with tissue deformation. The transition points (Inspiration to expiration or vice-versa) of the curve in the figure represent the points where the elastic force created by the lungs and chest wall is equal to the force generated by the air inside the lungs per unit area. Assuming a linear relationship between lung pressure and volume the diagonal in the figure represents the pressure generated by the elastic component(P_{el}). The abscissal distance from the axis of the ordinates to the inspiratory curve gives us the total inspiratory pressure (P_{in}) at a given lung volume. When subtracted from P_{el} we get $P_{in} - P_{el}$ as sum of the pressure required to overcome air viscance and turbulent forces as well as the pressure required to overcome tissue deformation ($P_{alv} + P_{td}$). The next thing to do is to plot the various values of $P_{in} - P_{el}$ with the instantaneous velocity of the air $\frac{dV}{dt}$ and fit the points with the method of residuals Fig. 2 to get the equation of the curve of the form

$$P_{avl+td} = k'\left(\frac{dV}{dt}\right) + k''\left(\frac{dV}{dt}\right)^2$$

we can subtract P_{alv} from this equation to get the pressure required to overcome the tissue deformation. So let's say we call it P_{td} and it is of the form

$$P_{td} = k_5\left(\frac{dV}{dt}\right) + k_6\left(\frac{dV}{dt}\right)$$

finding p_{td} for each 0.1-second interval and adding and subtracting it from P_{el} will give the pressure required to overcome the tissue deformation during inspiration and expiration respectively. These are represented as the broken line in the Fig. 3

So we have the total force required for breathing as

$$P_{\sigma} = kV + k'\left(\frac{dV}{dt}\right) + k''\left(\frac{dV}{dt}\right)^2$$

2.4 Work done in breathing

We have the pressure-volume curve for our breathing cycle so we can easily find out the work done during each breath. The area of the triangle formed by the diagonal, the horizontal broken line, and the axis of ordinates in 3 represents the amount of work done during inspiration in overcoming elastic resistance. The area bounded by the diagonal and the curved line labeled inspiration is the additional work required to overcome the viscous and turbulent resistance of inspiration. This area may be subdivided into work done on non-elastic resistance of tissue (area between diagonal and broken line) and work done in overcoming air distance and turbulent resistance. Ideally, the elastic energy stored during inspiration and represented by the triangle is available as a power supply for expiration. However, only that portion bounded by the diagonal and the curve labeled expiration is used in this instance to overcome viscous and turbulent forces; the remainder is spent in working against the continued action of the respirator which opposes expiration during the first part of this phase of the breathing cycle. If we assume that the pressure equation given at the end of the previous section holds then the work done can be calculated for any velocity pattern. For example, let's say that the velocity pattern of inspiration is a sine wave. then we have

$$\frac{dV}{dt} = asinbt$$

here $\frac{dV}{dt}$ is the velocity of airflow, a is the maximal velocity and $b/2\pi$ is the frequency of breathing. The total volume of air that moves in during inspiration known as the tidal volume can be given by

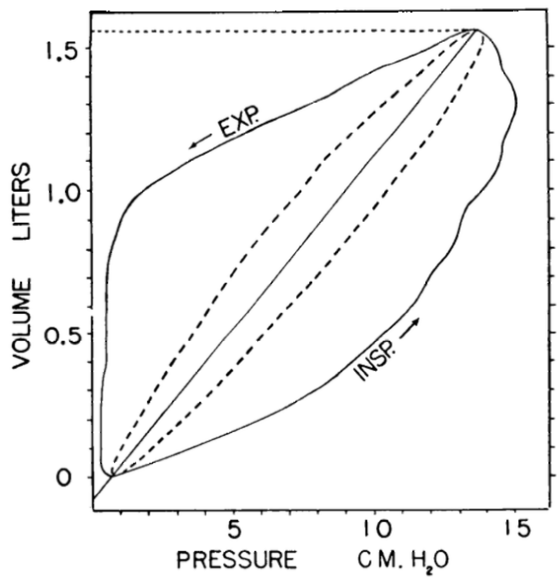

Figure 3: Pressure and Volume during breathing References 3.

$$V_T = \int_0^{\pi/b} a \sin bt dt = \frac{2a}{b} = \frac{a}{\pi f}$$

Using $dW = pdV$ we have the equation of work using the equation from the previous section as

$$dW = KVdV + K'a^2 \sin^2 btdt + K''a^3 \sin^3 btdt$$

We can calculate the total work done during inspiration by integrating the equation as follows.

