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Clinical and Physiological Analysis of Very Long Apneas in Premature Infants

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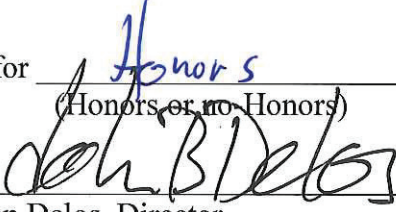
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for the degree of Bachelor of Science in Physics from
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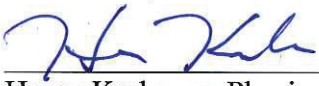
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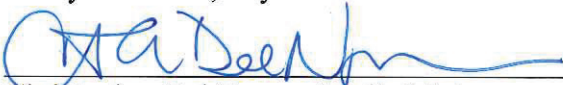
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Clinical and Physiological Analysis of Very Long Apneas in Premature Infants

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Senior Honors Thesis

Department of Physics

The College of William and Mary

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Abstract

Apnea is common in premature infants, and in severe cases it may impair development. Data recorded during apnea events by hospital monitors at the University of Virginia Neonatal Intensive Care Unit (NICU) include EKG, chest impedance, and pulse oximetry signals. In previous work, an apnea detection algorithm was developed that filtered the cardiac artifact from the chest impedance signal to improve detection of apneas [1]. An unexpected result was the discovery that Very Long Apneas (VLAs) lasting more than 60 seconds are not rare. We use this findings in our research to provide new information about these apneas and to test a model describing the rate of decrease of blood oxygen in apneas of various lengths.

We study 86 very long apneas, along with 285 shorter apneas (10 - 40 s duration), to analyze the properties of VLAs. We begin with a quantitative measure of the oxygen deficit or the heartbeat deficit resulting from the apnea, concluding that both are roughly proportional to the duration of the apnea.

We observe that heart rate and oxygen saturation decrease much more slowly in a VLA than in a short apnea, and the initial oxygen saturation prior to VLAs is unusually high. This raises the question of whether babies are hyperventilating before a VLA. To answer this, we have analyzed respiration rates preceding apneas of various durations, and have shown that VLAs are associated with a significantly increased respiration rate immediately prior to the apnea.

Lastly, we have used the theory provided by [2] to model the rate of decrease in oxygen saturation during individual apnea events. The resulting model confirms our observation that higher initial levels of oxygen saturation result in slower rates of decrease.

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Chapter 1

Introduction

1.1 Physiological Background

Apnea, the cessation of breathing, is a common affliction among infants. About half of the infants born under 1500 g (very low birth weight or VLBW) and the majority of infants under 1000 g (extremely low birth weight or ELBW) experience apnea [1]. We limit our focus to apneas of prematurity, which involve infants younger than 37 weeks of gestational age.

Apnea of prematurity is associated with many infections and health problems, such as sepsis, hypoglycemia, or anemia [1], [3]. Immediate consequences of apnea are bradycardia and oxygen desaturation, and death or cerebral dysfunction can result in severe cases [3]. Apnea of prematurity is an important issue concerning neonatal care. The causes of these apneas are related to their classification: central, obstructive, and mixed.

1.1.1 Central Apnea

Central apnea occurs when the central nervous system fails to provide respiratory drive to muscles needed for breathing [4]. Like maintaining a pulse, respiration is a vital process that must be continuously functional. Under normal conditions, the brain provides oscillatory drive for constant stimulation of respiratory muscles [5]. Neural sensors in the body respond with feedback for the respiratory generator.

Two types of chemoreceptors are sensitive to chemical concentrations. *Central* chemoreceptors, or medullary neurons, sense changes in proton concentration (pH level). This relates to CO_2 concentration in the cerebral spinal fluid [4], [6]. *Peripheral* chemoreceptors in the carotid body detect the partial pressures of O_2 and CO_2. These neurons are stimulated by low O_2 or high CO_2 partial pressures [6].

Chemical feedback helps to maintain ideal chemical concentrations. Premature infants, with underdeveloped central nervous systems, are thus prone to problems regulating respiration. If this feedback system is hyper- or hypo-sensitive, abnormal breathing results. Studies show that premature infants may have higher feedback system gains, resulting in overcorrection and unstable respiration [4]. In addition, undeveloped central nervous systems can have delays in feedback response that cause fluctuations in breathing [3], [4]. Premature infants have fewer neural synapses and myelination of the brain stem, which may help to explain their central problems in respiration [3].

Another abnormality concerning premature infants is their reaction to hypoxia (low O_2) and hypocapnia (low CO_2) levels. In utero, oxygen is supplied via the umbilical cord. Thus, breathing in the womb apparently serves muscle and lung development [7]. Under hypoxic conditions, the fetus limits unnecessary energy expenditure by decreasing ventilation. This reaction is referred to as hypoxic ventilatory depression [6]. Premature infants are shown to adapt to ex utero conditions around 35 weeks gestational age. Past this point, infants will increase respiration in hypoxic conditions, which is the response seen in adults and in term infants.

