Investigations Into
Transient Respiratory Control using the
Work Rate of Breathing
and a Non-linear Breather

by

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Abstract

An optimal and feedback control routines were developed in this thesis to control simulations of a respiratory system with a muscle and lung compartments. The optimal model was used to find the alveolar ventilation and the Van der Pol constants ($\alpha$, $\omega$, and $\epsilon$) that could be used in the body during the steady-state of exercise for each work load. Then, the feedback control model was used to simulate the transient exercise states. The alveolar ventilation was calculated in the feedback control model using a proportional (mean) and a derivative (rate) control. Then, the Van der Pol constants were found from the alveolar ventilation found in the optimal routine. In addition, simulations were done in the steady-state for 3 %, 5 %, and 6 % carbon dioxide inhalation.

Once the controller constants had been found, the transient-state of the feedback model showed great promise as the partial pressure of arterial carbon dioxide did not become more than 3.8 % greater than the value that is maintained in the body. The carbon dioxide inhalation tests came within 3 % of the experimental values given by Reynolds (1972).

The results from this thesis show that using a Van der Pol oscillator as the breather in the model seems to keep the partial pressure of arterial $CO_2$ around the value that is maintained in the body for aerobic exercise and $CO_2$ inhalation.
I would like to thank Dr Harry H. Robertshaw for his much needed support and guidance. I would also like to thank my friends and family without whom I never would have finished.
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<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$BTPS$</td>
<td>body temperature and pressure</td>
<td></td>
</tr>
<tr>
<td>$CSF$</td>
<td>cerebral spinal fluid</td>
<td></td>
</tr>
<tr>
<td>$CC$</td>
<td>mean controller gain</td>
<td></td>
</tr>
<tr>
<td>$C_{aCO_2}$</td>
<td>arterial concentration of $CO_2$</td>
<td>$l/l$ blood</td>
</tr>
<tr>
<td>$C_{vCO_2}$</td>
<td>venous concentration of $CO_2$</td>
<td>$l/l$ blood</td>
</tr>
<tr>
<td>$C_{umCO_2}$</td>
<td>venous concentration of $CO_2$ in the muscle</td>
<td>$l/l$ blood</td>
</tr>
<tr>
<td>$f$</td>
<td>frequency</td>
<td>breaths/min</td>
</tr>
<tr>
<td>$F_{aCO_2}$</td>
<td>arterial fraction of the concentration of $CO_2$</td>
<td></td>
</tr>
<tr>
<td>$H$</td>
<td>hydrogen ion concentration of arterial blood</td>
<td></td>
</tr>
<tr>
<td>$k$</td>
<td>elastic resistance</td>
<td>$cm H_2O/l$</td>
</tr>
<tr>
<td>$k'$</td>
<td>turbulent and viscous resistance of air</td>
<td>$cm H_2O/(l/s)$</td>
</tr>
<tr>
<td>$k''$</td>
<td>resistance of tissue deformation</td>
<td>$cm H_2O/(l/s)^2$</td>
</tr>
<tr>
<td>$M$</td>
<td>metabolic $CO_2$ production</td>
<td>mmHg</td>
</tr>
<tr>
<td>$O_2$</td>
<td>oxygen</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P$</td>
<td>pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{aCO_2}$</td>
<td>arterial partial pressure of $CO_2$</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{aCO_2}$</td>
<td>mean value of $P_{aCO_2}$</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{aCO_2, max}$</td>
<td>maximum positive arterial partial pressure of carbon dioxide</td>
<td>mmHg/sec</td>
</tr>
<tr>
<td>$P_{aO_2}$</td>
<td>arterial partial pressure of $O_2$</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{atm}$</td>
<td>atmospheric pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{ACO_2}$</td>
<td>alveolar partial pressure of $CO_2$</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{CBO_2}$</td>
<td>mean value of partial pressure of arterial $CO_2$ at the carotid bodies</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>partial pressure of $CO_2$</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>partial pressure of $O_2$</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{set}$</td>
<td>normal setting of $P_{aCO_2} = 40$ mm Hg</td>
<td>mmHg</td>
</tr>
<tr>
<td>$P_{TCO_2}$</td>
<td>partial pressure of the tissue concentration</td>
<td>mmHg</td>
</tr>
<tr>
<td>$SCV$</td>
<td>derivative controller gain</td>
<td></td>
</tr>
<tr>
<td>$STPD$</td>
<td>standard temperature and pressure(dry)</td>
<td></td>
</tr>
<tr>
<td>$u$</td>
<td>lung switch function</td>
<td></td>
</tr>
<tr>
<td>Character</td>
<td>Definition</td>
<td>Units</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>$\dot{V}$</td>
<td>ventilation</td>
<td>$l/sec$</td>
</tr>
<tr>
<td>$\dot{V}_{ave}$</td>
<td>minute-averaged ventilation</td>
<td>$l/min$</td>
</tr>
<tr>
<td>$\dot{V}_{e}$</td>
<td>expired ventilation</td>
<td>$l/min$</td>
</tr>
<tr>
<td>$\dot{V}_{max}$</td>
<td>maximum of ventilation output</td>
<td>$l/min$</td>
</tr>
<tr>
<td>$V_M$</td>
<td>volume of blood in the muscle</td>
<td>$l$</td>
</tr>
<tr>
<td>$\dot{V}_{MCO_2}$</td>
<td>metabolic production rate of $CO_2$ in the muscle</td>
<td>$l/sec$</td>
</tr>
<tr>
<td>$\dot{W}$</td>
<td>work of breathing</td>
<td>$lb \cdot ft/sec$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>amplitude of breathing</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>frequency of breathing</td>
<td></td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>shape of breathing</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

The control of respiration has fascinated researchers for many years. Since the first mathematical model of pulmonary control was published in 1946 by Gray, a considerable amount of research into respiratory control has resulted. One problem that researchers have had to contend with is the increase of respiration during muscular exercise, despite little increase in the intensities of chemical stimulation to breathing. During exercise (a metabolic carbon dioxide ($CO_2$) load), ventilation increases while the partial pressure of arterial $CO_2$ ($P_{aCO_2}$) stays at the same level or is isocapnic. However, when a person is not exercising but inhales $CO_2$ as if exercise were occurring ($CO_2$ inhalation), the $P_{aCO_2}$ rises. This observation has motivated numerous theories about the structure of the respiratory controller. Researchers have studied both transient and steady-state pulmonary control mechanisms extensively but still do not have a satisfactory answer.

One way that this has been studied by researchers is by producing a mathematical model of the pulmonary control system. A hypothesized controller is used to maintain the level of $P_{aCO_2}$ at the level that is maintained in the body. At first researchers used only proportional or mean control as they tried to find what body
physics were used in the controller. Then the research was directed at the controller. Saunders (1980a,b) was the first person who tried a controller that had only the derivative or rate control. This was later expanded by Ellis (1984) who used the derivative control that Saunders tried, in addition to the proportional control. Ellis tried both steady-state and transient control but, although the results from his model were moderately good, there is a 12.5% error or a rise of about 5 mm Hg in $P_{aCO_2}$ above the 40 mm Hg which is maintained by the body.

A different approach to the problem was first suggested by Roher (1925) who thought that the balance between tidal volume and respiratory frequency may be guided by some optimization mechanism. As opposed to conventional reflex control schemes, Poon (1987) used this approach by producing an optimal control model, such that the net challenge due to the conflicting chemical and mechanical costs of breathing is minimized. Poon's model derived a ventilatory drive that balanced the chemical cost of regulation with the mechanical cost of breathing. In this way, the model regulated the $P_{aCO_2}$ under a metabolic load and increased the $P_{aCO_2}$ under an airway load. Although Poon obtained good results using the optimal control model in the steady-state, he did not try the transient-state.

The purpose of this study is to investigate the shape of the respiratory pattern as a variable in respiratory control. A small subset of all possible shapes that are included in the Van der Pol equation are incorporated in this model. The best values for the Van der Pol equation were found by determining the lung volume represented and these were the values that were tested.
Two different control concepts were developed in order to simulate the transient pulmonary control in $CO_2$ inhalation and the onset of exercise. The first control concept is in the steady-state optimal model which was used to find the Van der Pol constants ($\alpha$, $\omega$, and $\epsilon$) for each work load. The $\alpha$ is inversely proportional to the amplitude, the $\omega$ is the frequency and $\epsilon$ defines the shape of the curve. Although the optimal model does not have the controller explicitly in the model, the controller is implicitly contained in the performance index. The second controller is in the feedback model. Once the optimal model has been run for each work load, the feedback model takes the steady-state optimal control constants of the Van der Pol equation and uses them in the transient-state of the feedback controller. After the controller constants have been found, the feedback models response to the onset of exercise and $CO_2$ inhalation is tested.

Grodins (1973) hypothesized the strategy of the respiratory controller to balance the desire for regulation of $P_{aco_2}$ with the associated work of breathing. This was taken into account by Poon (1985, 1987) and Swanson (1985) who used the work of breathing in an optimal model. Poon developed an optimal control model that balances the chemical and the mechanical costs of breathing. The work of breathing was calculated as part of the cost function but was not used in the model equations. Saunders and Ellis’ models did not have the work of breathing because the energy cost of breathing is considered to be minimal and was not included in the model. The energy cost of breathing is minimal at low exercise rates and the body must breath more as the exercise increases causing the work of breathing to increase almost 42 %. In this thesis, the work of breathing is calculated and added to the metabolic production rate in the muscle compartment.
In the models used by Saunders, Ellis and Poon, the sinusoidal equation is used as the ventilator. The amplitude and the frequency can be changed but the shape of the curve remains fixed. In this thesis, the Van der Pol equation is used as the ventilator. A Van der Pol breather will allow the shape of the curve to change, as well as the amplitude and the frequency. The work of breathing may cause changes in the shape of the curve of the ventilator as exercise begins.

The results of this thesis give an indication that there could be an optimal controller that works with a chemosensory feedback controller in the body. Although the optimal model was only run for steady-state results, it produced a $P_{aCO_2}$ that stayed just above 40 mm Hg. Whereas, Poon's steady-state optimal model produced a $P_{aCO_2}$ above 45 mm Hg under resting conditions within the range of minute ventilation that was used in this thesis. The feedback model gave very good results in the transient-state of the controller as the $P_{aCO_2}$ was 2% above 40 mm Hg, while in Saunders (1980a,b) paper it was 3.8% above 40 mm Hg and 8% in Ellis'(1984) thesis. The tests of the $CO_2$ inhalation were off the most by only about 3% from experimental data taken by Reynolds (1972) for 6% $CO_2$ inhalation.

A review of publications pertaining to respiratory control during exercise is presented in the next chapter. In addition to mathematical models of respiratory control during exercise, those containing transient response information and ventilatory control concepts are also discussed. A review of the optimal and the feedback model is presented in the model development section, Chapter 3. A knowledge of respiratory physiology is needed to understand the models presented and, also the
simulations performed. The results of the simulations are discussed in Chapter 4 and some conclusions are made in Chapter 5.
Chapter 2

Literature Review

The control of respiration has fascinated researchers for many years. If respiratory control mechanisms were known or could be described, the system response to various stimuli could be predicted. Unfortunately, a satisfactory description of respiratory control mechanisms has yet to be determined. As a result of intense studies in this area, researchers have improved their techniques in attaining information about this complex mechanism.

After Gray presented his multiple factor theory in 1945, there has been an abundance of work into what the controller does, what kind of model it works on, and what kind of controller the respiratory system uses. Researchers began by using a simple system and gradually, as the computer became easier to use with more computing power, it has become more complex. Now that researchers have an idea about how to model the system, they have turned to the controller.

The control concept has been very much in debate. Researchers have discovered that it is the partial pressure of carbon dioxide ($P_{CO_2}$) that the body measures to control respiration, with the partial pressure of oxygen ($P_{O_2}$) and $pH$ second in
importance (Casaburi (1977, 1978), Ward (1983)). In this thesis, only the main driving component for breathing is dealt with.

There are many different ways in which the controller concept has been researched. Researchers have looked into proportional (mean) control, derivative (rate) control, a combination of both, and some have proposed breathing control laws which optimize some performance index. All of these concepts will be discussed in more detail in this section.

A review of publications pertaining to respiratory control during exercise is presented in this chapter. In addition to mathematical models of respiratory control during exercise, those containing transient response information and ventilatory control concepts are also discussed. They are classified in three categories and have been arranged according to model characteristics.

The first category is the experimental study of respiration. These are experimental studies done on dogs and humans to discover more about the respiratory controller. The second category models the body physics. There is a mathematical model in this category, but the controller is of secondary importance. Instead, the body physics (what is important in the respiratory controller) is studied. The last category deals with models of control mechanisms. The controller is of primary importance in these models. Therefore, most of the models presented have a standard type of body chemistry and the controller is the major difference. There are three main types that will be discussed. The first just has proportional (mean) control, the
second has proportional and (or) derivative (rate) control, and the last section deals with optimal control.

2.1 Study of Respiration

The transient and steady-state response studies are concerned with the dynamic relationship between ventilation and gas exchange variables during exercise. There is no model and no direct control. Statements made about possible control mechanisms broadly classify them as central (medullary) control or peripheral (carotid body) control concepts. The peripheral control is fast and responds to the disturbance first. Then, the central controller takes over and comes to a steady-state in a slower fashion (Grodins, 1978). The peripheral or rapid ventilatory component of the response was defined as being phase 1, the central or slow rise to the steady-state as phase 2 and the steady-state itself as phase 3 (Whipp, 1978). In this case, the peripheral control (phase 1) is what we are concerned with. In the following, the study of respiration will be discussed.

Wasserman et al. (1974) tried to determine if acute increases in cardiac output ($\dot{Q}$) could increase the ventilation. Precise regulation of $CO_2$ by the respiratory control system was assumed to be the result of a change in ventilation appropriate to the increase in blood flow, when venous $CO_2$ tension has not yet had time to change. They hypothesized that if breathing control functioned to regulate $CO_2$ precisely, ventilation should increase with an increase in $\dot{Q}$. 
To test this hypothesis, they induced $\dot{Q}$ changes in dogs by isoproterenol infusion or cardiac pacing. Minute ventilation and $\dot{Q}$ where measured breath-by-breath and beat-by-beat respectively, before and after abrupt increases in $\dot{Q}$ in unanesthetized and anesthetized dogs. The increased $\dot{Q}$ resulted in hyperpnea occurring during the breath following the start of cardiovascular effects. Increasing $\dot{Q}$ by cardiac pacing also resulted in abrupt hyperpnea. Sudden ventilatory changes associated with these procedures provided evidence that a mechanism exists by which hyperpnea is initiated by an increase in $\dot{Q}$. Wasserman et al. concluded that $\dot{Q}$ could be used as a controller stimulus.

Casaburi et al. (1977) tried to define the interrelationship among respiratory variables in exercise. They did this by taking five subjects exercising on a cycle ergometer for 30 minutes at work rates which fluctuated sinusoidally. The dynamic relationship between ventilation and gas exchange variables during exercise were determined using frequency analysis techniques. Digital computer routines extracted amplitude and phase relations between each variable and the perturbing work load.