$$W = \int_0^V TVdV + \int_0^{\pi/b} \left(K'a^2 \sin^2 bt + K''a^3 \sin^3 bt\right) dt$$
$$W = \frac{1}{2}KV_T^2 + \frac{1}{4}K'\pi^2 fV_T^2 + \frac{2}{3}K''\pi^2 f^2 V_T^3$$

The mean rate of doing work is the work per breath times the frequency of breathing. Mean rate of work =

$$\frac{1}{2}KfV_T^2 + \frac{1}{4}K'\pi^2 \left(fV_T\right)^2 + \frac{2}{3}K''\pi^2 \left(fV_T\right)^3$$

A note to mention here is that even though this is the work done during inspiration per unit time, it can be considered as total work done if expiration is assumed to be completely passive (resting state)

If the tidal volume is divided into an effective or alveolar portion, V_a (effective portion of the lungs where actual exchange of gases takes place) and dead space portion V_D then the equation of work per unit time becomes:

$$\frac{1}{2}Kf\left(\frac{\dot{V}_A}{f}+V_D\right)^2+\frac{1}{4}K'\pi^2\left(\dot{V}_A+fV_D\right)^2+\frac{2}{3}K''\pi^2\left(\dot{V}_A+fV_D\right)^3 \tag{1}$$

where $V_A f = \dot{V}_A$ = alveolar ventilation (effective ventilation, resulting in the exchange of gasses).

2.5 Optimizing work done to obtain the frequency of breathing

The equation 1 from the previous section which gives us the amount of work done in terms of alveolar ventilation and frequency of breathing can be optimized after plugging in the other values for obtaining the frequency of breathing. Of course, varying the parameters would lead to different frequencies. But this model gives us a definite value of f given that we have all the other parameters such as alveolar ventilation $\dot{V}_A$ and volume of dead space V_D. This minimum occurs because when the frequency is too low, much elastic work is required to produce the large tidal volumes, and when the frequency is too high, much work is uselessly done in ventilating the dead space with each breath. The ideal way to go about this is to substitute the obtained parameters and plug in the equation of work done, then differentiating the equation with respect to frequency and finding the roots for frequency of breathing.

This model provides a good framework to interrelate the respiratory process and work done. The authors however claim that the model should be used only as a first approximation and might not exactly represent the respiratory apparatus. One of the other shortcomings is primarily visible when we are looking at active respiration during high-intensity exercises and the model fails to give a good approximation because of the assumption of passive expiration. Jere Mead came up with another theory for the optimal breathing frequency. He came up with different experiments and asserted in his thesis that the optimum frequencies are somewhat greater than the ones that minimize the respiratory work. These frequencies actually arise from the minimization of the work done by the respiratory muscles rather than the total work done in the respiratory cycle as described in the above sections. Experimentally he tried to influence the the parameters in the expression for work given by Otis and tried to observe the change in optimal frequency but did not find any significant changes. He also observed that frequency changes were only observed when changes happened internally in the parts of the lungs. This quantity (Work done by respiratory muscles) however turns out to be hard to calculate and the above-discussed model of Otis remains to be a well-accepted model so far.

3 Compartmental Models

Respiration has long been studied in two broad categories: 1. control of ventilation and 2. control of breathing patterns. This has been the case due to the general belief that each level is governed by different physiological systems. However, one may think of them as interrelated, the breathing rate has to be dependent on the ventilation. Let's take an example to assert this claim, during exercise muscles require more oxygen due to increased output hence ventilation should be more and that is why the rate of breathing increases. When we go at higher altitudes the amount of oxygen in the air is less and the breathing rate is increased to satisfy that breathing rate. There have been theories proposed, like the one proposed by Priban and Finchan (1965) which proposed that the objective of the integrated control mechanism is to 'maintain arterial blood gas homeostasis with the minimum respiratory effort'. Along these lines, the here discussed model provides a good framework for observing the integration of work done in mechanical breathing and chemical ventilatory output. The model hypothesis is that all the tidal respiratory responses, including breathing patterns and ventilation, are a direct outcome of the optimization of the inspiratory neural drive.

3.1 The Model

We model the respiratory control system as a closed-loop feedback control system comprising four major functional blocks: the controlled system, the feedback paths, the controller, and the actuator/effector. The ventilatory output ($\dot{V_E}$) results from a joint effect of chemical and neuromechanical feedback signals. The chemical feedback signals are modulated by the chemoreceptors to maintain constant levels of CO_2 and pH. With considerable approximation, the response of the neuromechanical feedback signal is assumed to be directly related to the respiratory neural output. The model postulates that $\dot{V_E}$ is always actively chosen by the controller to minimize the operating cost J of the form,

$$J = \alpha^2 (Pa_{CO_2} - \beta)^2 + lnW = J_c + J_m$$

where

$$W = \frac{\dot{V_E}^2}{(1 - \dot{V_E}/\dot{V_{max}})^2}$$

Here α and β are the apparent sensitivities and threshold of the CO_2 receptors and their values have been derived by other researchers. W is the measure of respiratory effort, J_c and J_m are the chemical and mechanical operating costs, and $\dot{V_{max}}$ is the maximum ventilation that can be sustained by the respiratory muscles. The gas exchanger is the compartment where the actual ventilation of the air (O_2 inspiration and CO_2 expiration) takes place. The exchange of these gases is given by the following equation.