Hypoxic ventilatory depression is the second stage of a biphasic response to hypoxia. The first is an initial increase in respiration rate and tidal volume [3]. However, in a study of premature infants < 30 weeks gestational age, they did not exhibit this initial response. Instead, they only decreased respiration [8]. This finding suggests an association between prematurity and the strength of hypoxic ventilatory depression [7]. While it cannot be proven that this response *causes* apnea in premature infants, it is an example of one underlying abnormality in central regulation that results in hypoventilation [9].

Detection and response to CO_2 levels also contribute to ventilatory complications in preterm infants. As respiration also serves to expel CO_2, chemoreceptors inhibit breathing at low CO_2 concentrations. This minimum CO_2 level is referred to as the "apneic threshold," and is typically 3.5 Torr (in units of partial pressure) below normal levels of CO_2 in healthy adults [10]. A study of premature infants found a threshold only 1-1.3 Torr below normal levels [11]. This result indicates that apneic thresholds close to normal levels destabilize the respiratory feedback system, leading to unstable breathing and multiple short apneas [7], [11]. The effect of low CO_2 levels on breathing prompted carbon dioxide inhalation to be used as a treatment. In a two hour period, it was shown to stabilize breathing in infants, though long-term studies have not yet been conducted [12], [7].

1.1.2 Obstructive and Mixed Apneas

Unlike central apnea, obstructive apnea occurs when there is still effort to breathe, but the respiratory canal is blocked [4]. While its start is different from central apneas, transitions from one type to another are more common than either isolated type of apnea [1], [3]. Neural input is necessary to keep the upper airway muscles engaged. Thus, without stimulation, muscles may relax and cause airway obstruction [4].

Furthermore, there is evidence for an association between the decrease of upper airway muscle tone and central apnea [7]. A study measuring airway openings in 41 premature infants found blocked airways in 585/4456 central apneas [13]. Thus, what originates as central apnea can cause the relaxation of muscles needed for respiration, increasing apnea severity due to blocked airways [7].

Similarly, an obstructive apnea can impair respiratory drive. Upton et al. obstructed the airway in 23 premature infants and found central apneas during 19% of the obstructions [13]. In [14], Waggener examined respiratory oscillations in premature infants and found that all three types of apnea occurred at the same point in the respiratory cycle, indicating a common origin for all types. Thus, classification is dependent upon the first part of the respiratory system to fail— the diaphragm (central) or the upper airway (obstructive) [7].

Either type of apnea can result from medical conditions in premature infants that affect their central nervous systems. Issues common to premature infants include the inability to regulate temperature, intracranial bleeding, or infections such as meningitis [15]. Apnea of prematurity is also associated with other illnesses, such as sepsis (bacterial or viral infection) and hypoglycemia. Whether the apnea causes or results from the other conditions is unknown. Premature infants are also prone to lower resting lung volumes, which result in shorter breathing times and apneas due to the Hering-Breuer deflation reflex [7].

The relationship between immature respiratory control and apnea is supported by the fact that apnea incidence decreases with increased gestational age [3]. Apnea typically resolves by 37 weeks gestational age [15]. This is also when hypoxic ventilatory depression reverses and infants stabilize temperature regulation and respiratory feedback control [15]. Many conditions are correlated with apnea, though their role in the development of apnea is unclear.

1.1.3 Apnea Event Criteria

Cessation of breathing alone is not harmful unless it persists long enough for hypoxia (low O_2) and hypercapnia (high CO_2) to develop. These conditions could be potentially fatal or hazardous to neural development. While irregular breathing is common
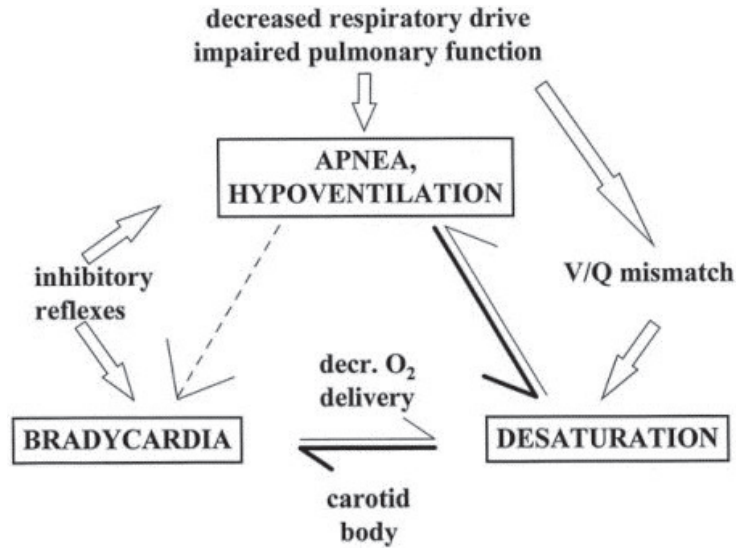
FIGURE 1.1: As shown, bradycardia and oxygen desaturation are immediate effects of apnea. However, these conditions also inhibit respiratory drive, which may either cause or worsen apnea. Reproduced from Martin et al. in [16].

in infants, apnea occurs with a cessation of breath greater than 20 s. Alternatively, apnea is clinically significant if an absence of breathing longer than 10 s is accompanied by either bradycardia (heart rate (HR) below 100 beats per minute (bpm)) *or* oxygen saturation (SaO_2 below 80%). Thus, although the term apnea refers only to a cessation in breathing, our research is focused on Apneas associated with Bradycardia and oxygen Desaturation (ABD events). While the heart rate and oxygen levels both decrease at the onset of apnea, their relationships are more complex. Their mutual connections are summarized in Figure 1.1.