Casaburi found that the ventilatory responses to sinusoidal workload perturbations did not suggest a significant rapid component. Instead, the finding of very close correlation between the dynamics of $CO_2$ production and ventilation suggested that exercise hyperpnea is closely linked to $CO_2$ flow in the lung. The fact that ventilatory response is precisely matched to the rate at which $CO_2$ reached the lung suggested to them that the sensory system is located more centrally at the lungs or in the arterial circulation instead of at the site of metabolism. This showed that exercise hyperpnea is linked to metabolism via $CO_2$ production.
In Casaburi’s next paper (1978), he was determined to find the role of receptors sensitive to variations in the rate of limb movement. The design of this study was intended to produce wide fluctuation in the rate of limb movement while minimizing the variation in the metabolic cost of the exercise. He found that ventilatory fluctuations were in close amplitude and phase relation with $CO_2$ output fluctuations. The dynamic interrelation of ventilatory and $CO_2$ production is, apparently, the same whether the $CO_2$ is produced by variation of pedaling rate or by variation of work rate.

Casaburi stated that their results provided additional evidence that the exercise hyperpnea is linked to metabolism through the associated $CO_2$ production and argued against an appreciable role for mechanoreceptive afferents from the exercising limbs. Again, this proved that exercise hyperpnea is related to $CO_2$ production.

Pearce and Milhorn (1977) studied the transient response of a large number of variables including the respiratory frequency, tidal volume and minute ventilation before, during, and after exercise. They wanted to investigate the dynamics of the peripheral or fast component of ventilation.

A study of the transient respiratory responses to step changes in work load ranging from 0 to 800 kpm/min on a cycle ergometer were determined. The experiments were then averaged on a five second interval basis and a breath-by-breath analysis was completed.
The results indicated that a fast component was found in the transient responses varying with workload. The breath-by-breath variability in ventilation was smaller than that of respiratory frequency and tidal volume. Therefore, this implied that minute ventilation is the controlled variable with respiratory frequency and tidal volume varying to maintain the required ventilation.

The link between ventilation and cardiac output (\(\dot{Q}\)) was shown again in the work by Ward et al. (1983). Ward did a study on the depletion of body CO\(_2\) stores and the effect they have on the ventilatory dynamics of exercise. If pulmonary CO\(_2\) flow (the product of \(\dot{Q}\) and mixed venous CO\(_2\) content) is important in respiratory control, Ward thought that the depletion of these stores should slow the response at the onset of exercise until the stores are replenished.

Lowering the body's CO\(_2\) stores was accomplished by controlled volitional hyperventilation with care not to cause temporary apnea. Earlier investigations (Asmussen, 1973) having put the subject in an apneic state at the onset of work. The exercise test consisted of a series of 100 Watt (W) square-wave inputs on a cycle ergometer.

Ward concluded that the slowed dynamics of the exercise hyperpnea that are associated with the reduction of body CO\(_2\) stores are the consequence of the corresponding slowing of the pulmonary CO\(_2\) flow response. This test seemed to show that CO\(_2\) is an important stimulus in transient respiratory control.
2.2 Models of the Body Physics

In this section, the body physics of the respiratory control system is discussed. The researchers tried to find what body physics were used in the controller. So, in this case, it is not the controller that is important but what was used as the controller stimulus.

Gray (1945) was the first researcher who concluded that the respiratory cycle might involve more than just one unique stimulus. Researchers who had previously used just one of the factors (oxygen \((O_2)\), \(CO_2\), \(pH\), etc.) had found an answer to some very specific problems but their theories did not explain any other problems. Gray's multiple factor theory shows that there is more than just one factor involved in respiration.

In his theory, Gray attempted to describe quantitatively the integrated action of the various factors which control respiration regardless of their sites of action or mechanisms. He concluded that a number of factors exert independent effects on ventilation postulating that these factors have an additive effect on respiration. The actual ventilation is defined as the algebraic sum of the partial effects of the agents.

\[
\dot{V} = 0.22H + 0.262P_{CO_2} - 18.0 + 105/10^{(0.038P_{O_2})}
\]

where \(H\) is the Hydrogen-ion concentration of arterial blood, \(P_{CO_2}\) is the arterial tension of \(CO_2\), and \(P_{O_2}\) is the arterial tension of \(O_2\). A change in any one of them usually brings about changes in the others.
Gray's multiple factor theory worked fairly well for anoxia resulting from exposure, $CO_2$ inhalation, and acidosis. Although he thought that passive and active exercise as a stimulus would work in his model, he did not try this. Although Gray did not figure out the exercise stimulus, he completed the most important step of getting research started in the respiratory control system.

After Gray's theory, there was a multitude of research done into the respiratory system. Grodins et al. (1954) produced a respiratory model with the control engineering approach to the pulmonary system. The model, shown in Figure 2.1, was used to determine the response of the respiratory system to $CO_2$ inhalation.

Grodins used a two-compartment model with a lumped representation of the lung and tissue reservoirs. The lung was assumed to be a box of constant volume with zero dead space. The circulation delays between compartments and cyclic ventilation were neglected. The $CO_2$ dissociation curve used in this model was assumed to be a linear equation, which is a reasonable assumption since the curve is nearly linear in the operating range of the model.

The controller used in this simulation was a proportional feedback controller, shown in the block diagram in Figure 2.2, using the partial pressure of the tissue concentration ($P_{T_{CO_2}}$). $P_{T_{CO_2}}$ was used instead of the $P_{aCO_2}$ because of the zero-time circulation delay between compartments.
Figure 2.1: A Diagram of the Respiratory Model of Grodins et al. (1954)
Figure 2.2: A Diagram of the Proportional Feedback Controller Used by Grodins et al. (1954)
Compared with experimental data for step inputs of $CO_2$ and $O_2$, this model gives surprisingly good results. However, Grodins et al. (1954) realized that the model was incomplete and did not cover all the aspects of the respiratory system.

Work done after Grodins et al. (1954) is generally an expansion of their respiratory model. Defares et al. (1960) split the tissue reservoir into two distinct compartments: brain and body tissues. $P_{CO_2}$ was used as the controlled variable. The model agreed with the results of Grodins but there was a difference in the transients of $CO_2$ inhalation. Defares' model showed an undershoot in the off-transient (cessation of $CO_2$ inhalation), while the model by Grodins et al. showed an overshoot under the same conditions. Defares does not attempt to explain this and admits only that they are different.

Milhorn et al. (1965), shown in Figure 2.3, took Defares model and added the effects of $O_2$ as a controller of ventilation and time delays in the transport of gases from the lungs to the two tissue reservoirs. These factors were considered to be important in describing the respiratory control. They obtained transient and steady-state solutions for both positive and negative step input disturbances of inspired $CO_2$ and $O_2$ concentrations. Since Grodins et al. and Defares et al. previously considered both steady-state and transient transfer functions to be identical, so does Milhorn et al. although he did realize the limits it set.

The model included a brain, lung and lumped body tissue compartments and had both $CO_2$ and $O_2$ in the system equations. The circulation time delay between
Figure 2.3: A Diagram of the Respiratory Model of Milhorn et al. (1965)
compartments were included while the cyclic changes in ventilation were ignored. The brain blood flow was assumed to be a function of $P_{aO_2}$.

The ventilatory control was a form of Gray's multiple factor theory in that the control variables were added forms of $P_{CO_2}$ and $P_{O_2}$. Hydrogen ion ($H^+$) concentrations was accounted for indirectly since it is a function of $P_{aCO_2}$.

The results showed that the computer transients to $CO_2$ step inputs were more rapid than those found experimentally in man. Milhorn et al. postulated that the controller equations might have a derivative (rate) control, in addition to the proportional (mean) control. This was the first time that this was acknowledged but it took several years to be considered.

2.3 Models of Control Mechanisms

In models of control mechanisms, mostly the controller is being analyzed in the steady-state and the transient-state. Some of the researchers have analytical, as well as, experimental results. There are three main types that will be discussed. The first just has proportional (mean) control, the second has proportional and(or) derivative (rate) control, and the last section deals with optimal control.
2.3.1 Proportional Control

A large detailed model of the respiratory system, shown in Figure 2.4, was presented by Grodins, Buell and Bart (1967). This model was developed to simulate $CO_2$ inhalation, hypoxia at sea level, altitude hypoxia and metabolic disturbances in the acid-base balance. Simulations of the transient and the steady-state response were performed.

The model included the brain compartment with a cerebral spinal fluid (CSF) reservoir, as well as the lungs and the tissue. The system equations were developed from nitrogen, $O_2$ and $CO_2$ mass balances around each compartment. A variable cardiac output which is a function of $P_{CO_2}$ and $P_{O_2}$ was included, as well as, circulation time lags. The complexity of this model leads to differential-difference equations which were solved by a digital simulation.

Two different controller algorithms were presented with this model. One controller added inputs from the brain, $H^+$, $P_{CO_2}$, and $P_{aCO_2}$ at the peripheral chemoreceptors. While the other uses CSF $H^+$ and both arterial $H^+$ and $P_{O_2}$ at the peripheral receptors incorporated by the recent findings of their roles in ventilation (Dejours (1963), Mitchell (1963)). These controllers added the individual effects of each variable, and no multiplicative or derivative effects were included. A variety of forcings were studied including $CO_2$ inhalation, hypoxia at sea level, metabolic acidosis, and altitude hypoxia.
Figure 2.4: A Diagram of the Respiratory Model of Grodins, Buell, and Bart (1967)
The results from the first controller were good for \( CO_2 \) inhalation but a short period of hypoxia led to an interval of periodic breathing. Although this behavior was probably just a computational error, it did not appear in the experimental data.

The second controller gave the most satisfactory results. Although the entire time course of the response to metabolic acidosis was obtained, the forcings were introduced in a highly artificial manner. However, it is interesting that a stable solution was obtained. Although Grodins, Buell and Bart (1967) do not attempt to account for exercise hyperpnea, they mention that the model should work if a general description of the control of cardiac output and regional blood flow was included.

Yamamoto (1978) developed a respiratory model, shown in Figure 2.5, for the study of the hyperpnea of exercise and \( CO_2 \) inhalation. The behavior of this model was used to postulate a hypothesis for the humoral component of respiratory regulation of \( CO_2 \) exchanges.

The model was a three-compartment model consisting of brain, tissue, and lung components. Each compartment consisted of a cellular space, an extra-cellular space and a capillary blood volume. This model had cyclic ventilation and the cardiovascular considerations presented by Grodins, Buell, and Bart (1967) and Defares et al. (1960). Only \( CO_2 \) exchanges were included because \( O_2 \) exchanges are not closely coupled to ventilatory regulation under \( CO_2 \) control.
Figure 2.5: A Diagram of the Respiratory Model of Yamamoto (1978)
This model contained a couple of interesting approaches. In the first one, the cardiac output was not a function of $P_{aCO_2}$ like the model of Grodins, Buell and Bart (1967). Instead, it was a function of the metabolic production of $CO_2$. The next interesting aspect about this model was the modeling of the blood as a series of slugs of constant chemical composition. Yamamoto used one hundred slugs of blood to give a total systemic blood volume of 6.0 litres. This makes the blood gases look like discrete or sample and hold values when in fact they are continuous.

The controller used three variables: extra-cellular brain $PCO_2$, intercellular brain $PCO_2$, and the time lagged signal of the temporal $P_{aCO_2}$ (covariance). Again, there was no derivative control. Various forms of controller functions were introduced to discover one structure that would simulate both the steady-state hyperpnea of venous $CO_2$ infusion, and the well-documented observations on pulmonary ventilation when $CO_2$ is inhaled.

To demonstrate the effects of each controller component on ventilation, several hundred different cases of the model were run, taking between six to ten hours for each case to run. From these runs, six were selected that established the possibility that this analytic form met the constraints or demonstrated the contribution of each component to the solution.

One of the models (Model 5) gave the best results for the hyperpnea of $CO_2$ inhalation ($P_{aCO_2}$ increases) and the increased $CO_2$ production ($P_{aCO_2}$ stays the same). The controller was required to use all three of the variables (extra-cellular brain $PCO_2$, intercellular brain $PCO_2$, and the time lagged signal of the temporal $P_{aCO_2}$).
The principle weakness in this model was the expression that simulated the dependence of cerebral blood flow on $P_{aCO_2}$. Yamamoto stated that the model was sufficient to relate one humoral component, $CO_2$, to its possible role in the regulation of ventilation.

Damokosh-Giordano et al. (1979) investigated the interaction between the characteristics of the respiratory controller and $CO_2$ stores by studying the results of the model shown in Figure 2.6. The rate of change of $P_{aCO_2}$ and tissue $CO_2$ storage following either $CO_2$ inhalation, rebreathing, or apnea was evaluated using both experimental and theoretical results.

The experimental results were accomplished on dogs using two anesthetized rats, one more deeply then the other. In general, $CO_2$ elimination in the dogs following rebreathing decreased less for a given decrease in ventilatory response slope then when there was a concomitantly large increase in the $P_{aCO_2}$ intercept or threshold. There was no clear pattern in the effect of increased anesthesia on the rate of $CO_2$ storage during the on-transient.

The theoretical results investigated the effect of variations in controller sensitivity on $CO_2$ storage. The mathematical model used was a lumped-parameter multi-compartment system. There were four compartments: muscle, brain, lung and "all other" tissues. The system equations were derived from mass balances around each compartment.
Figure 2.6: A Diagram of the Respiratory Model of Damokosh-Giordano et al. (1979)
Two controller characteristics were considered: the sensitivity of the controller and the controller threshold, and the minimum level of $P_{CO_2}$ needed to excite spontaneous breathing. The ventilatory controller was based on the relationship between the alveolar ventilation, and blood $pH$ and $P_{O_2}$.

The results showed that it was necessary to have a high $CO_2$ response given a level of resting $P_{aCO_2}$ for $CO_2$ elimination. However, this was at the expense of maintaining a high level of steady-state $P_{CO_2}$. This seems to indicate that a variable gain may be employed by the body depending upon physiologic conditions.

2.3.2 Proportional and/or Derivative Control

K.B. Saunders et al. (1980a) produced a four-compartment model, shown in Figure 2.7, that was similar to the one presented by Grodins, Buell, and Bart (1967). The major change was that the $P_{CO_2}$ in the lungs was allowed to oscillate, allowing blood gas concentrations and $pH$ to change. Other modifications included a dead space where no gas exchange occurs, a lung blood shunt to model the non-oxygenated bronchial circulation, and a muscle compartment separate from the rest of the model.

Mean blood gas partial pressures ($P_{CO_2}$, $P_{O_2}$) were used in the control algorithm to determine ventilatory drive. Saunders takes the values of blood gas partial pressures and filters them so that the controller only deals with the mean values. The controller uses the filtered values for $P_{aCO_2}$ and $P_{aO_2}$ in a proportional equation. The control sensor was located in the lung.
Figure 2.7: A Diagram of the Respiratory Model of K.B. Saunders et al. (1980)
Saunders found that this model worked for steady-state and dynamic results for increased $CO_2$ concentration whether it was increasing in the blood or the lung. However, Saunders found that the controller did not work well for hypoxic gas mixtures, exercise, and $CO_2$ breathing. The exercise on-transients showed an unreasonable delay in the ventilatory response to exercise. Accompanying this delay was an overshoot in tidal volume and an undershoot in $P_{aCO_2}$. Saunders suggested that these problems “would be more appropriately corrected by adjusting the controller rather than the controlled system.”