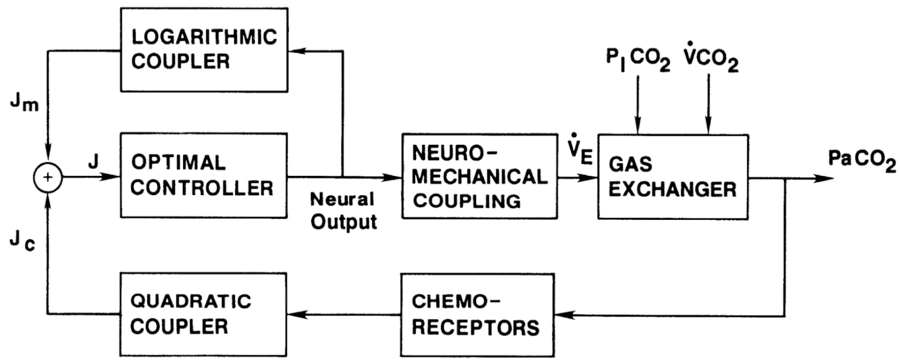

Figure 4: Compartmental Model Reference 1

$$Pa_{CO_2} = PI_{CO_2} + \frac{863\dot{V_{CO_2}}}{V_E(1-\dot{V_D}/V_T)}$$

Here Pa_{CO_2} is the pressure of CO_2 in the arteries PI_{CO_2} is the pressure of CO_2 in the inhaled air. $\dot{V_{CO_2}}$ is the metabolic output CO_2, V_D and V_T are the respiratory dead space and Tidal volume respectively. This equation was given by CS Poon (1). The idea of this effector system is based on a lumped parameter model proposed by Younes and Riddle for the relation between respiratory neural and mechanical outputs. They proposed the following first order equation which will also be exploited in this model, it originates from the idea of modelling dynamic Pneumatic Systems. Human lung itself being a Pneumatic system has to have equations which model the change in the volume and pressure w.r.t time. The equation is given as follows:

$$P(t) = \dot{V(t)}R_{rs} + V(t)E_{rs}$$

Here, the parameters R_{rs} and E_{rs} are the respiratory system's total flow-resistance and volume elastic components. These include the lungs, chest wall, and airways. The pressure wave shape is divided into two components, the inspiratory phase and the expiratory phase. During inspiration, time $0 < t < t_1$,the wave given by the form

$$P(t) = a_0 + a_1 t + a_2 t^2$$

Using the first-order dynamical system we get the equation of volume for time $0 < t < t_1$ as

$$\begin{aligned} &\mathrm{V}(t) = \left\{A_1 t + A_2 t^2 + A_3\left[1 - \exp\left(-t/\tau_{\mathrm{rs}}\right)\right]\right\} \tau_{\mathrm{rs}}/\mathrm{Rrs} \\ &+ \mathrm{V}_0 \exp\left(t/\tau_{\mathrm{rs}}\right) \end{aligned}$$

where

$$\mathrm{V}_0 = \mathrm{V}(0) = \mathrm{V}\left(t_1 + t_2\right)$$

and

$$A_1 = a_1 - 2a_2\tau_{\mathrm{rs}}$$
$$A_2 = a_2$$
$$A_3 = a_0 - a_1\tau_{\mathrm{rs}} + 2a_2\tau_{\mathrm{rs}}^2$$

Here, a_0, a_1, a_2 are hyperparameters and $\tau_{rs} = \frac{R_{rs}}{E_{rs}}$ is the time constant of the respiratory system. It is a measure of how quickly the system responds to changes in pressure or volume. The elastance is also sometimes used in its inverse form called compliance $C_{rs} = \frac{1}{E_{rs}}$ During expiration, time $t_1 < t < t_2$ we have the following equations of pressure and volume.