The heart rate slows as oxygen level decrease, though the specific reason for this is unknown. In a study of the relationship between hypoxic conditions and heart rates, bradycardia occurred 4.8 s (median) after the beginning of an apnea and 4.2 s (median) after oxygen desaturation [17]. Bradycardia is related to both oxygen supply and apnea, due to different neural inputs that signal heartbeats [7].

One is mediated by a chemoreceptor reflex caused by hypoxia. In an oxygen deficit, peripheral chemoreceptors signal the heart to slow down. It is the lack of oxygen, and not the apnea itself, responsible for this reaction [7]. However, further studies indicate that the absence of lung inflation, or signal from the pulmonary reflex, could also cause bradycardia. Thus, apnea alone may result in bradycardia [7]. A study of dogs [18] found that deceases in heart rates were more severe if hypoxia was accompanied by apnea. Therefore, it is not just the chemoreceptor input that is responsible for bradycardia. The conclusion was that bradycardia results from the lack of oxygen in the blood, but is worsened by the apnea itself [7].

The other condition associated with an ABD event is arterial oxygen saturation, or

S_aO_2. This is the ratio of oxygenated hemoglobin (hemoglobin that is carrying oxygen molecules) over the total amount of hemoglobin in a given volume. Oxygen saturation reflects how much oxygen the blood transports throughout the body, and is related to the partial pressure of oxygen in the lungs. The normal level of oxygen saturation in the blood is around 95%. As mentioned above, we define a desaturation event to be at O_2 saturation of 80% or lower.

Detecting trends among the vital signs—respiration rate, heart rate, and oxygen saturation—at times surrounding the apnea event will improve understanding of apnea's effect on the body [1]. While it is difficult to determine if developmental issues are specifically apnea-related, we can try to improve understanding of apnea's specific relations to other medical conditions [15]. As mentioned previously, apnea's damage to the body is inflicted by deficits in heartbeats and O_2 transported in the blood. Thus, we will focus on heart rate and oxygen saturation signals, along with chest impedance, in our study. [7].

1.2 Methods of Detection

The University of Virginia (UVa) NICU is a 45-bed facility that admits over 500 infants a year. Roughly 25% of these infants are very low birth weight (VLBW) infants (under 1500 g). We study the 335 VLBW infants admitted between January 2009 to March 2011. The collection of data was approved by the UVa Institutional Review Board with waiver of consent and shared with William and Mary upon approval by the William and Mary Protection of Human Subjects Committee.

The data set has about 5 Terabytes of electronic signals, with all electronic signals for about 50 baby-years. It is the only one of its kind in the world. The data was shared with William and Mary under an approved protocol, and it is stored on the SciClone cluster.

Data collected and stored includes all data from all NICU bedside monitors (GE Medical models Solar 8000M and I and Dash 3000) using a BedMaster central network server (Excel Medical, Jupiter, FL) [19]. The infant's condition is tracked using three electrocardiogram (EKG) leads collected at 240 Hz, with electrodes on both sides of the heart to record its electrical activity. Heart pulses are detected, and a heart rate is calculated.

Chest impedance waveforms are collected with the same leads at 60 Hz by passing a high frequency signal through the leads. By measuring the high frequency current across the chest, one can determine the chest impedance using Ohm's Law (V = IR). Impedance changes with breaths due to the fluctuations of air in the lungs. Air is a poor conductor of electricity, so its volume inside the lungs determines the observed

impedance.

Photoplethysmographic waveforms for pulse oximetry are collected at 120 Hz [19]. This noninvasive technique attaches to a finger or toe, where it emits red and infrared light. Oxygenated hemoglobin absorbs more infrared light, while regular hemoglobin absorbs more red light. Based on the absorption ratio of the two different wavelengths, the machine calculates the fractional oxygen saturation in the blood [20]. Hospital monitors calculate and store heart rates (from EKG signals), respiration rates (from chest impedance signals), and O_2 saturation (from pulse oximetry).

1.3 Prior Work at William and Mary

The College of William and Mary's physicists and the University of Virginia's clinicians have collaborated to improve apnea detection and understanding. One project focused on optimizing the chest impedance signal for more accurate respiration rates. To do this, they removed the cardiac artifact.

Besides the air volume in the lungs, chest impedance is also affected by blood pumping through the heart. Unlike air, blood is a good conductor of electricity. While air in the lungs causes an impedance fluctuation of a couple of ohms, blood movement via heartbeats can change the impedance by about half an ohm [1].