In Saunders (1980b) next paper, he addressed the problem of the controller in an effort to model the exercise hyperpnea (increase of respiration) response. Saunders continued to use the same structural model with no changes. The new control algorithm was a function of the maximum positive slope of $P_{aCO_2}$ plus the old feedback controller which is characterized by $f(Lloyd)$ in courtesy to its origin (Lloyd, 1958).

$$\dot{V} = 6.15[\dot{P}_{aCO_2}]_{max} - 1.0 + f(Lloyd)$$

This time the control sensor was assumed to be the carotid body. The associated circulatory time delay between the lung and carotid body was added.

The results of the new controller in modelling exercise hyperpnea were apparently quite good, although Saunders does not show the time response of $P_{aCO_2}$. Instead, the ventilation versus $P_{aCO_2}$ was shown. The final $CO_2$ inhalation response during exercise was shown as having the same slope as the response at rest. Saunders was the first person who tried using the derivative response in the controller and, from this, the work of Mann (1983) and Ellis (1984) was done.
Mann (1983) developed a model, shown in Figure 2.8, that combined some of the features of Saunders (1980a, 1980b) and Yamamoto's (1978) models. Although Mann's model did test peripheral chemoreceptor control at the onset of exercise, there were many limitations. Mann desired to find out what the carotid body detected at the start of exercise if the $P_{aCO_2}$ was isocapnic (stayed the same) and if the body could function on just a derivative controller.

The model was limited to CO$_2$ exchanges since it is known to be the contributing factor in the respiratory control system. The residual volume and the dead space were kept constant. Mann included a left ventricle that acted as a mixing chamber for the blood before it reached the carotid body. There was no brain compartment since the brain has been shown to have a minimal effect on ventilation under transient conditions. The lung was cyclically ventilated and a fixed lung blood volume of 0.15 liters was assumed.

Mann used the slope of $P_{aCO_2}$ as the controlled variable. This controller was the same as one of Saunders' (1980b) controlled variables except the gain has been lowered.

The results were good though discontinuities occurred twice when the model missed a breath. Mann suggested that a mean-only control be tested to see if the 5 mm Hg hypercapnic response occurred in the steady-state as it does on subjects who have had carotid body resections. Mann found that the derivative only controller did not stabilize the $P_{aCO_2}$ as well as Saunders controller.
Figure 2.8: A Diagram of the Respiratory Model of Mann (1983)
More recently, Ellis (1984) has enlarged upon Saunders’ work. Ellis developed three mathematical models of varying complexity (first, third, and tenth-order models) to simulate transient pulmonary response. These models were used to test control algorithms that the body may use in transient pulmonary control and also to determine what physiologic structures are important to obtain a meaningful working model.

In addition, transient response data from one individual was included to verify the model responses. Only one subject was tested since the averaging of test data from many individuals was thought to allow too much variation in control variables. Only the controller constants need to be redefined if another subject is tested, not the model itself.

The transient response data from the subject was taken on a treadmill for a work load of 100 W and 250 W. For the work load of 100 W, the $P_{aCO_2}$ values and ventilation appeared too low possibly because of gas mixing and dead space in the lung. Results from the 250 W work load were similar to the 100 W work load except the $P_{aCO_2}$. During rest it was the same as the 100 W work load, but during exercise the steady-state value falls. The diversity in these two tests made it difficult to determine which test the model should be compared to.

Three mathematical models were used to determine the minimum physiologic structure necessary to obtain an accurate model. The first-order model, Model A (shown in Figure 2.9), had only the cyclic gas exchange of $CO_2$ with no provisions for dead
Figure 2.9: A Diagram of the Respiratory Model (Model A) of Ellis (1984)
space. The cyclic ventilation allows for a time variation of $P_{CO_2}$ in both the alveolar air and the capillary blood. Model B, a third-order model shown in Figure 2.10, added a variable-volume dead space and a muscle compartment. The circulation time delays between the lung and muscle were added, as well as the delay between the lung and the carotid body. Model C, a tenth-order model, had two more physiologic compartments, a brain and "other" non-muscle tissue. In addition, the circulation time delays associated with these compartments were included. A lung blood shunt was added to allow for the non-oxygenated bronchial circulation (blood that feeds the lung). It was essentially the same as that presented by Saunders (1980a).

The controller in each model is given below. The carotid body was used as the control sensor in all models.

Model A:

$$\dot{V} = SCV[\dot{P}_{aCO_2}]_{max} + CC(\bar{P}_{CO_2} - 40)$$

Model B and C:

$$\dot{V} = SCV[\dot{P}_{aCO_2}]_{max} + CC(\bar{P}_{dCO_2} - 40)$$

$SCV$ and $CC$ are constants and $\bar{P}_{dCO_2}$ is the mean value of the partial pressure of arterial $CO_2$ at the carotid bodies.

Ellis concluded that a control algorithm containing both proportional and derivative control gave the best results for simulating an isocapnic response to exercise. Model A gave good results with only a derivative control. Anytime a proportional
Figure 2.10: A Diagram of the Respiratory Model (Model B) of Ellis (1984)
control was added to the controller, there was an offset in the arterial partial pressure after the onset of exercise. In Model B, there was a slight digression of $P_{aCO_2}$ at high simulation time with the derivative controller. The deviation from a mean steady-state value was so slow that Ellis thought that the mean value may not be controlled peripherally. This model seems to contain the minimum function that gives reasonable results. Although Model C was originally intended to verify the results from the reduced order models, it was so erratic that this was not possible. Ellis suggested using a different method of expressing ventilation and an explicit mathematical description of blood gas dissociation curves to simplify the computation.

2.3.3 Optimal Control

Optimality principles were first applied to the respiratory system in the study of respiratory airflow pattern (Yamashiro (1971,1973), Ruttimann (1972), Wasserman (1975)). These studies showed that the control of certain respiratory patterns is consistent with the minimization of the work rate of breathing. It was not until the early 1980's that optimality principles were explored for application to the ventilatory control system.

The distinction between an optimal control model and a feedback control model will first be analyzed. The feedback control mechanism consists of a central controller that responds directly to chemosensory measurements. To explain the isocapnic hyperpnea of exercise, a proportional signal is required correlated to metabolic $CO_2$ production that will appropriately drive ventilation (ie. the maximum slope of
\( \dot{P}_a CO_2 \). The optimal controller structure, on the other hand, chooses a ventilation rate based on minimization of a cost function which balances conflicting chemical and mechanical costs of breathing.

The study of optimality principles in the respiratory airflow patterns will be discussed first, then the application to the ventilatory control system will be explored. There are only two researchers who have explored using optimality principles in the ventilatory control system. Of these two researchers, Poon has done the most work on the optimal control system.

In 1982, Poon proposed an optimal controller structure, shown in Figure 2.11, that may be operative in ventilatory control. This model had a controller which minimized a total cost due to chemical stimulation and the work of breathing. Poon was the first researcher who used the optimal control principal in exercise.

Poon used a model based on Karmann (1972) where gas exchange equations of \( CO_2 \), \( O_2 \) and \( H^+ \) describe the dependence of the arterial blood gases on the total ventilation and other disturbances. The total chemical stimulation level was obtained as the sum of the central and peripheral chemoreceptor responses plus a constant term. These equations were derived from published data on the in-vivo response characteristics of the cat’s carotid bodies (Biscoe (1970), Lahiri (1975)).

The controller equation was based on optimizing a cost function in time. The first term being the square of the total chemical stimulation level and the second term being a measure of the work of breathing.
Figure 2.11: A Diagram of the Respiratory Model of Poon (1982)
where $P_{aCO_2}$ is the partial pressure of arterial $CO_2$, $\dot{V}_e$ is the ventilatory output and $\alpha$ and $\beta$ are constants. The logarithmic form suggested that only relative changes in the cost function with respect to $\dot{V}_e$ were important to the controller. Poon says that "it is quite possible that other cost functions may produce the same results or are consistent with a broader experimental data base."

The optimal model provided accurate predictions for the ventilatory responses to hypoxia, hypercapnia, and acidosis in a way that is compatible to the chemoreflex theory. Although this model did not work for exercise hyperpnea, it allowed a quantitative description of the ventilatory system.

In Poon's next paper (1983), he extended the earlier model to include the respiratory stimulation level. In this way, the formulation provided a more general framework for the understanding of the mechanisms of respiratory control.

In the new cost function, the first term was the same for the chemical stimulation level but differed in the second term. The work of breathing varies with respiratory pattern so that the second term had just the work rate.

$$J = (\alpha P_{aCO_2} - \beta)^2 + \ln \dot{W}$$

where $\dot{W}$ is the work rate of breathing. Poon only deals with the effects of hypercapnic exercise, so he assumed the levels of $O_2$ and $H^+$ were constant.

The results where essentially the same as those predicted by the previous model. Poon postulated that both ventilation and pattern responses result from the same
optimization mechanism of the respiratory controller. The optimization of the breathing patterns satisfied the demands of the chemical and mechanical drives to breathe, which in turn determined the total ventilation. Poon stated that the mechanical work rate expression could probably include some negative work component which represents the elastic mechanical power being returned to the muscles as the muscles relax.

Swanson (1986) suggested an alternative optimal controller behavior which incorporated an underlying additive structure where the \( CO_2 \) response is additive in metabolic \( CO_2 \) production and arterial \( CO_2 \) tension. Whereas, Poon's controller had an underlying multiplicative behavior where the \( CO_2 \) response is multiplicative in metabolic \( CO_2 \) production and arterial \( CO_2 \) tension. Swansons motivation for this work was due to the inability of Poon's original model to predict \( CO_2 \)-exercise interaction.

Swanson predicted that the optimal controller minimized a cost function where the additive controller depended on estimates of the metabolic \( CO_2 \) production (\( \dot{M} \)).

\[
J = (\alpha P_a CO_2 - \beta)^2 + 2\dot{M} \ln \dot{V}_e
\]

The only difference between this and Poons controller was \( \dot{M} \) which is introduced in the muscle compartment. Swanson does the formulations for a multiplicative and an additive structure.

In all of this, Swanson was mainly opposing Poons view of the optimal controller. His objections were that the optimal controller required a "knowledge" of the ventilation value achieved to calculate the cost. This implies a vagus feedback mechanism
and information about the dead space in order to yield a viable exercise response. The controller also required "knowledge" of $P_{aCO_2}$ to calculate the cost. He also points out that the optimal controller model cannot separate a metabolic $CO_2$ load from an airway $CO_2$ load via bolus $CO_2$ breathing or added dead space and predicted an isocapnic response. Poon's modification of the original model to include the effects of respiratory-mechanical limitation allowed his modified controller to reproduce the observed $CO_2$-exercise interaction.

In 1985, Poon did a study on the $CO_2$-exercise interaction in man. The discrepancies in previous studies of the experimental results led him to examine the $CO_2$-exercise interaction in terms of the ventilatory response to exercise under conditions of controlled hypercapnia.

In this study, eight males underwent a sequence of 5 min incremental treadmill exercise runs from rest up to a maximum $CO_2$ output in four successive steps. In all the exercise runs, the conditions of isocapnia and constant chemical drives were established.

The study showed that a distinct positive interaction between hypercapnia and exercise in ventilatory control could be consistently demonstrated. Sustained hypercapnia at a constant level enhanced exercise hyperpnea by augmenting not only the resting ventilation but also the ventilatory sensitivity to exercise. These efforts were observed in all subjects tested and at all levels of moderate hypercapnia and
exercise. From this, Poon was able to conclude that the CO₂-exercise interaction was important in the control of exercise and it was included in his next optimal controller.

The optimal controller structure was extended by Poon (1987), shown in Figure 2.12, to include the effects of respiratory-mechanical limitation and neuromechanical efficiency of the respiratory pump. This was necessary to be able to reproduce the observed CO₂-exercise interaction (Poon, 1985).

The respiratory-mechanical factors play a role in ventilatory control implied by studies showing that changes in respiratory mechanical impedance elicit changes in respiratory drive (Cherniak, 1981). Therefore, Poon included a term in the cost function which acknowledged the influence of respiratory-mechanical factors on the control of ventilation. Relative changes in respiratory effort were important to the controller since a reduction in respiratory work is always favored.

Poon’s optimal controller structure actively chose the ventilatory output (\( \dot{V}_e \)) to minimize the following cost function.

\[
J = \alpha^2 (P_{aCO_2} - \beta)^2 + \ln\left(\frac{\dot{V}_e^2}{(1-\dot{V}_e/\dot{V}_{max})^2}\right)
\]

where \( \dot{V}_{max} \) is the maximum of the derivative of ventilatory output. In this cost function, the first part represented the balancing of the chemical cost of the control and the second part represented the cost of breathing. An optimal ventilation rate was reached when these conflicting mechanisms were chosen to minimize \( J \). In this model, the work function (\( \dot{V}_e^2 \)) was normalized by a factor which represented the neuromechanical efficiency of the respiratory pump.
Figure 2.12: A Diagram of the Respiratory Model of Poon (1987)
Poon found that this model duplicated the normal ventilatory responses to hypercapnia, exercise and mechanical loading. Poon concluded that problems with the experimental procedure, as well as, validity of some equations used in his model could have caused it to fail when predicting the observed hypercapnic response to inhaled $CO_2$ bolus or an increase in deadspace. Poon suggested that the controller may respond to the magnitude, as well as the temporal pattern of the chemical signal, and testing under a wider range of conditions and more experimental data was needed to verify the model.
Chapter 3

Computer Model Development

The fourth-order model, presented by Saunders (1980a), was used as the basis for the second-order, two-compartment model used in both the feedback and optimal simulations. Although Saunders model is four-compartment (lung, muscle, brain, and "other tissue"), the brain and "other tissue" compartments were not included in order to keep computing times within practical limits. These compartments seemed of lesser importance for our purposes and so were reluctantly deleted. Therefore, a two-compartment model with just the lung and the muscle compartments was used to verify the controller equations. Both the feedback and the optimal models are the same except for the controller.

In this chapter, both of the models will be explained as one until the controllers are presented. The two-compartment model is presented by first discussing the Van der Pol equation and, then, the work of breathing, followed by the lung equations and, then, the muscle equations. The last section deals with the controllers for the feedback and the optimal models.
3.1 Van der Pol Oscillator

Both Saunders (1980a, 1980b) and Ellis (1984) used a sinusoidal function for the ventilation. In this thesis, ventilation is determined by the Van der Pol equation. This equation allows the shape of the curve to change, in addition to the amplitude and frequency. This becomes important when the work of breathing is calculated.