$$\mathrm{P}(t) = \mathrm{P}(t_1)exp(-(t - t_1)/\tau)$$

and

$$\mathrm{V}(t) = \frac{\mathrm{P}\left(t_1\right)}{\mathrm{Rrs}\left(1/\tau_{\mathrm{rs}} - 1/\tau\right)} \times \left\{\exp\left[\left(t_1 - t\right)/\tau\right] - \exp\left[\left(t_1 - t\right)/\tau_{\mathrm{rs}}\right]\right\} \quad + \left[\mathrm{V}\left(t_1\right)\exp\left[\left(t_1 - t\right)/\tau_{\mathrm{rs}}\right]\right.$$

3.2 Work done and frequency optimization

In this section, we will consider a dynamic framework to calculate the work done based on the inspiratory and expiratory Pressure-Volume equations. A detailed study of the derivation of the formulas of work done during inspiration and expiration couldn't be carried out in the interest of time. However, here is a brief introduction.

During inspiration, the work done is given by the following equation
Work Done:

$$\mathrm{W_I} = \frac{1}{\mathrm{TT}}\int_0^{\mathrm{t1}} \frac{\mathrm{P}(t)\dot{V(t)}}{\xi_1^n\xi_2^n}\mathrm{d}t$$

The equations are derived from the idea $W(t) = P(t)\dot{V(t)}$ where ξ_1, ξ_2 are the efficiency factors that account for the effects of respiratory-mechanical limitation and the decrease in neuromechanical efficiency with the increasing effort given by;

$$\xi_1 = 1 - \frac{P(t)}{P_{max}}$$

$$\xi_2 = 1 - \frac{\dot{P(t)}}{\dot{P_{max}}}$$

Here the values of $P_{max}, \dot{P_{max}}$ are experimentally taken. The values of efficiency factors are important in determining the efficiency of neuromechanical coupling. A decreased value of the efficiency factor could be an outcome of a disease that causes muscle weakness. The maximum pressure and velocity of the inspired air are simultaneously expected to be low in such cases. The parameter n describes the nonlinear variation of the efficiency. For given values of P_{max} and $\dot{P_{max}}$ the values of efficiencies decrease with an increase in n. Work done during expiration:

$$\mathrm{W_E} = \frac{1}{\mathrm{Tt}} \int_{\mathrm{t_1}}^{\mathrm{Tt}} \mathrm{P}(t)\dot{\mathrm{V}}(t)\mathrm{d}t$$

Here, t_1 is the ending time of inspiration and Tt is the total breathing time.

The total mechanical work done is given by the following equation

$$J_m = \mathrm{W_I} + \mathrm{W_E}$$

Now, we can go back to our previous equation of total work done

$$J = J_c + J_m$$

We have J as the total work done and for the conditions of minimal work done we need to minimize J w.r.t parameters

$$[a, a_1, a_2, t_1, t_2, \tau]$$

then we can have the frequency of breathing as $f = \frac{1}{t_1+t_2}$.

4 Conclusion and Future Work

In this report, we saw a few models of breathing and from the principle of least action, we tried to find the parameters of breathing, especially the frequency. Then we looked at more complex models that took into consideration not just the mechanical work done but the work done by inspiratory neural drive. These models give us an idea of how respiration works and how we can mathematically formulate its model from different perspectives. We are in the process of implementing these equations by fine-tuning the parameters to create a full model of the human respiratory system Link. We can then try to see how it is affected in diseased situations like Obstructive Sleep Apnea. It would also be useful to find if the model replicates these situations by hypertuning the parameters. Identifying the changes in time constants is another work that can be carried out from the model.

5 References

1. Poon CS. Ventilatory control in hypercapnia and exercise: optimization hypothesis. J Appl Physiol (1985). 1987 Jun;62(6):2447-59. doi: 10.1152/jappl.1987.62.6.2447. PMID: 3112108.
2. Poon CS, Lin SL, Knudson OB. Optimization character of inspiratory neural drive. J Appl Physiol (1985). 1992 May;72(5):2005-17. doi: 10.1152/jappl.1992.72.5.2005. PMID: 1601812.
3. OTIS AB, FENN WO, RAHN H. Mechanics of breathing in man. J Appl Physiol. 1950 May;2(11):592-607. doi: 10.1152/jappl.1950.2.11.592. PMID: 15436363.
4. Mead, J. (1960). Control of respiratory frequency. Journal of Applied Physiology, 15(3), 325-336. https://doi.org/10.1152/jappl.1960.15.3.325
5. Calabrese P, Baconnier P, Laouani A, Fontecave-Jallon J, Guméry PY, Eberhard A, Benchetrit G. A simple dynamic model of respiratory pump. Acta Biotheor. 2010 Sep;58(2-3):265-75. doi: 10.1007/s10441-010-9108-7. Epub 2010 Jul 23. PMID: 20652727.