During an apnea, the absence of breaths allows the heartbeat to dominate the chest impedance. The heart rate slows so that there is more time for the heart to fill with blood, causing larger fluctuations in impedance [1]. Without larger impedance fluctuations due to breathing, impedance changes caused by blood may be misinterpreted as breaths. Figure 1.2 shows how the chest impedance synchronizes with heartbeats during an apnea event, reflecting the cardiac artifact instead of breathing. This misinterpretation by the hospital monitors causes the respiration rate to increase during apnea, which prevents apnea alarms from alerting clinicians of the event.

To solve this problem, John Delos, Hoshik Lee, and others from both the College of William and Mary and the University of Virginia developed a filtering method to remove the cardiac artifact from the chest impedance [1]. Even though cardiac frequencies are typically higher than those for breathing, a simple frequency filter is still inadequate. During an apnea, the heart rate slows down and can move into respiratory frequency ranges. Thus, a low-pass filter of the Fourier transform of chest impedance frequencies is insufficient [1].

Hoshik et al. overcame this issue by changing the time units from seconds to heartbeats. This way, as long as the chest impedance is synchronized to heartbeats, it always has a frequency of 1, no matter the heart rate. Thus, in Fig. 1.3, the clear spike at a frequency of 1 in (b) using this latter timescale to allow a clean removal of the cardiac
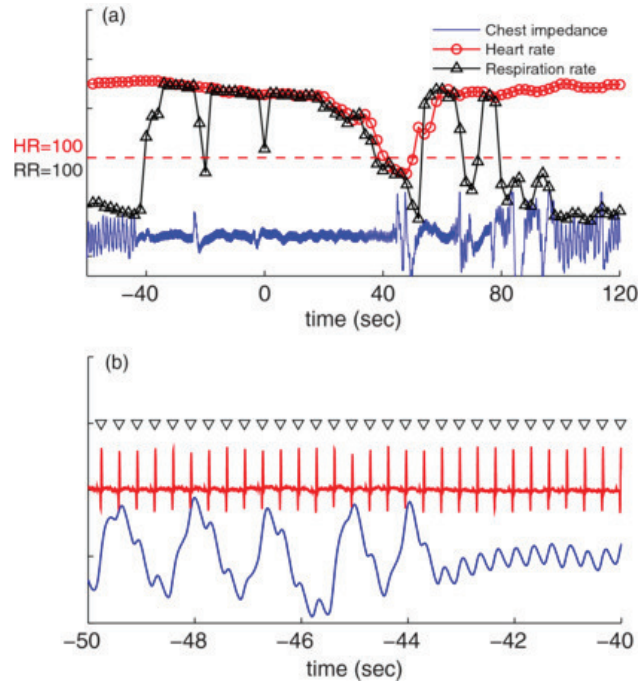
FIGURE 1.2: (a) At the onset of apnea around -40 s, monitors report increased respiration rates that approach heart rate levels. This shows that the chest impedance signal is synchronized to heartbeats. (b) Triangles mark heartbeats, proving that the chest impedance and heartbeats are at the same frequency during apnea, beginning around -44 s. Reproduced from Hoshik et al. in [1].

artifact.

The chest impedance signal was then renormalized using an envelope function. From this signal's standard deviation, Hoshik et al. calculated the probability of apnea. High fluctuations, i.e. large standard deviations, indicate normal breathing, and thus have low apnea probability. Minimal fluctuations occur during an apnea, resulting in high apnea probability.

After applying the filtering algorithm to a randomly selected sample of 237 apnea episodes occurring for five infants, three clinicians at the University of Virginia unanimously agreed on 234. Out of these cases, 212 were confirmed apneas, resulting in a 91% accuracy rate [1]. In analysis of their filtered signal's ability to detect apneas, they found an 11% false-positive rate and a 37% false-negative rate based on random sampling. This decreased the monitor's false-alarm rate by about half [1].

As this technique has proven useful and more reliable than the respiration rates calculated by hospital monitors, we will use this chest impedance signal in all future discussions. The improved chest impedance signal and apnea probability provide a novel way for us to study properties of very long apneas.
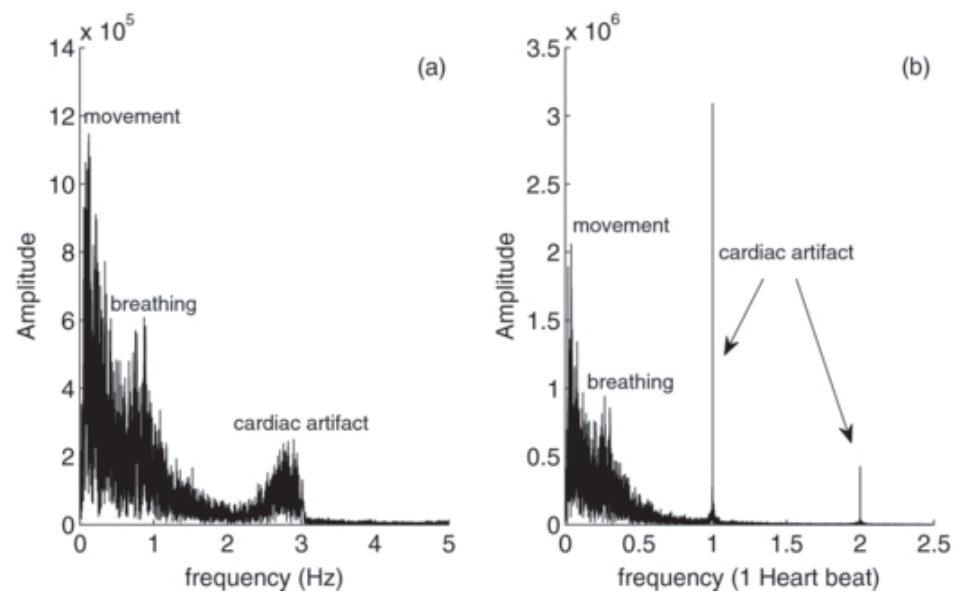
FIGURE 1.3: (a) Fourier transform of chest impedance using units of seconds. (b) Resampled Fourier transform using heartbeats as the time unit. In this approach, we can see a clear spike at 1 that belongs to cardiac artifact. Reproduced from Hoshik et al. in [1].