The Van der Pol oscillator simulates the breathing more realistically than the sinusoidal equation because the shape of the curve can be modified. In the sinusoidal function, the shape of the curve remains fixed while the amplitude and the frequency change. If the sinusoidal breathing pattern is used in the model, there is a 56.1 % increase in the work of breathing between a work load of 0 and 100 Watts (W). When the Van der Pol equation is used, there is a 24.4 % increase in the work of breathing between the same work loads. The sinusoidal breathing pattern increases the work of breathing beyond what the Van der Pol representation does because the shape of the curve is fixed. This becomes important in both the feedback and optimal models where the work of breathing is added into the muscle compartment.

The Van der Pol breather can produce different shapes. The curve can be almost sinusoidal to being an unusual shape (Figure 3.1). When the ventilation is fast (Figure 3.2) the breathing curve becomes more normal.

The Van der Pol equation is

\[ \dot{V} = \epsilon (1 - \alpha \dot{V}^2)V - \omega^2 V \]

where \( V \) is the volume in the lung and \( \alpha, \omega \) and \( \epsilon \) are constants. If one of the
Figure 3.1: The Van der Pol Oscillator (freq = 16 radians/min)
Figure 3.2: The Van der Pol Oscillator (freq = 20 radians/min)
constants is changed, the amplitude, frequency and the shape of the curve of the oscillator will change slightly. This makes it more difficult to have the Van der Pol equation as the ventilator in the models.

The optimal model is an open-loop, steady-state control model. Since the amplitude, frequency and the shape of the curve of the oscillator are not changed within the model, $\alpha$, $\omega$ and $\epsilon$ are used throughout and the amplitude and frequency are not calculated. The optimal model changes these three parameters ($\alpha$, $\omega$ and $\epsilon$) until the minimum performance index, discussed later in this chapter, is reached. Then, $\alpha$, $\omega$ and $\epsilon$ are given as the optimal solution for that particular work load.

In the feedback model, the controller produces the minute-averaged ventilation, $\dot{V}_{ave}$, that the model needs to keep the $P_{aCO_2}$ at 40 mm Hg. The $\dot{V}_{ave}$ is also calculated in the optimal model from the $\alpha$, $\omega$, and $\epsilon$ that the model produces for each work load. Therefore, $\alpha$, $\omega$, and $\epsilon$ can be found for every $\dot{V}_{ave}$ that the controller generates by interpolating the $\alpha$, $\omega$, and $\epsilon$ from the $\dot{V}_{ave}$ that the optimal model produces. In this way, the Van der Pol breather can be used as the ventilator in the model and the amplitude, frequency, and the shape of the curve need not be calculated.

### 3.2 Work of Breathing

Both the feedback and the optimal model calculate the work of breathing. There are different ways to derive the work rate of breathing depending on whether it is to be calculated simultaneously or each breath, and what breathing function is used. Otis, Fenn and Rahn (1950) derived the work rate for a single inhalation and ex-
halation of breath. Their derivation of the work rate used the sinusoidal breathing function and was evaluated each breathing cycle. Poon (1987) also used a sinusoidal breathing function in his optimal model but evaluated the logarithmic value of the work rate instantaneously. In this thesis, the Van der Pol equation is used as the breather instead of the sinusoidal function and the work rate of breathing is calculated and used instantaneously.

Although Poon (1987) calculated the instantaneous work rate, he did not use the calculated work rate in any of the equations of the muscle or the lung. Rather, the work rate was calculated just for the performance index. In this thesis, the work that the model does to breath is added to the metabolic rate in the muscle compartment. Therefore, the mean value of the work of breathing is calculated instantaneously and used in the muscle equation as it would be in the body. The following is the work rate function derived for use by the Van der Pol breather.

The power that is associated with the work rate of breathing is

\[ \frac{dW}{dt} = P \frac{dV}{dt} \]

\[ \dot{W} = P \dot{V} \]

where \( \dot{W} \) is the work rate of breathing, \( P \) is the pressure required for breathing, and \( \dot{V} \) is the volume flow rate of the lung. The pressure required for breathing was taken from Otis, Fenn, and Rahn (1950). When this is replaced in the above equation the work rate of breathing becomes,

\[ \dot{W} = (kV + k'(\dot{V}) + k''(\dot{V})^2)\dot{V} \]

where \( k \) represents the elastic resistance overcome during inhalation and exhalation,
$k'$ is the turbulent and viscous resistance of air in moving through the respiratory tract, and $k''$ is the resistance of tissue deformation. These values were taken from Otis, Fenn and Rahn (1950) and are the mean of their experiments on three subjects ($k = 8.52 \text{ cm } H_2O/l$, $k' = 3.5 \text{ cm } H_2O/(l/s)$, and $k'' = 1.5 \text{ cm } H_2O/(l/s)^2$).

As the ventilation increases, the work rate of breathing and the work load increases as more exercise is being done. At 0 W work load, when the body is at rest, the work rate is 11.8 % of the metabolic rate. At a work load of 25, 50, and 75 W the work rate increases to 15.7 %, 33.9 %, and 43.7 % of the metabolic rate, respectively. Until the work rate of breathing reaches 53.3 % of the metabolic rate at a work load of 100 W. Therefore, the work rate of breathing increases 41.5 % from a work load 0 W to a work load of 100 W as more exercise is being done.

### 3.3 Lung Compartment

The major difference between the model used by Saunders (1980a, 1980b) and the models used in this thesis is that the brain and "other tissue" compartments have not been included. These compartments are not directly involved in respiratory control and would make the model too complex to run in a timely fashion. The bronchial circulation (blood flow to the lungs or the lung-blood shunt) was deemed unnecessary to include in this project since this shunt actually represents only 1% of the blood flow. In addition, the lung dead space is modelled as part of the lung rather than as a separate compartment.
The lung is modelled as having a fixed lung blood volume \( V_b \) and variable \( CO_2 \) concentration. The total lung volume \( V_L \) is composed of the dead space \( V_D \) and the alveolar space \( V_a \), where actual gas exchange occurs. The lung volume relations used are as follows,

\[
V_L = V_a + V_D
\]
\[
\dot{V}_L = \dot{V}_a + \dot{V}_D
\]

The dead space is determined from the volume of air inhaled and exhaled during a normal breath or the tidal volume \( V_T \). This is taken from Saunders (1980a).

for \( V_T < 0.875 \)

\[
V_D = 0.0
\]

for \( V_T > 0.875 \)

\[
V_D = 0.2 V_T - 0.175
\]

An approximate value of the derivative, \( \dot{V}_D \), is calculated by dividing the difference in \( V_D \) for a time step by the time increment.

The differential equation describing the partial pressure of arterial \( CO_2 \) \( (P_{aCO_2}) \) is obtained by conducting a mass balance around the lung compartment. Since the lung blood comes into equilibrium in the pulmonary capillaries of the lung, the alveolar partial pressure of \( CO_2 \) \( (P_{ACO_2}) \) is set equal to \( P_{aCO_2} \). The non-linear differential equation describing \( P_{aCO_2} \) obtained from the mass balance is as follows,

\[
\frac{d}{dt}(V_b C_{aCO_2}) = \dot{Q}(C_v CO_2 - C_{aCO_2}) \left( \frac{863}{P_{atm} - 47} \right)
- V_a F_{aCO_2} - u \dot{V}_a (F_{aCO_2} - F_{iCO_2})
\]

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where $\dot{Q}$ is the blood flow rate, $P_{atm}$ is the atmospheric pressure, $C_{aCO_2}$ is the arterial and $C_{vCO_2}$ is the venous concentration of $CO_2$, and $F_{iCO_2}$ is the fractional concentration of $CO_2$ ($i = a$ for the alveolar compartment and $i = I$ for inhaled air).

A switch function, $u$, is used to model inhalation and exhalation, with lung volume being positive for inhalation.

$$u = \begin{cases} 
0 & \text{for } \dot{V}_a < 0.0 \\
1 & \text{for } \dot{V}_a > 0.0 
\end{cases}$$

A conversion factor of $863/(P_{atm} - 47)$ is used to change gas volume expressed in standard temperature and pressure, dry ($STPD = 0.0 \ C, 760 \ mm \ Hg, \ pH20 = 0.0 \ mm \ Hg$), to volumes expressed in body temperature and pressure, wet ($BTPS = 370 \ C, \ P_{atm} \ mm \ Hg, \ pH20 = 47 \ mm \ Hg$). This is necessary since ventilation is expressed in BTPS by convention, whereas metabolic rates and gas concentrations in the blood are normally expressed in STPD.

A better form for obtaining a solution can be found by use of the following relations (Saunders, 1980a).

$$P_{iCO_2} = F_{iCO_2}(P_{atm} - 47)$$

$$\dot{P}_{iCO_2} = \dot{F}_{iCO_2}(P_{atm} - 47)$$

Therefore,

$$F_{iCO_2} = \frac{P_{iCO_2}}{(P_{atm} - 47)}$$

and

$$\dot{C}_{iCO_2} = 0.35K1P_{iCO_2} - 0.65\dot{F}_{iCO_2}$$
where

\[ i = a \quad \text{for the alveolar compartment} \]
\[ i = I \quad \text{for inhaled air} \]

and

\[ K1 = 0.01(14.9 - 1.4 \ SAT) \]

The \textit{SAT} is the percent saturation of \textit{O}_2 in hemoglobin (which is the \textit{O}_2 carrying molecule in the blood). The effect that \textit{O}_2 has on \textit{CO}_2 dissociation (the Haladane effect) is ignored in this function by setting the \textit{SAT} term to a constant, in this case 0.90.

Substituting these equations into the differential equation describing \( P_{aCO_2} \) and rearranging, the equation becomes

\[
\dot{P}_{aCO_2} = \frac{1}{0.35K1V_6(P_{aCO_2}^{-0.44} + V_6/(P_{atm}-47))} \times \]
\[ [\dot{Q}(C_{vCO_2} - K1P_{aCO_2}^{0.35})]/(P_{atm}-47)] + \]
\[ uV_6[C_{ICO_2} - P_{aCO_2}/(P_{atm} - 47)] \]

The inputs to the system are \( \dot{Q} \) (blood flow rate) and the venous concentration of \textit{CO}_2, \( C_{vCO_2} \). \( \dot{Q} \) is a function of the work load. Values of \( \dot{Q} \) for various workloads (0, 25, 50, 75, and 100 W) are obtained from Saunders’ Table 3 (1980a). Values for \( C_{vCO_2} \) come from the values of the concentration of \textit{CO}_2 in the muscle compartment (\( C_{MCO_2} \)). It is assumed that the alveolar lung gas equilibrates perfectly with the capillary blood, mixing within the compartment instantaneously and completely.
3.4 Muscle Compartment

The differential equation describing the concentration of CO$_2$ in the muscle compartment ($C_{MCO_2}$) is obtained by conducting a mass balance around the muscle compartment.

\[
\frac{d}{dt}[V_M C_{MCO_2}] = \dot{V}_{MCO_2} + \dot{Q}(C_{aCO_2} - C_{vMCO_2})
\]

where $V_M$ is the volume of blood in the muscle, $\dot{V}_{MCO_2}$ is the metabolic production rate of CO$_2$ in the muscle, $\dot{Q}$ is the blood flow rate, $C_{aCO_2}$ is the arterial concentration of CO$_2$ and $C_{vMCO_2}$ is the venous concentration of CO$_2$ in the muscle compartment. Since the blood comes into equilibrium in the capillary beds of the muscle, $C_{MCO_2}$ is set equal to $C_{vMCO_2}$. The differential equation describing $C_{MCO_2}$ obtained from the mass balance is as follows,

\[
\dot{C}_{MCO_2} = \left(\frac{1}{V_M}\right)\left[\dot{V}_{MCO_2} + \dot{Q}(C_{aCO_2} - C_{MCO_2})\right]
\]

The metabolic production rates for various work loads (0, 25, 50, 75, and 100 W) was taken from Saunders' Table 3 (1980a). In simulating exercise, the maximum level of 100 W work load was used because it is below the anaerobic threshold at which lactate begins to be generated. The partial pressures of gases in the muscle compartment are equal to the pressures in the venous blood and mixing is instantaneous and complete.

3.5 Control Algorithms

Two different controllers were used in this thesis. The open-loop, steady-state optimal control model is modelled after Poons optimal controller. The feedback model
is a closed-loop system that has the derivative control added to the proportional control that Saunders (1980) used. Ellis (1984) used the same control algorithm as is used in the feedback model although the constants were changed to accommodate the Van der Pol oscillator. The optimal model was used to find the Van der Pol constants that were then used in the feedback model to do transient ventilatory control. First the optimal model, then the feedback model will be discussed.

3.5.1 Optimal Model

The optimal control model does not include a controller explicitly in the model. Instead, it contains an open-loop, steady-state algorithm where different values of $\alpha$, $\omega$ and $\epsilon$ are tried until a minimum performance index is found.

The respiratory system has the Van der Pol oscillator within the model as shown in Figure 3.3. The metabolic rate ($MR$) and the alveolar lung volume ($V_a(t)$) is added into the respiratory system while the work rate of breathing is calculated within the model. The performance index is calculated from the $P_{aCO_2}$ and the optimization algorithm produces the Van der Pol constants that are tried. The optimal model iterates different values of these constants until the performance index is at the lowest value. Then, the optimal model gives the Van der Pol constants and the alveolar ventilation for that work load.

In Poons optimal model, the performance index used both the chemical feedback (mean control) and the mechanical feedback or the work rate of breathing. In this thesis, the performance index has only the mean control. The mechanical feedback is
Figure 3.3: Optimal Routine
contained implicitly in the performance index through the work of breathing which is included in the muscle compartment.

The performance index ($PI$) used in the optimal model is,

$$PI = \overline{(P_{aCO_2} - P_{set})^2}$$

where $\overline{P_{aCO_2}}$ is the mean value of $P_{aCO_2}$ and $P_{set}$ is the normal setting of $P_{aCO_2}$ which is the level the body would like to maintain. In these simulations, $P_{set}$ is 40 mm Hg.

The performance index ($PI$) is calculated each time the model comes to a steady-state trying different values of $\alpha$, $\omega$ and $\epsilon$ until the $PI$ is at its lowest value. At this point, the values of $\alpha$, $\omega$ and $\epsilon$ are saved as the optimal solution for that particular work load.

### 3.5.2 Feedback Model

The closed-loop control algorithm used in the feedback model includes filtered values of both the mean and derivative control of $P_{aCO_2}$. The filtered values make changes in the control algorithm gradually, as would happen in the body. The control algorithm combines the derivative controller used by Saunders (1980b) with the mean controller used by Mann (1983) and is the same, with the exception of the controller constants, as that used by Ellis (1984). Again, the respiratory system has the Van der Pol oscillator within the model as shown in Figure 3.4. The $MR$ and the $V_a(t)$ is added into the respiratory system while the work rate of breathing is calculated within the model. The $P_{aCO_2}$ is sensed by the carotid body in the carotid artery and
Figure 3.4: Feedback Routine
the derivative and proportional controllers plus their constants are added together to form the new aveolar ventilation ($\dot{V}_a$).

The control algorithm used in the feedback model is,

$$\dot{V}_{ave} = SCV(\dot{P}_{aCO_2})_{max} + CC(P_{aCO_2} - P_{set})$$

where $\dot{V}_{ave}$ is the minute-averaged ventilation, $(\dot{P}_{aCO_2})_{max}$ is the maximum positive derivative of $P_{aCO_2}$, and $P_{aCO_2}$ is the mean value of $P_{aCO_2}$. $SCV$ and $CC$ are the control constants.

The values of $\alpha$, $\omega$ and $\epsilon$ for each work load corresponding to $\dot{V}_{ave}$ is found by the optimal model. The controller equation calculates $\dot{V}_{ave}$ and the values of $\alpha$, $\omega$ and $\epsilon$ are then selected from the optimal solution. Several different values of $SCV$ and $CC$ were investigated using the steady-state of the feedback model until the best solution was found. Then, the transient-state of the feedback model were simulated.
Chapter 4

Computer Model Analysis and Results

The results of the computer simulations for both the feedback and the optimal model are presented in this chapter. The Van der Pol equation is used as the breather in both of the models. Unlike the sinusoidal breathing function, the shape of the curve can be changed as well as the amplitude and frequency. A comparison of the solutions to the Van der Pol equation is shown versus the sinusoidal equation in Figure 4.1. There is not much difference in the lung volume as long as $\epsilon$ stays low, although there is more of a difference between the derivative of the lung volume (Figure 4.2). When $\epsilon$ is high ($\epsilon = 0.6$) the plots look much different, as shown in Figure 4.3 and Figure 4.4. This becomes important in both of the models when the work of breathing is calculated.

The shape of the Van der Pol equation changes as the parameters of this equation are changed. The work of breathing can also be significantly different (18 %) when the alveolar lung volume is constant and the shape of the curve is changed. These changes in the shape of the curve were used to investigate the respiratory control.
Figure 4.1: Van der Pol Versus the Sinusoidal Equation ($\epsilon = 0.2$)
Figure 4.2: The Derivative of Van der Pol Versus the Sinusoidal Equation ($\epsilon = 0.2$)
Figure 4.3: Van der Pol Versus the Sinusoidal Equation ($\epsilon = 2.0$)
Figure 4.4: The Derivative of Van der Pol Versus the Sinusoidal Equation ($\epsilon = 2.0$)
In this thesis, two controller concepts are explored. The steady-state optimal model is used to find the Van der Pol constants (\( \alpha, \omega, \) and \( \epsilon \)) for each work load. Although in the optimal model there is not a controller explicitly in the model, the controller is implicitly contained in the performance index. After the optimal model has been run for each work load, the feedback model takes the steady-state optimal control constants of the Van der Pol equation and uses them in the transient-state of the feedback controller.

Both of the models were written using Matlab, a high-performance, interactive software package. The optimal model was run on a 486 MHz personal computer. The feedback model took only about 20 min to run and, therefore, a 386 MHz personal computer was used. The Van der Pol equation was integrated using a step of 0.01 with the Euler integration routine. Although, a second-order and third-order Runge-Kutta integration routine was explored, the models took longer to run and there was less than a 10 % difference in the ventilation between the euler integration and the Runge-Kutta integration routine, as seen in Figure 4.5. Eulers integration routine was also used to integrate differential equations describing the muscle and the lung compartments. The optimal model finds the minimum of a function of several variables using the FMINS function in Matlab.

In this chapter, the results of the computer simulations of both the feedback and the optimal model will be presented. Discussion of the results for each simulation case using the optimal model are presented. Then, the simulations of the feedback model in the steady-state and the transient-state are presented.
Figure 4.5: Euler Versus Runge-Kutta Integration of the Lung Volume
4.1 Optimal Model Results

The Van der Pol constants ($\alpha$, $\omega$, and $\epsilon$) and the performance index ($PI$) were recorded for each work load as the optimal model was run. The optimal model chooses the best option for each work load by choosing the lowest $PI$. Initially the model is run for the $\alpha$, $\omega$, and $\epsilon$ that are given as the initial conditions and saves the $PI$ produced. Then different values of $\alpha$, $\omega$, and $\epsilon$ are tried and the resulting $PI$ is compared to the $PI$ that is saved. The lowest $PI$ is chosen and the values of $\alpha$, $\omega$, and $\epsilon$ and the new value of $PI$ is saved. After it has systematically changed the values of $\alpha$, $\omega$, and $\epsilon$ many times and the $PI$ is always higher than the $PI$ that is saved, the results of the optimal model for $\alpha$, $\omega$, and $\epsilon$ are given for that particular workload.

The performance index ($PI$) is plotted versus the work load, shown in Figure 4.6. The $PI$ for a work load of 0 W is between 93 % and 99 % higher than the other work loads. Although 15 different simulations of the optimal model for a work load of 0 W using initial guesses that covered the range for each $\alpha$ and $\omega$ with the range of $\epsilon$ being from 0.2 to 1.0 were run, none produced a lower $PI$.

The optimal model was then run for a work load of 10 W and 20 W. The values of the metabolic production rate and blood flow were interpolated from the plots shown in Figure 4.7 for these work loads. The $PI$ for these work loads came out to be $7.873 \epsilon^{-12}$ and $2.854 \epsilon^{-13}$, respectively. A plot of the $PI$ versus the work load from 0 W to 25 W is shown in Figure 4.8. The $PI$ goes down as the work load increases from 0 W to 25 W. Although not many simulations were run for a work
Figure 4.6: The Performance Index Versus the Work Load
Figure 4.7: The Metabolic Production Rate and Blood Flow for a Work Load of 0 W to 25 W
Figure 4.8: The Performance Index Versus the Work Load from 0 W to 25 W
load of 10 W and 20 W, the PI still comes out to be higher for the 10 W work load than the 20 W work load. Since different simulations were run that covered the range for each $\alpha$ and $\omega$ with the range of $\epsilon$ being from 0.2 to 1.0 for a work load of 0 W, it seems likely that the PI is higher for this work load, although more simulations should be run perhaps with the $\epsilon$ greater than 1.0.

Plots of the derivative of the partial pressure of arterial carbon dioxide ($\dot{P}_{aCO_2}$) and the lung volume ($V_l$) for a work load of 100 W is shown in Figure 4.9. Plots for the other work loads were similar and are not shown. This shows the phase relation between the two variables. The biased shape of the $\dot{P}_{aCO_2}$ plot (the $\dot{P}_{aCO_2}$ becomes flat as it reaches around 1.5 mm Hg/sec) is caused by the effect of the dead space volume. At the end of exhalation, the only air left in the lungs has a high carbon dioxide ($CO_2$) level. As inhalation begins, the dead space is diluted with the high oxygen, low $CO_2$ inspired air. At the same time, the venous blood is still transporting $CO_2$ to the lungs. Until the lungs inhale sufficient levels of $O_2$ to overcome the $CO_2$ coming to the lungs, the arterial $CO_2$ concentration continues to rise. This causes the bias at the maximum value on the top of the $\dot{P}_{aCO_2}$ curve.

A plot of $\dot{P}_{aCO_2}$ and $P_{aCO_2}$ for 0 W work load are shown in Figure 4.13. There is a difference in the curves for $\dot{P}_{aCO_2}$ from Ellis' (1984) thesis. Ellis has the maximum $\dot{P}_{aCO_2}$ just before the end of inhalation. Whereas in this thesis, as in Saunders paper, the maximum is near the beginning of inhalation. Also, the $\dot{P}_{aCO_2}$ from Ellis' thesis has a 66.7% larger volume. Whereas, there is no perceivable difference between the volume of $\dot{P}_{aCO_2}$ in Saunders paper and this thesis. Although Ellis does not mention
Figure 4.9: Phase Relation Between the Derivative of the Arterial Partial Pressure of $CO_2$ and Lung Volume (100 W work load)
Figure 4.10: The Relation Between the Arterial Partial Pressure of CO$_2$ and its Derivative (0 W work load)
what the controller constants are or what work load his plot shows, it is assumed to be a work load of 0 W as he compares it to Saunders’ paper.

For a work load of 0 W, the optimal model produced a $PI$ of $1.025 \times 10^{-11}$. The $P_{aCO_2}$ is shown in Figure 4.11. The $P_{aCO_2}$ for work loads from 25 W to 100 W are shown in Figure 4.12- 4.15. The $PI$ is $1.0917 \times 10^{-14}$, $6.833 \times 10^{-13}$, $4.3362 \times 10^{-13}$, and $1.188 \times 10^{-13}$ for the work loads 25 W, 50 W, 75 W, and 100 W, respectively. The $P_{aCO_2}$ becomes stable after 25 seconds (sec) for a work load of 0 W. This is the longest time the $P_{aCO_2}$ ever takes to become stable as it takes 20 sec, 8 sec, 15 sec and 15 sec for the work loads 25 W, 50 W, 75 W, and 100 W, respectively. These are fast times as the $P_{aCO_2}$ becomes stable under 50 sec. In Ellis’ thesis, the $P_{aCO_2}$ becomes stable after about 100 sec and is not shown in Saunders paper.

As the work load increases the frequency of breathing goes up and the oscillations of the $P_{aCO_2}$ increase. In the first 10 sec the $P_{aCO_2}$ oscillates about $2 \frac{3}{4}$ times for 0 W work load. The $P_{aCO_2}$ oscillations go up by half a step in the first 10 sec for each work load until, for a work load of 100 W, the $P_{aCO_2}$ oscillates 5 times. This shows that the $\dot{V}_a$ increases as the work load increases.

Although the amplitude of $P_{aCO_2}$ is almost the same for each work load, the way the alveolar ventilation ($\dot{V}_a$) changes for each work load is shown in Figure 4.16. For a work load of 0 W, the ventilation is nearly sinusoidal. As the work load increases, the amplitude and frequency of the ventilation increases. Although the optimal
Optimal Model: Work Load = 0 W

Figure 4.11: The $P_{aCO_2}$ for a Work Load of 0 W
Figure 4.12: The $P_aCO_2$ for a Work Load of 25 W
Optimal Model: Work Load = 50 W

Figure 4.13: The $P_aCO_2$ for a Work Load of 50 W
Figure 4.14: The $P_{aCO_2}$ for a Work Load of 75 W
Figure 4.15: The $P_{aCO_2}$ for a Work Load of 100 W
Figure 4.16: The Alveolar Ventilation for All Work Loads
model stays at an $\epsilon$ that is below 1.0, the shape of the curve becomes less sinusoidal as the work load increases.

The $\alpha$ that the optimal model produced for all the work loads is plotted against the $\dot{V}_a$, as shown in Figure 4.17. The amplitude calculated from the $\alpha$ for all the work loads is plotted against the $\dot{V}_a$, as shown in Figure 4.18. The $\alpha$ and the amplitude are exactly opposite in shape. As the amplitude goes up, the $\alpha$ goes down and vice versa. So, the following discussion could also be applied to $\alpha$.

Although one would assume that the amplitude of $P_aCO_2$ would go down as the work load increases, this did not happen in this model. The amplitude for 0 W and 25 W work load does decrease but the amplitude increases again suddenly by 3.6 % for a work load of 50 W. Then, from 50 W to 100 W work load, the amplitude decreases as expected. This may be because until a work load of 50 W is achieved, the shape of the curve changes to accommodate the changes needed to keep the $P_aCO_2$ at around 40 mm Hg. As the work load increases, the shape of the curve alone cannot not expel the extra $CO_2$ adequately. So, the amplitude of breathing must decrease as the frequency of breathing increases.

The frequency plotted against the $\dot{V}_a$ for all work loads is shown in Figure 4.19. A plot of $\epsilon$ versus $\dot{V}_a$ is shown in Figure 4.20. The frequency and $\epsilon$ give good results showing an increase in almost a linear fashion as the work load increases.
Figure 4.17: $\alpha$ for All Work Loads
Figure 4.18: Amplitude for All Work Loads
Figure 4.19: \( \omega \) Transposed into Frequency for All Work Loads
Figure 4.20: $\epsilon$ for All Work Loads
The optimal model gave good results for the $\alpha$, $\omega$, and $\epsilon$ and satisfactory results for the amplitude. The $PI$ for 0 W work load is high but no other initial conditions produced a lower $PI$. Although the amplitude jumps around a little, there is such a small difference in the amplitude values that it becomes inconsequential. $\alpha$, $\omega$, and $\epsilon$ that the optimal model calculates as being the optimal solution for each work load is used in the steady-state and the transient-state of the feedback model.

4.2 Feedback Model Results

The $\alpha$, $\omega$, and $\epsilon$ from the optimal model for each work load are used in the feedback model. $\dot{V}_a$ from the feedback model is shown as $\dot{V}_{anew}$ so the results can be presented in a more orderly fashion. The new values of $\alpha$, $\omega$, and $\epsilon$ in the feedback model were found from the value of $\dot{V}_a$ from the optimal model. If the value of the $\dot{V}_{anew}$ was over (or under) the range of the $\dot{V}_a$ that the optimal model came up with, the value of the highest (or lowest) $\dot{V}_a$ was chosen. If the value of the $\dot{V}_{anew}$ was within the range of $\dot{V}_a$ that the optimal model produced, the new value of $\alpha$, $\omega$, and $\epsilon$ was interpolated. The new values of the $\alpha$, $\omega$, and $\epsilon$ were updated every breath.

The values of $\alpha$, $\omega$, and $\epsilon$ outside of the range of $\dot{V}_a$ produced in the optimal model were considered to be invalid. This was because the optimal model produced the mean of the $P_aCO_2$ at about 40 mm Hg with these values of $\alpha$, $\omega$, and $\epsilon$. Although, other values of $\alpha$, $\omega$, and $\epsilon$ could possibly produce reasonable results, the value of $P_aCO_2$ would most likely be above or below 40 mm Hg and, therefore, were not considered here.
Table 4.1: Table of the Tests Run

<table>
<thead>
<tr>
<th>Test</th>
<th>Work Load</th>
<th>Dynamics</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>0</td>
<td>Steady-state</td>
<td>find SCV and CC</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>Steady-state</td>
<td>see if SCV and CC give V̇ₐ values within the range</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Steady-state</td>
<td>given by the optimal model</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>Steady-state</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>Steady-state</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>Transient-state</td>
<td>see what the model does in the transient-state</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>Transient-state</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>75</td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>Transient-state</td>
<td></td>
</tr>
</tbody>
</table>

A table of all the tests is shown in Figure 4.1. The first six tests are done for a work load of 0 W to find the controller constants (SCV and CC) which give the value of V̇ₐ within the range found in the optimal model. The next four tests (Tests 7 - 10) show that the SCV and CC values keep the value of V̇ₐ within the range given by the optimal model. Test 11 through Test 14 are the transient-state results of the feedback model for a work load of 0 W to 100 W.