Chapter 2

Apnea Burden

The filtering algorithm previously discussed also led Hoshik et al. to discover 553 apneas lasting longer than 60 s. Two groups of two clinicians each reviewed half of these cases. We focus on the unanimous cases of apnea that were also accompanied by bradycardia and oxygen desaturation. We are left with 86 confirmed Very Long Apneas (VLAs). Because apnea alone is not harmful except for its consequences on heart rate and oxygen supply, we focus on these two signals to understand the effect of VLAs. We ask how these quantities decrease during an apnea, and if this is different from apneas of shorter durations.

To begin investigation of VLAs, we compare heart rate and oxygen saturation decreases between apnea duration groups. Figure 2.1 shows the average heart rate and oxygen saturation levels during apnea for different apnea durations. Examining the slopes, we observe that on average, longer apneas are associated with slower decreases in heart rate and oxygen saturation. This could imply that VLAs are not necessarily more dangerous than shorter apneas, as they take the longest to reach critical levels.

We seek a quantitative measure to describe the effects of apnea on heart rate and oxygen saturation by studying their differences from a normal level. Instead of focusing on either the magnitude or duration of these differences from normal levels prior to apnea, we use a comprehensive calculation: the product of depth and duration. Applied to heart rate and oxygen saturation data, this calculation refers to the integral or area of the deviation from "normal" baseline levels.

We define two baselines for this study: a "normal" baseline and a "critical" baseline. The "normal" baseline is unique to each apnea case. For each signal, we define a range in which the signal is stable i.e. before the apnea event takes effect. We find the mean of this range, μ, and define the "normal" baseline as
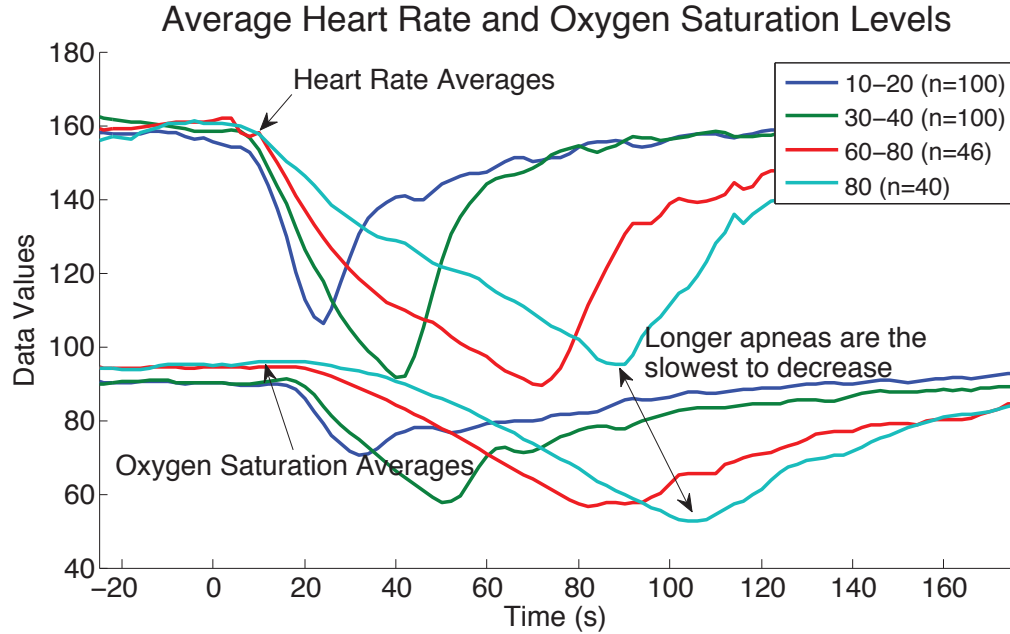
FIGURE 2.1: Average heart rate and oxygen saturation levels for apneas of different lengths. Dark blue and green curves represent shorter apneas, while VLAs are represented by red and light blue curves. Note that the longer apneas have the lowest slopes, or rates of decrease, for both heart rate and oxygen saturation levels. Reproduced from Mohr et a. in [19].

$$baseline_1 = \mu - 2 \cdot \sigma \qquad (2.1)$$

where σ is the standard deviation of the data between our chosen range. This ensures that we are using a baseline that is significantly below the average such that the deviation cannot be regarded as a random fluctuation.

The second "critical" baseline is defined by the criteria for ABD events:

$$baseline_2 = \begin{cases} 100 \text{ bpm} \\ 80\% \text{ S}_a\text{O}_2 \end{cases}$$

If a patient's vital signs approach these thresholds and remain below for a couple of seconds, the hospital monitors signal an alarm. The necessity of immediate attention indicates that these levels are far below what are considered healthy values. If we use these levels as our chosen baselines, we will find the heartbeat or oxygen deficit below critical levels. Visual representation of this procedure for both heart rate and oxygen saturation is shown in Fig. 2.2.

To control for confounding variables unique to different patients, we focus on one
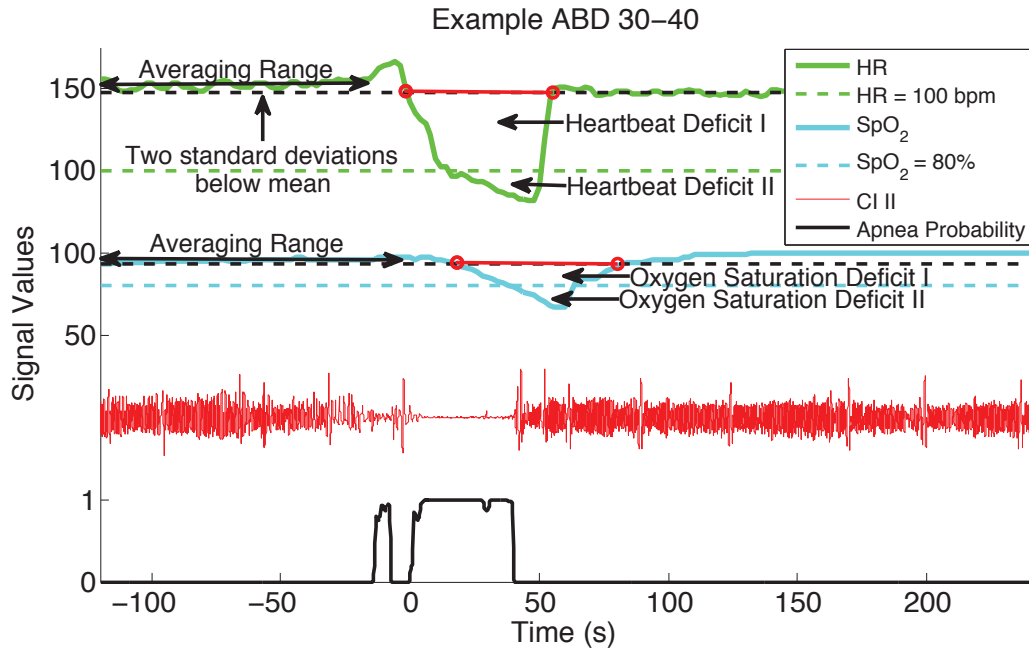
FIGURE 2.2: Here we show our method to calculate apnea burdens for each case. For heart rate, we take the average over the range shown and create a "normal" baseline 2σ below this level (black dotted line). We then find the total area of heart rates underneath the red line. We repeat for the critical baseline (dotted green line), and do the same for oxygen saturation.

single preterm infant who experienced many apneas of different durations. We study only isolated apneas (as opposed to those followed or preceded directly by another apnea). Within this smaller subset of data, we then calculate the *reduction* in heart beats and oxygen transported associated with each apnea.

2.1 Calculations

For each chosen baseline within an apnea event, we look at the times at which the vital signs fell under the baseline.

Focusing on heart rate first, we call t_1 to t_2 the timespan in which the heart rate is below this level. Because heart rate is in beats/min, we can see

$$\text{beats/min} \times \text{min} = \text{beats} \tag{2.2}$$

Thus, the product will give us the deficit of heartbeats associated with apnea. Applied to the heart rate signal from the monitor, we can calculate this product with the integral

$$\int_{t_1}^{t_2} \frac{[\text{HR}_{\text{baseline}} - \text{HR(t)}]}{60} \text{dt} \tag{2.3}$$

with HR(t) being the heart rate at any given time. We divide by 60 because the heart rate is recorded in beats/minutes, but time is reported in seconds.