The α, ω, ε and V̇ₐ from the optimal model for each work load are used in the feedback model. The results from the steady-state tests for the controller constants, SCV and CC, are discussed and the transient-state results are presented with the chosen controller constants. Then, the CO₂ inhalation tests are conducted and compared to experimental results from Reynolds (1972).
4.2.1 Steady-state Results

Many simulations were run with a work load of 0 W in order to get close to the controller constants (SCV and CC) which give the value of $\dot{V}_a$ within the range found in the optimal model. These simulations are discussed in the next section. Although the SCV and CC controller constants are assumed to remain the same through all of the work loads, there is a chance that this assumption could be wrong and there might be different controller constants for each work load. After the best SCV and CC values are found, the feedback model was run at a steady-state with a work load of 25 W to 100 W to make sure that the value of $\dot{V}_a$ is within the range found in the optimal model.

Controller Constants - Work Load 0 W

The $\dot{V}_a$ from the optimal model ranged from 0.4369 liter/sec (l/s) for a work load of 0 W to 0.7906 l/s for 100 W work load, about a 45 % increase. In the following tests, the value of SCV and CC where changed to try to find the best values that gave the $\dot{V}_a$ near 0.4369 l/s for a work load of 0 W. The range of the SCV and CC values was found by running the model and looking at the results. The $P_{aCO_2}$ was unstable and the $\dot{V}_a$ was too large if the SCV value was above 0.5. Likewise, if the CC value was above 0.1 the $P_{aCO_2}$ was too low or it came out good but the $\dot{V}_a$ became negative. Therefore, a SCV ranging from 0.3 to 0.2 and a CC ranging from 0.01 to 0.1 is shown in this thesis.
The first test on the steady-state feedback model was done with the SCV and CC values at 0.2 and 0.1, respectively. The start-up phase of the model is about 25 sec. Although the results are plotted for 100 sec, the model was run for 200 sec to see if it becomes stable. The results are shown in Figs. 4.21-4.25.

The $P_{aCO_2}$ oscillates from a mean value of approximately 34 to 39 mm Hg. The model is unstable and keeps on oscillating. The mean value of $P_{aCO_2}$, $\overline{P_{aCO_2}}$ does not follow the curve of $P_{aCO_2}$ very well. $\overline{P_{aCO_2}}$ seems to follow the $P_{aCO_2}$ with not as large of an oscillation and is offset by about 5 sec in the beginning to being less than 1 sec after it has run for 80 sec. This is because the the $\overline{P_{aCO_2}}$ has about a 5 sec lag time and has a hard time following such large oscillations in such a short time.

The derivative of $P_{aCO_2}$, $\dot{P}_{aCO_2}$ shows a slight increase around 9 sec where the value of $\dot{P}_{aCO_2}$ becomes larger increasing the length of the curve as well as picking up speed. This only lasts through the start-up phase of the model which is about 25 sec. The $\dot{P}_{aCO_2}$ range is about 5.4 mm Hg/sec and becomes stable in about 10 sec. This does not change much as the SCV and CC values are changed, although for most tests they are a little different.

The lung volume ($V_i$) is steady with the mean being about 2.9 l and the range being 0.5 l. The derivative of the alveolar lung volume, $\dot{V}_a$, oscillates from about 0.2 to 1.1
Figure 4.21: Arterial Partial Pressure of $CO_2$ (Test 1)
Figure 4.22: Mean Arterial Partial Pressure of CO$_2$ (Test 1)
Figure 4.23: Derivative of Arterial Partial Pressure of CO$_2$ (Test 1)
Figure 4.24: Lung Volume (Test 1)
Figure 4.25: Derivative of Alveolar Lung Volume (Test 1)
1/s. Although the $\dot{V}_a$ oscillates, it is within the range of $\dot{V}_a$ that give the best results. These values of the controller constants give the model continuous oscillations and, therefore, a instability results.

Test 2

The second test was run with the SCV and CC values at 0.2 and 0.01, respectively. The model was run for 100 sec. The results of this test are shown in Figure 4.26-4.30.

The $P_{aCO_2}$ comes out very good for this test. The start-up phase only lasts less then 10 sec and the $P_{aCO_2}$ becomes stable. $\overline{P_{aCO_2}}$ is 39.3 mm Hg. $\dot{P}_{aCO_2}$ steadies out quickly, also in less than 10 sec. The range of $\dot{P}_{aCO_2}$ being 5.5 mm Hg/sec. $V_i$ is steady with the mean being about 2.9 l and the range being 0.5 l. The $\dot{V}_a$ shows the stability of this test as it comes to a steady-state in about 15 sec, but slowly descends until it is just around 0.36 l/s. The $\dot{V}_a$ is still a little low, being 17.6 % below 0.4369 l/s which is needed.

Test 3

The value of SCV is the only thing that changes in Test 3. The SCV value is 0.3 and the CC value is still 0.01. This test and the next two tests were run for 200 sec because it takes about 60 sec to come to a steady-state instead of 25 sec. The results of this test are shown in Figs. 4.31-4.35.
Figure 4.26: Arterial Partial Pressure of CO₂ (Test 2)
Figure 4.27: Mean Arterial Partial Pressure of CO$_2$ (Test 2)
Figure 4.28: Derivative of Arterial Partial Pressure of $CO_2$ (Test 2)
Figure 4.29: Lung Volume (Test 2)
Figure 4.30: Derivative of Alveolar Lung Volume (Test 2)
Figure 4.31: Arterial Partial Pressure of $CO_2$ (Test 3)
Figure 4.32: Mean Arterial Partial Pressure of $CO_2$ (Test 3)
Figure 4.33: Derivative of Arterial Partial Pressure of CO₂ (Test 3)
Figure 4.34: Lung Volume (Test 3)
Figure 4.35: Derivative of Alveolar Lung Volume (Test 3)
The $P_{aCO_2}$ drops down to a mean value of about 36.7 mm Hg, as shown in $P_{aCO_2}$. At around 100 sec, the $P_{aCO_2}$ as well as the $P_{aCO_2}$, goes back up about 0.07 mm Hg until it comes to a steady-state. This is the only test where the value of $P_{aCO_2}$ goes down below 39 mm Hg. This could be because the frequency of breathing increases from about 3 cycles per 20 sec to about 4 cycles in 20 sec, although the total range of $V_t$ is the same.

The range of $\dot{P}_{aCO_2}$ goes up to about 6.5 mm Hg/sec and the frequency increases from about 6.0 radians in Test 2 to about 7.5 radians per 20 sec. The $\dot{V}_a$ goes up to a value of about 0.6 l/sec. This is within the range that $\dot{V}_a$ gave for the optimal model but the value of $P_{aCO_2}$ is too low.

**Test 4**

The fourth test was run with the SCV and CC values at 0.3 and 0.1, respectively. Although the results are plotted for 200 sec, the model was run for 400 sec too see if the oscillations would decrease and become steady. The results of this test are shown in Figs. 4.36- 4.40.

The $P_{aCO_2}$ keeps on oscillating longer than the 400 sec this test was run for. Although, the oscillations of $P_{aCO_2}$ seems to get smaller and eventually may come to a steady-state as time goes on. The $P_{aCO_2}$ suggests that it does come to a steady-state as the oscillations decrease as time goes on. The $\dot{P}_{aCO_2}$ shows these oscillations also but the range of $\dot{P}_{aCO_2}$ is still within 5.5 mm Hg/s.
Figure 4.36: Arterial Partial Pressure of CO$_2$ (Test 4)
Figure 4.37: Mean Arterial Partial Pressure of $CO_2$ (Test 4)
Figure 4.38: Derivative of Arterial Partial Pressure of $CO_2$ (Test 4)
Figure 4.39: Lung Volume (Test 4)
Figure 4.40: Derivative of Alveolar Lung Volume (Test 4)
\( V_l \) is the same as it is in Test 3. The \( \dot{V}_a \) is within the range that is needed but oscillates also. \( \dot{V}_a \) starts out at 0.53 l/s but then settles down to around 0.45 to 0.49 l/s. The oscillations decrease over time but it does not seem to settle out even though this model was run for 400 sec. Although the value of \( \dot{V}_a \) is within the low end of the range, the fact that it does not come to a steady-state makes using a CC of 0.1 for this range of SCV values impossible.

Test 5

Since a value of 0.01 for CC with the SCV being 0.3 was close, the \( \dot{V}_a \) being high and the \( P_{aCO_2} \) being too low, the value of SCV was lowered to 0.25. The model was run for 200 sec and the results of this test are shown in Figs. 4.41- 4.45.

The mean of \( P_{aCO_2} \) oscillates continually by 0.05 mm Hg as seen in \( \overline{P_{aCO_2}} \). The value that \( \overline{P_{aCO_2}} \) comes to is approximately 39.7 mm Hg, although it oscillates some also. The \( \dot{P}_{aCO_2} \) shows these oscillations also but the range of \( \dot{P}_{aCO_2} \) moves between a value of 5.5 and 5.3 mm Hg/s. The \( P_{aCO_2} \) would oscillate over a larger range except that the curve when \( \dot{P}_{aCO_2} \) becomes positive is biased by the effect of the dead space as explained in the beginning of this chapter.

\( V_l \) oscillates over 15 sec repeatedly. The range of \( V_l \) moves between the values of 0.47 and 0.53 l. The \( \dot{V}_a \) is within the range that is needed but oscillates also. \( \dot{V}_a \) starts out at just above 0.45 l/s coming down to around 0.433 to 0.445 l/s. The oscillations stays the same over time, although the value of \( \dot{V}_a \) is just about the value that is needed.
Figure 4.41: Arterial Partial Pressure of $CO_2$ (Test 5)
Figure 4.42: Mean Arterial Partial Pressure of $CO_2$ (Test 5)
Figure 4.43: Derivative of Arterial Partial Pressure of CO$_2$ (Test 5)
Figure 4.44: Lung Volume (Test 5)
Figure 4.45: Derivative of Alveolar Lung Volume (Test 5)
Test 6

Since Test 5 gave us approximately the value of $\dot{V}_a$ that is wanted, a value of 0.01 for $CC$ with the $SCV$ being 0.24 was tried. The model was run for 200 sec. The plots only show the first 100 sec to give a clearer picture since none of the plots change from 100 sec to 200 sec. The results of this test are shown in Figs. 4.46- 4.50.

This test gave the best results as the model was stable and came very close to the optimal model results. The $P_{aCO_2}$ is steady after about 25 sec. The oscillations going from 37.7 to 40.9 mm Hg with the $P_{aCO_2}$ coming out to be 39.3 mm Hg. The $\dot{P}_{aCO_2}$ is also steady with the range being 5.5 mm Hg/s.

The $V_I$ is steady, the range being 0.5 l and the $\dot{V}_a$ is 0.43 l/s. These are the $SCV$ and the $CC$ values that were used in the steady-state for each work load, as well as, the transient-state because the $\dot{V}_a$ is within 1% of the lowest value of the $\dot{V}_a$ from the optimal model.

**Controller Constants - Work Loads 25 W to 100 W**

These tests were all run with a $SCV$ value of 0.24 and a $CC$ value of 0.01. The $V_I$ was not plotted for these runs (Test 7 to Test 10) because the range of $V_I$ does not change much staying around 0.5 l. Only the frequency of the oscillations changes from 7.25 oscillations per 25 sec for a 25 W work load to 11 oscillations per 25 sec for a 100 W work load. These tests were run to see what value the $P_{aCO_2}$ comes
Figure 4.46: Arterial Partial Pressure of $CO_2$ (Test 6)
Figure 4.47: Mean Arterial Partial Pressure of $CO_2$ (Test 6)
Figure 4.48: Derivative of Arterial Partial Pressure of $CO_2$ (Test 6)
Figure 4.49: Lung Volume (Test 6)
Figure 4.50: Derivative of Alveolar Lung Volume (Test 6)
out to be in the steady-state so that a comparison with the transient-state can be made. Also, the value of $\dot{V}_a$ is checked to see if it comes out to be within the range of 0.4369 to 0.7906 l/s for all the work loads. The $\dot{V}_a$ becomes stable at or before 45 sec for all the work loads except for a work load of 100 W. In this test, Test 10, the $\dot{V}_a$ becomes stable after 70 W.

**Test 7**

Since a 0 W work load was run in Test 6, Test 7 was run for 100 sec at a work load of 25 W. The results of this test are shown in Figs. 4.51-4.54.

The $P_{aCO_2}$ goes up slowly after the start-up phase and does not become stable until 50 sec. The $P_{aCO_2}$ takes longer to become stable until it reaches a value of 41 mm Hg at 80 sec. $\dot{P}_{aCO_2}$ becomes stable quickly after 20 sec and the range is bigger than for a work load of 0 W by about 0.14 mm Hg/s, a 2.4% increase. The $\dot{V}_a$ is 0.4601 l/s.

**Test 8**

The work load of 50 W was run for 100 sec. The results of this test are shown in Figs. 4.55-4.58.

The $P_{aCO_2}$ goes up slowly after the start-up phase and does not become stable until 40 sec. The $P_{aCO_2}$ takes longer to become stable as it reaches a value of 41.1 mm
Figure 4.51: Arterial Partial Pressure of CO₂ (Test 7)
Figure 4.52: Mean Arterial Partial Pressure of CO$_2$ (Test 7)
Figure 4.53: Derivative of Arterial Partial Pressure of $CO_2$ (Test 7)
Figure 4.54: Derivative of Alveolar Lung Volume (Test 7)
Hg at 80 sec. $\dot{P}_{aCO_2}$ becomes stable quickly at 10 sec and the range is 6.7 mm Hg/s, a 17.7 % increase above that of a 0 W work load. The $\dot{V}_a$ is 0.5445 l/s.

Test 9

The work load of 75 W was run for 100 sec. The results of this test are shown in Figs. 4.59- 4.62.

The $P_{aCO_2}$ goes up slowly after the start-up phase becoming stable at 50 sec. The $\dot{P}_{aCO_2}$ takes longer to become stable and reaches a value of 41 mm Hg after 60 sec. The $P_{aCO_2}$ does not change much while the work load increases even at a steady-state because the $\dot{V}_a$ goes up instead. As the $\dot{V}_a$ goes up the values of the three parameters $\alpha$, $\omega$, and $\epsilon$ change to keep the $P_{aCO_2}$ at almost the same level. So, the $P_{aCO_2}$ does not change much during Test 7 through Test 10. $\dot{P}_{aCO_2}$ becomes stable quickly at 20 sec and the range is 7.7 mm Hg/s, a 28.3 % increase above a 0 W work load. The $\dot{V}_a$ comes out to be 0.6222 l/s.

Test 10

The work load of 100 W was run for 200 sec, although the results were plotted for 100 sec. All the other work loads were run for 100 sec but, in this test it took longer then 1.3 min to settle into the steady-state. The results of this test are shown in Figs. 4.63- 4.66.