Similarly, the same method can be used to find the deficit in oxygen transport. The units for oxygen saturation, however are not a rate, so our product gives

$$\% \text{ saturation} \times \min = \frac{\% \text{saturation} \cdot \min}{100} \equiv \chi_{deficit} \tag{2.4}$$

with $\chi_{deficit}$ being the product in fractional form. $\chi_{deficit}$ is directly proportional to deficit in moles O_2, shown by

$$O_2 \text{ deficit} = \chi_{\text{deficit}} \times M_p \tag{2.5}$$

where M_p is the number of O_2 moles that the hemoglobin could possibly carry, or

$$M_p = 4 \times \underbrace{[Hb]}_{moles/vol} \times \underbrace{\dot{Q}}_{vol/min} \tag{2.6}$$

where $\dot{Q}$ is the cardiac output, or the blood pumped per unit time by the heart. The factor of 4 reflects that 4 molecules of O_2 can be bound to 1 molecule of Hb. [Hb] refers to the concentration of hemoglobin. M_p is thus in units of moles/time, giving the maximum possible amount of moles of O_2 that can be transported in a given amount of time. Therefore, the product of oxygen saturation in %-minutes is directly proportional to the amount of moles O_2 corresponding to the deficit.

For individual infants and events, cardiac output and hemoglobin concentration are unknown, so we cannot carry out the final step to obtain the oxygen deficit precisely. Nevertheless, we propose that the area measure in %-minutes is the best measure of apnea severity in terms of oxygen transport.

If we select a baseline for "normal" oxygen saturation and call the range t_3 to t_4 as the time it is under this value, we can find the oxygen deficit with:

$$\int_{t_3}^{t_4} [\text{S}_a\text{O}_{2\text{baseline}} - \text{S}_a\text{O}_2\text{(t)}]\text{dt} \tag{2.7}$$

with $\text{S}_a\text{O}_2\text{(t)}$ being the oxygen saturation reported by the monitors at a given time.

2.2   Method

We obtained plots of heart rate and oxygen saturation two minutes before and four minutes after each apnea event (Figure 2.2). Adding our chosen baselines, we find the points at which the heart rate and oxygen saturation decrease below these values.

Following Eq. 2.3, we determine the heartbeat deficit by integrating under our baselines. As the recorded data is sampled every 2 s, our signal comes as discrete data points instead of a smooth curve. Thus, we use trapezoidal summation to approximate integration. For heart rates, this changes Eq. 2.3 to

$$\sum_{i=1}^{n} \frac{1}{2} \left[(HR_{baseline} - HR_i) + (HR_{baseline} - HR_{i+1}) \right] \Delta t \tag{2.8}$$

With similar calculations for oxygen saturation, we determine the oxygen deficit in the blood associated with the apnea.

Because we are investigating the relationship between apnea severity and duration, we must also calculate the length of apnea. We find the duration by integrating the apnea probability over time, or

$$\int_{t_0}^{t_f} \mathrm{P_{apnea}(t)dt} \tag{2.9}$$

We then divide by its scale factor of 50.

2.3   Results

Here we show the results for both the "normal" and critical baseline levels. Figures 2.3 and 2.4 plot the deficits (heartbeat and oxygen transported) vs. apnea duration using each baseline.

For heartbeat deficit (Fig. 2.3), there is a clear positive linear relationship between duration of apnea and deficit using the "normal" baselines. As apnea duration increases, heartbeat deficit also increases. However, under the critical level of 100 bpm, the number of heartbeats missed is independent of apnea duration. Thus, apneas of different durations spend similar amounts of time under this critical level.

In regards to oxygen saturation, both baselines exhibit a positive linear relationship (Fig. 2.4). The slope of the least-squares regression line is about twice as large for the "normal" baselines (0.31 %-minutes/second of apnea) as it is for the critical 80% baseline (0.17 %-minutes/second of apnea). The maximum deficits are about 35
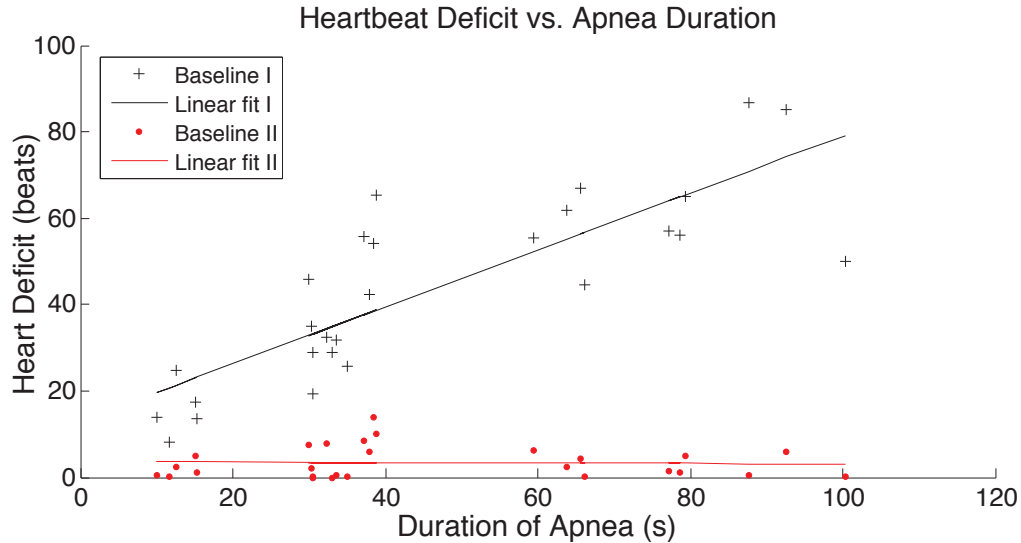
FIGURE 2.3: Heartbeat deficit vs. apnea duration. Crosses are results with our "normal" baseline, while red dots show results for the critical baseline. We can see a clear positive relationship with the "normal" baseline. For critical baselines, apnea duration appears to be independent of heartbeat deficit.

and 15 %-minutes for our "normal" and critical baselines, respectively. Generally, we see stronger relationships between apnea durations and burden if we use our "normal" baselines.