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Figure 4.55: Arterial Partial Pressure of $CO_2$ (Test 8)
Figure 4.56: Mean Arterial Partial Pressure of $CO_2$ (Test 8)
Figure 4.57: Derivative of Arterial Partial Pressure of CO₂ (Test 8)
Figure 4.58: Derivative of Alveolar Lung Volume (Test 8)
Figure 4.59: Arterial Partial Pressure of $CO_2$ (Test 9)
Figure 4.60: Mean Arterial Partial Pressure of CO₂ (Test 9)
Figure 4.61: Derivative of Arterial Partial Pressure of CO₂ (Test 9)
Figure 4.62: Derivative of Alveolar Lung Volume (Test 9)
Figure 4.63: Arterial Partial Pressure of $CO_2$ (Test 10)
Figure 4.64: Mean Arterial Partial Pressure of CO$_2$ (Test 10)
Figure 4.65: Derivative of Arterial Partial Pressure of $CO_2$ (Test 10)
Figure 4.66: Derivative of Alveolar Lung Volume (Test 10)
After the start-up phase, the $P_{aCO_2}$ goes up slightly above the 41 mm Hg it stabilizes at, reaching stability after 80 sec. Although the $P_{aCO_2}$ did this very slightly for a work load of 50 W, the overcompensation was much more noticeable for this work load. This is most likely because the $P_{aCO_2}$ goes down at first during the start-up phase. For a work load of 50 W the $P_{aCO_2}$ goes down slightly within the first two breaths it takes. For a work load of 75 W the $P_{aCO_2}$ goes down within the first three breaths it takes, and it goes down within the first four breaths with a workload of 100 W. Because the $P_{aCO_2}$ must compensate for going down, it goes up quickly overcompensating for 40 sec until it comes back down slowly reaching the level of 41 mm Hg. None of this shows up on the $P_{aCO_2}$ as it is such a small deviation. The $P_{aCO_2}$ takes a little longer to come to a steady-state so that it does not follow these small oscillations. $P_{aCO_2}$ becomes stable at 20 sec and the range is 8.7 mm Hg/s, a 32.2 % increase above 0 W work load. The $\dot{V}_a$ is 0.7080 l/s well within the maximum value of 0.7906 l/s found in the optimal model. These values of $SCV$ and $CC$ seem to give the best results and they keep the $\dot{V}_a$ within the range found in the optimal model.

4.2.2 Transient-state Results

The model was run at 0 W work load through the start-up phase for 50 sec. Then, the work load was increased instantaneously to 25, 50, 75, or 100 W depending on the test. The model came to the same values for all the plots in the steady-state as it did when the work load was increased and the model went through a transient-state first. The range of $V_i$ and $\dot{V}_a$ are the same as in the steady-state. The $V_i$ runs at 0.5 l for 50 sec at 0 W work load for all the tests. Then, while the model increases it's
work load instantaneously, the $V_I$ drops down in range from 0.48 l for 25 W work load to 0.40 l for a 100 W work load for one breath only and resumes the normal level for that particular work load. Since the model results for $V_I$ came out to be essentially the same as in the steady-state, plots of $V_I$ are not shown. All the tests were run for 300 sec.

Instead of presenting these tests in the order they were performed, the $P_{aCO_2}$ and $P_{aCO_2}$ will be presented first. Then, the changes seen in $P_{aCO_2}$ and, finally, $V_a$ will be presented.

**Changes in $P_{aCO_2}$ and $P_{aCO_2}$**

The $P_{aCO_2}$ and $P_{aCO_2}$ are quite good in all of these tests. The mean value of $P_{aCO_2}$ is 39.3 mm Hg for the first 50 sec in all of the tests. At 50 sec, the blood flow and the metabolic production rate is raised as the increased work load is applied instantaneously. The $P_{aCO_2}$ overshoots slightly in the first test but jumps up to a high value for the other work loads coming down quickly to the steady-state. The $P_{aCO_2}$ and the $P_{aCO_2}$ of Tests 11 through 14 are shown in Figs. 4.67- 4.74.

The $P_{aCO_2}$ for the 25 W work load (Figure 4.67) rises slowly and comes to a steady-state in about 130 sec or 2.2 minutes. There is a very slight overshoot lasting about 40 sec. One can see that this work load does not put too much stress on the breather as the $P_{aCO_2}$ comes out slowly to 41 mm Hg overcompensating a very small amount.
Figure 4.67: Arterial Partial Pressure of $CO_2$ (Test 11)
Figure 4.68: Mean Arterial Partial Pressure of $CO_2$ (Test 11)
Figure 4.69: Arterial Partial Pressure of CO$_2$ (Test 12)
Figure 4.70: Mean Arterial Partial Pressure of $CO_2$ (Test 12)
Figure 4.71: Arterial Partial Pressure of CO₂ (Test 13)
Figure 4.72: Mean Arterial Partial Pressure of $CO_2$ (Test 13)
Figure 4.73: Arterial Partial Pressure of $\text{CO}_2$ (Test 14)
Figure 4.74: Mean Arterial Partial Pressure of CO₂ (Test 14)
The $P_{aCO_2}$ for a work load of 50 W (Figure 4.69) rises up to a mean value of 41.5 mm Hg, stays up there for a few breaths and comes back down again slowly to a steady-state in about 140 sec. There is a more dramatic jump as the rise in $P_{aCO_2}$ goes quickly up in three breaths taking about 15 sec. Where as, the rise in $P_{aCO_2}$ for a work load of 25 W takes 30 sec and at least eight breaths.

For a work load of 75 W, the $P_{aCO_2}$ shown in Figure 4.71 does not rise slowly, relative to a 25 W and 50 W work load, but jumps up to a mean value of 42 mm Hg in one breath. From here it goes down slowly until it reaches a steady-state in about 125 sec. This work load seems to produce a more radical treatment of $P_{aCO_2}$ and, although there is more of a jump, the mean value becomes stable in about 15 sec faster than the 25 and 50 W work load. This is probably due to the fact that the $P_{aCO_2}$ does not overcompensate but jumps directly to a higher value and comes down to the steady-state value from there.

There is not much difference between the work load of 75 W and 100 W. The $P_{aCO_2}$, as shown in Figure 4.73, makes a faster, more dramatic, jump up to a mean value of 42.8 mm Hg which is higher than the 75 W work load but it comes down to a steady-state in about the same time. This is about 100 sec less than the value that Ellis showed. The steady-state is approximately the same for all the work loads.

The $P_{aCO_2}$ shows an overcompensation for all the work loads. It reaches a steady-state value of approximately 41 mm Hg in all of the tests. $P_{aCO_2}$ for a work load of 100 W shows the most overcompensation reaching a value of 41.5 mm Hg as shown
in Figure 4.74. This value does not follow the high peak of the $P_{aCO_2}$ because it takes about 5 sec for the $P_{aCO_2}$ to move and then it goes up slowly.

Both mean and derivative control was used in two different simulations of Model B in the thesis by Ellis (1984) and these tests are compared to the tests run here. Ellis only ran his models for a work load of 100 W having a 10 sec ramp for the blood flow and the metabolic production rate. In the first test, Case 4, it does not seem to come to a steady-state value even though the model was run for 500 sec. The $P_{aCO_2}$ is still coming down slowly but reaches a value of 45 mm Hg in the 500 sec run. In the second test, Case 7, the $P_{aCO_2}$ comes to a steady-state around 46 mm Hg. In both of these cases, the $P_{aCO_2}$ is about 11 % to 13 % too high. Whereas in the feedback model presented in this thesis, the $P_{aCO_2}$ is only about 4 % off which is the same as Saunders (1980a,b).

**Changes in $\dot{P}_{aCO_2}$**

Ellis (1984) and Poon (1987) did not show any plots of $\dot{P}_{aCO_2}$ and Saunders (1980a,b) did a plot of $\dot{P}_{aCO_2}$ with the same results as in this thesis, although the time units are not shown. The range of $\dot{P}_{aCO_2}$ is 0.55 mm Hg/s during the first 50 sec. Then, as the different work loads are applied in each test, the $\dot{P}_{aCO_2}$ takes two breaths at a higher $\dot{P}_{aCO_2}$ value increasing the load until it comes to a steady-state. When it reaches this steady-state, the $\dot{P}_{aCO_2}$ has the same range as it did in the steady-state for each work load. These plots are shown in Figs. 4.75-4.78.
Figure 4.75: Derivative of Arterial Partial Pressure of \( CO_2 \) (Test 11)
Figure 4.76: Derivative of Arterial Partial Pressure of $CO_2$ (Test 12)
Figure 4.77: Derivative of Arterial Partial Pressure of CO₂ (Test 13)
Figure 4.78: Derivative of Arterial Partial Pressure of CO₂ (Test 14)
$\hat{P}_{aCO_2}$ for a work load of 25 W becomes stable quickly at 70 sec, 20 sec after the work load has been applied as shown in Figure 4.75. The inhalation of breath is again biased due to the effect of the lung volume, as it is for all the work loads.

For a work load of 50 W, $\hat{P}_{aCO_2}$ becomes stable at 110 sec, 60 sec after the work load has been applied. A plot of $\hat{P}_{aCO_2}$ is shown in Figure 4.76. This is the longest it takes for the $\hat{P}_{aCO_2}$ to become stable as it takes the longest for the $P_{aCO_2}$ to become stable. The frequency of breathing has increased slightly, as has the range of $\hat{P}_{aCO_2}$.

$\hat{P}_{aCO_2}$ for a work load of 75 W and 100 W becomes stable after 110 sec, as shown in Figure 4.77 and Figure 4.78. After 50 sec in both of these tests, unlike Tests 11 and 12, the $\hat{P}_{aCO_2}$ comes out to be 6.25 % less for a work load of 75 W and 11.4 % less for a workload of 100 W than it is at the steady-state. This is more pronounced in the 100 W workload. Then the range comes slowly to the steady-state value.

The biased shape of the $\hat{P}_{aCO_2}$ plot becomes greater as the work load increases. This is due to the high carbon dioxide ($CO_2$) level left in the lungs at the end of exhalation. As inhalation begins, the venous blood transports $CO_2$ to the lungs in greater quantities as the work load increases causing a greater bias in $\hat{P}_{aCO_2}$ plots.

**Changes in $\dot{V}_a$**

The $\dot{V}_a$ comes to the steady-state value of 0.46 l/s in the first 53 sec in all the tests. Then, at 50 sec a work load of 25, 50, 75, and 100 W is applied according to what
test is being done. It takes about 3 sec until the $\dot{V}_a$ begins to move because the values of the ventilation are changed every breath. The value of $\dot{V}_a$ is the same when it reaches the steady-state as it was for the same workload at the steady-state. The results of the $\dot{V}_a$ for Tests 11 to 14 are shown in Figs. 4.79- 4.82.

For a work load of 25 W, the $\dot{V}_a$ goes up to 0.49 l/s at 52 sec for 5 sec and comes down slowly to about 0.47 l/s until it reaches a steady-state in about 30 sec. The $\dot{V}_a$ for a work load of 50 W does the same thing except it goes up to a value of 0.57 l/s and drops back down to 0.52 l/s in 3 sec. Then, it slowly rises to the steady-state in about 110 sec from the beginning.

The $\dot{V}_a$ is similar for the 75 W work load as the 100 W work load. $\dot{V}_a$ jumps up to a value of 0.63 l/s for the 75 work load and a value of 0.71 l/s for the 100 W workload. It stays up here only for about 3 sec, then drops back down again and slowly rises to the steady-state. The 100 W work load, Test 14, is more dramatic as it takes a bigger jump and overshoots its steady-state value. $\dot{V}_a$ takes 115 sec to come to a steady-state for a work load of 75 W but takes 170 sec for a work load of 100 W. It is funny that for the 100 W work load the $\dot{V}_a$ jumps up to 0.71 l/s at first, then drops back down only to slowly work its way back up to the same value. The other work loads jumped up higher then the steady-state value at which the $\dot{V}_a$ comes too.

In Poons (1987) model the alveolar ventilation for 100 W work load is about 0.47 l/s although the $P_{aCO_2}$ is around 40 mm Hg for the steady-state. This is a little strange since the ventilation is low while the $P_{aCO_2}$ is at the correct level. In Ellis'
Figure 4.79: Derivative of Alveolar Lung Volume (Test 11)
Figure 4.80: Derivative of Alveolar Lung Volume (Test 12)
Figure 4.81: Derivative of Alveolar Lung Volume (Test 13)
Figure 4.82: Derivative of Alveolar Lung Volume (Test 14)
model, the ventilation is still low at around 0.57 l/s. Whereas, for Saunders model, it is about the same, 0.7 l/s.

4.2.3 CO₂ Inhalation Results

In 1909, Haldane first noticed that hyperpnea produced by rebreathing expired air and hyperpnea produced by muscular exercise was the same. Later it was discovered that both exercise and inhalation of CO₂ increased respiration but that only the inhalation of CO₂ caused the $P_{aCO₂}$ to rise. This is an artificial way to see if the controller works since we breathe in such a small percentage of CO₂ in normal circumstances. Although artificial, it has been tested periodically both experimentally and theoretically, and is commonly used, along with hypoxia, breath-holding, metabolic disturbances, etc. to test out a hypothesis of a respiratory controller.

In the CO₂ inhalation tests, the inhaled concentration of CO₂, $C_{ICO₂}$, is not zero as it is in exercise. The $C_{ICO₂}$ is set at 3 %, 5 %, and 6 % CO₂ inhalation for each test, while in all of the tests (Test 15, 16 and 17) work load was equal to 0 W. These tests are then compared to experimental data by Reynolds et al. (1972).

The $P_{aCO₂}$ came out to be, at the most, 3 % different from the experimental values of Reynolds et al. (1972) for the three tests performed. The $P_{aCO₂}$ for 3 % CO₂ inhalation came out to be 44.8 mm Hg, as shown in Figure 4.83. While the experimental value was 1.1 % different having a value of 44.3 mm Hg. For 5 % CO₂ inhalation, as shown in Figure 4.84, the $P_{aCO₂}$ was 44.5 mm Hg and the experimental value was 47.5 mm Hg, a 2.1 % difference. The $P_{aCO₂}$ for 6 % CO₂ inhalation, shown in
Figure 4.83: The $P_{aCO_2}$ and $P_{aCO_2}$ for 3 % $CO_2$ inhalation
Figure 4.84: The $P_{aCO_2}$ and $\overline{P_{aCO_2}}$ for 5 % $CO_2$ inhalation
Figure 4.85: The $P_{aCO_2}$ and $\overline{P_{aCO_2}}$ for 6% $CO_2$ inhalation
Figure 4.85, came out to be 50.5 mm Hg. The experimental value for this level of CO₂ inhalation being 48.9 mm Hg, a 3.2 % difference.

The $P_{aCO₂}$ for all three of the tests has an initial start-up phase which lasts about 30 sec. The difference is in how high the $P_{aCO₂}$ goes up. The $P_{aCO₂}$ oscillations also decrease from about 2 mm Hg to 0.8 mm Hg. This is because as the CO₂ inhalation increases the $P_{aCO₂}$ in the venous blood becomes greater than the $P_{aCO₂}$ that is being expelled by breathing so that the oscillations of $P_{aCO₂}$ in the blood decrease as breathing continues.

The $\dot{V}_a$ goes down for each percentage of CO₂ inhalation so that the controller is not changing anymore. This is shown for 3 % CO₂ inhalation (Figure 4.86) and is SIMILAR for all of the tests. The controller is still working but the $\dot{V}_a$ goes below the $\dot{V}_a$ that was found in the optimal model so that the values of $\alpha$, $\omega$, and $\epsilon$ stay at the minimum $\dot{V}_a$. It would be good to get the optimal model results for a lower $\dot{V}_a$.

The CO₂ inhalation tests were run just to show that this model is a viable solution for the respiratory controller coming within 3 % of the experimental values presented by Reynolds et al. (1972). Although this solution of the respiratory controller has not been tested for all the conditions that the controller is know to perform under, it is a start that brings a new look into how the controller may react.
Figure 4.86: The $\dot{V}_a$ for 3% $CO_2$ inhalation
Chapter 5

Conclusions and Recommendations

A mathematical model of the respiratory system was used to explore the use of a Van der Pol oscillator as the ventilator. Two different control concepts were explored in this thesis. The first one was used in the optimal model to find the alveolar lung volume and the Van der Pol constants ($\alpha$, $\omega$, and $\epsilon$) that could be used in the body during the steady-state of exercise for each of five work loads investigated. The second controller was used in the feedback control model. The needed alveolar volume was calculated using a proportional (mean) and a derivative (rate) control and the Van der Pol constants, $\alpha$, $\omega$, and $\epsilon$, were found from the alveolar lung volume found in the optimal model for the transient-state of this model.

The amplitude and the frequency of breathing can be changed in the Van der Pol equation but, most importantly, the shape of the curve can be modified. In the sinusoidal equation, the amplitude and the frequency can be changed but the shape of the curve remains fixed. When the sinusoidal breathing pattern is used in the model, there is a 56.1% increase in the work rate of breathing between a work load of 0 and 100 Watts (W). If the Van der Pol equation is used, there is a 24.4%
increase in the work rate of breathing between the same work loads, there being a 56.5 \% difference between the two. This is a substantial difference and since the work rate of breathing is used in the model, it cannot be ignored. This becomes important in both of the models where the work rate of breathing is added into the muscle compartment.

The respiratory-mechanical mechanisms involved in breathing may have a role in ventilatory control (Cherniack, 1981). Although Poon (1988) calculated the work of rate breathing as part of the cost function in an optimal model, it was not used explicitly in the model equations. In this thesis, the work rate of breathing was calculated and added with the metabolic production rate to form the metabolic carbon dioxide ($CO_2$) rate in the muscle compartment. The work rate of breathing is about 25 \% of the metabolic production rate. In all the papers up until this point, the work rate of breathing has been ignored. This did not become important until the use of the Van der Pol equation as the breather. Since, the Van der Pol equation was used as the breather and the shape of the curve could be changed, the work rate of breathing must be included.

The effect of using the work of breathing and the Van der Pol breather in the model as the ventilator resulted in keeping the optimal model at a $P_{aCO_2}$ level close to 41 mm Hg throughout all of the work loads. This is only 1 mm Hg or a 2.2 \% difference for a work load of 0 W above the normal $P_{aCO_2}$ level (40 mm Hg) which is kept in the body. Poon's steady-state optimal model produced a $P_{aCO_2}$ of about 45 mm Hg (about 11 \% difference) under resting conditions within the range of minute ventilation used in our model. For 100 W work load, the $P_{aCO_2}$ came out to be 41.5
mm Hg or a 3.8% difference from the normal $P_{aCO_2}$ level. Whereas, Ellis' model was 13% higher with a $P_{aCO_2}$ of about 46 mm Hg.

The three tests of $CO_2$ inhalation were run with 3%, 5%, and 6% $CO_2$ to see how this model reacted. The $P_{aCO_2}$ goes up as it does in experiments by Reynolds (1972), there being, at the most, a 3% difference between the model presented here and experimental values.

There are some other aspects about this thesis that must be addressed. In using the Van der Pol equation as the breather, the constants, $\alpha$, $\omega$, and $\epsilon$, had to be limited. This became necessary since the Van der Pol oscillator became less like the breathing curve of a real person when the $\epsilon$ was above 1.0.

Another point that must be made is that the amplitude that the optimal model gave for the different work loads varied and was not linear. This was unexpected as the amplitude of the sinusoidal equation used in Ellis' model tends to go up linearly as the work load increased. This could be because the shape of the curve of the Van der Pol oscillator does not vary in a linear fashion. Different simulations should be performed using an optimal model that covers higher ranges of the values of $\alpha$, $\omega$, and $\epsilon$ to see the effect that the shape of the curve has on the amplitude.

Research using these techniques on a more advanced model of the respiratory system could be investigated. The model could be improved by including the time delays, as well as, oxygen transfers in the system. Experiments could be performed with only one test subject since the averaging of test data from many individuals is
thought to allow too much variation in control variables. To adjust the theoretical results for an individual with different transient response data, a redefinition of the controller constants would be all that is required.

The combination of using the Van der Pol equation as the breather and using the work rate of breathing in the model keeps the $P_{a\text{CO}_2}$ at a value that is at its greatest only 1.5 mm Hg above the value that is kept by the body. In this respect, the model gives very good results as the $P_{a\text{CO}_2}$ was kept close to 40 mm Hg.
References


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Gray, J.S., 1945, "The Multiple Factor Theory of Respiratory Regulation," Army Air Force School of Aviation Medicine Proj. Rept., No. 386 (1,2,3).


Appendixes

1. Appendix A: Feedback Routine

2. Appendix B: Optimal Routine
Appendix A

% The Feedback Controller

% modified on: 7/1/91

% This program does the steady-state or the transient-state
% with Euler integration and the Van der Pol breather

% REDUCED MODEL: EULER INTEGRATION
% - steady-state or transient-state
% - van der pol breathing
% - no time delays
% - controller

clear
load afe2.mat

% Set Blood Flow and Metabolic Rate Dependent on Workload
% work load: 1 WL = 0 W QD = 0.12 MR = 0.003033
% 2 25 QD = 0.14 MR = 0.014
% 3 50 QD = 0.1667 MR = 0.018
% 4 75 QD = 0.19 MR = 0.02133
% 5 100 QD = 0.2167 MR = 0.02483
WL = 1;
QD = QD1(WL);
MR = MR1(WL);

% Set Initial Frequency and Amplitude

A1 = AA(WL);
A = A1;
Amp1 = Ampp(WL);
Amp = Amp1;
f1 = ff1(WL);
f = f1;
w1 = pi*f1/30;
eps1 = e(WL);
esp = eps1;

% Set Time Step

H = .01;
TotalT = 100;
T = [0:H:TotalT]';

% Set Initial Conditions

t = 0;
Pn = 40.;
Px1 = 40;
Pmean = Px1;
C = .55;
CMIC = .55;
nn = 1;
nu = 1;
mark = 1;
WRx1 = 0;
Wmean = .001;
Pslope = 0;
FPmax = 0.1;
Pmax = 2.4;
FP = 0;

u1 = 0;
u2 = 0.3;

VD = 0.175;
VDold = VD;

% Set Controller constants

SCV = .24;
CC = .01;
%------------------Loop from Here------------------

for n=1:1:TotalT/H

% Transient-state Step Function

if(t >= 30.)
    if(t <= 30.01)

% Reset Blood Flow and Metabolic Rate Dependent on Workload

% work load: 1  WL = 0 W  QD = 0.12  MR = 0.003033
%           2  25    QD = 0.14  MR = 0.014
%           3  50    QD = 0.1667 MR = 0.018
%           4  75    QD = 0.19  MR = 0.02133
%           5  100   QD = 0.2167 MR = 0.02483

    WL = 2;
    QD = QD1(WL);
    MR = MR1(WL);
    end

end

% Van der Pol Breathing --- Euler Integration

u1x = u1 + H*u2;

u2x = u2 + H*(-w1^-2*u1 - eps1*(A1*u1^-2 - 1.)*u2);
V1 = 2.9 + 2*u1;
V1dot = 2*u2;
u1 = u1x;
u2 = u2x;

% Determination of Dead Space from Tidal Volume

if(2*Amp1 > 0.875)
    VD = 0.4*Amp1;
end
VDalv = VD - 0.175;

% Approximation of Dead Space Derivative

VDalvD = (VD - VDold)/H;
VDold = VD;

Vadot = V1dot - VDalvD;
Va = V1 - VDalv;

% Breath-by-Breath Update of Amp, Freq and Eps

if(u1 <= 0)
    mark = 0;
end
if(u1 > 0 & mark == 0)
    A1 = A;
    Amp1 = Amp;
    w1 = pi*f/30;
    eps1 = esp;
    mark = 1;
end

% The Lung Equation

mu = 0.;
if(V1dot>0.0)
    mu=1.;
end

dum = .1364*Pn^0.35;    % K1=0.1364

Pxn=Pn+H*((mu*Vadot*(FP-Pn)/713+QD*1.21038*(C-dum))...
           /(.007161*Pn^(-0.65)+Va/713));
Paco2D = (Pxn - Pn)/H;

% Derivative Control : Max Slope of Paco2D

if(Paco2D > Pslope)
    Pslope = Paco2D;
end

if(Paco2D < 0.0 & Pslope ^= 0.2)
    Pmax = Pslope;
end

if(Paco2D < 0.0)
    Pslope = 0.2;
end

% Filter for Pmax

FPmax2 = FPmax + H/0.3*(Pmax - FPmax);

% Proportional Control: Mean Value of Pacb

Px2 = Px1 + H/5*(Pn - Px1);

PmeanD = Pmean + H/20*(Px1 - Pmean);

Px1 = Px2;

% Controller

VaveD = SCV*FPmax + CC*(Pmean - 40);

% Determine what Amp, A, w and eps to use depending
% on VaveD
if(t >= 5)
    [Amp,f,esp,A] = vad(VaveD);
end

% The Work Rate Equation

K = .0852;
KK1 = .035;
KK2 = .015;

WR = Vadot*(K * Va + KK1 * Vadot + KK2 * Vadot^2);

% Mean Value of WR

WRx2 = WRx1 + H/50.*(WR - WRx1);
Wmean2 = Wmean + H/50*(WRx1 - Wmean);

% The Muscle Equation

C = CHIC + H*(MR + Wmean + QD*(dum - C))/24.;

Wmean = Wmean2;
WRx1 = WRx2;
Pmean = PmeanD;
FPmax = FPmax2;
Pn = Pxn;

  t = t + H;

  Wmean = Wmean2;

end
Appendix B

% The Optimal Model

% was fixed: 7/09/91

% This code is the beginning of the optimal model. It keeps coming back here after running the model (eg. Model1.m) until the minimum of PI is found. The esp, A, and f are printed out as the values that minimize the optimal model.

clear
%
    Amp   f   eps
PIO = [300 ; 18 ; .5];

[optimal, cnt, PIO, PIs] = fmin1('model1', PIO, 0.01);

optimal = optimal;
disp(' Amp   f   eps')
optimal

% MODEL1.M

% was updated: 5/10/91
This model does an open-loop circuit with no controller
The models in this simulation are OPT.M, MODE1.M

function PI = model(p)

REDUCED MODEL: EULER INTEGRATION
- open-loop
- steady-state
- van der pol breathing using euler integration method
- no time delays
- dead space
- no controller

% Set Blood Flow and Metabolic Rate Dependent on Workload

work load = 0 W    QD = 0.12    MR = 0.003033
25        0.14        0.014  
50        0.1667      0.018
75        0.19        0.02133
100       0.2167      0.02483

QD = 0.2167;
MR = .02483;
% Set Time Step

t = 0;
tf = 60;

% PI Initialization

PI = 0;

% Set Initial Frequency, Amplitude and Epsilon
% Amp f eps
p = [450. 20. .2];
Amp = p(1);
f = p(2);
w = pi*f/30;
epsilon = p(3);

% Set Time Step

T = [0:.01:tf]';
H = .01;

% Set Initial Conditions

nn = 0;
Pmean = 40;
P(1) = 40.;
Px1 = 40;
C = .55;
CMIC = .55;
WRx1 = 0;
Wmean = .001;
mark = 1;
Vdum = 0;

u1 = 0;
u2 = 0.3;

VD = 0.175;
VDold = VD;

%----------------- Loop From Here-----------------------------

for n=1:1:tf/H

% Van der Pol breathing --- euler integration

u1x = u1 + H*u2;
u2x = u2 + H*(-w^2*u1 - epsilon*(Amp*u1^2 - 1.)*u2);
\[ V_1 = 2.9 + 2u_1; \]
\[ V_{1,\dot} = 2u_2; \]
\[ u_1 = u_{1,x}; \]
\[ u_2 = u_{2,x}; \]

\% Determination of Dead Space from Tidal Volume

\[ \text{if}(2A > 0.875) \]
\[ V_D = 0.4A; \]
\[ \text{end} \]
\[ V_{Dalv} = V_D - 0.175; \]

\% Approximation of Dead Space Derivative

\[ V_{DalvD} = (V_D - V_{D,old})/H; \]
\[ V_{D,old} = V_D; \]
\[ V_{adot} = V_{1,\dot} - V_{DalvD}; \]
\[ V_a = V_1 - V_{Dalv}; \]

\% The Lung Equation

\[ \mu = 0.; \]
\[ \text{if}(V_{1,\dot}>0.0) \]
\[ \mu = 1.; \]
end

dum = .1364*P(n)^0.35;  % K1=0.1364

P(n+1)=P(n)+H*((-1*mu*Vadot*P(n)/713+QD*1.21038*(C-dum))...
    /(.007161*P(n)^(-0.65)+Va/713));
Paco2D = (P(n+1) - P(n))/H;

% Mean Value of Paco2D

Px2 = Px1 + H/10.*(P(n) - Px1);
PmeanD = Pmean + H/5*(Px1 - Pmean);
Px1 = Px2;

% The Work Rate Equation

K = .0852;
KK1 = .035;
KK2 = .015;

WR = Vadot*(K * Va + KK1 * Vadot + KK2 * Vadot^2);

% Mean Value of WR

WRx2 = WRx1 + H/50.*(WR - WRx1);
Wmean2 = Wmean + H/5*(WRx1 - Wmean);
% The Muscle Equation

\[ C = CMIC + H*(MR + Wmean + QD*(dum - C))/24.; \]

\[ Wmean = Wmean2; \]

\[ WRx1 = WRx2; \]

\[ t = t + H; \]

\[ Pmean = PmeanD; \]

end

\[ PI = (Pmean - 40)^2 \]
Carmel G. Villiger was born in Rapid City, South Dakota on March 8, 1964. She grew up in Hyattsville, Maryland later moving to Great Falls, Virginia. She went to three years of high school in Herndon, Virginia and then moved with her family to Alice Springs, Australia where she finished high school in 1982. She came back to the United States to attend college at Minot State College in North Dakota living with her sister for one year. Then, she transferred to Virginia Polytechnic Institute and State University where she co-oped with David Taylor Navel Research and Development Center and received a Bachelors of Science in Engineering Science and Mechanics in June, 1988. She had done her undergraduate research project with Dr. Robertshaw and decided to switch over to Mechanical Engineering for her Masters Degree which she will receive in September, 1991. Upon graduation she intends to go west to Washington state.