The novel result for the critical level in heart rates can be explained by hospital procedures and unique properties of VLAs. Hospital protocol calls for stimulating the infant when the heart rate falls below 95 bpm. Once stimulated, the heart rate will return to normal levels. As Fig. 2.1 shows, longer apneas take the longest to fall under these critical values. Thus, even though VLAs last longer, they spend only a short time under the critical baseline. This allows the areas below 100 bpm to be relatively equal even though apnea durations vary.

We reason that oxygen saturation does not follow the same pattern under the critical baseline due to NICU conditions and procedures. Clinical personnel respond quickly to bradycardia alarms, but not necessarily as urgently to apnea alarms ($\sim 2/3$ of which are false) or desaturation alarms. If they do not respond as quickly to oxygen saturation levels, they allow the signal to remain under its critical level. Due to the differences in urgency between alarms, we see different patterns between apnea duration and severity in regards to heartbeats and oxygen transport.

Thus, we have shown that without hospital intervention, longer apneas do in fact impose a larger burden on the patient in terms of heartbeat and oxygen deficit. However, VLAs are associated with slower decreases in vital signs, which decreases the time spent under critical levels.
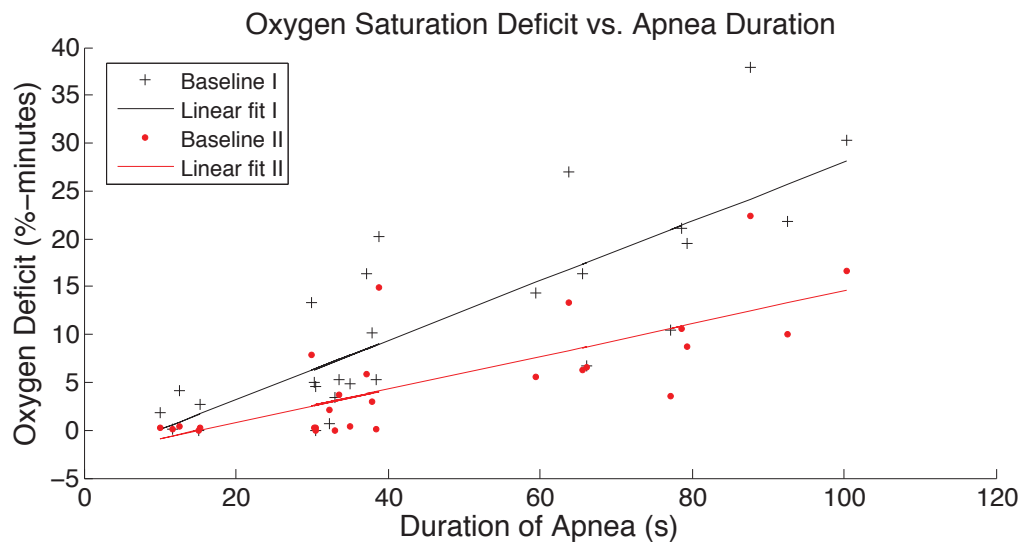
FIGURE 2.4: Oxygen saturation deficit vs. apnea duration. Crosses are results with our "normal" baseline, while red dots show results for the critical baseline. We can see clear positive relationships using both baselines. However, this linear relationship is stronger using our "normal" baseline.

Chapter 3

Respiration Rate Analysis

3.1 Motivation

As shown in Fig 2.1, longer apneas are associated with slower decreases in both heart rate and oxygen saturation. During VLAs, oxygen saturation not only takes the longest to decrease, but also begins at the highest levels. We now investigate if this higher initial oxygen supply is related to hyperventilation before a longer apnea. To test this relationship, will look at the lengths of breaths that precede VLAs to compare to breaths before shorter apneas. To understand the effect of apnea, we will also calculate breath length during normal breathing.

As we are investigating changes in breathing, we also ask whether inhale and exhale durations change together or separately. Due to the central regulation of breathing, understanding the breathing pattern before an apnea could indicate O_2 or CO_2 levels during this time. We will test if relative inhale/exhale lengths change during an apnea event.

3.1.1 Respiration Rate

Averages shown in 2.1 indicate that the longer apneas begin with higher initial oxygen saturation levels. Higher levels of oxygen in the blood could indicate either faster respiration rates or deeper breaths. While hospital data calculates respiration rates based on chest impedance, this is flawed due to cardiac and motional artifact, as discussed above. Thus, to understand respiration rates, we consider the doubly-filtered chest impedance signal supplied by [1]. Because this signal is renormalized, however, we can only study rates, and not depths, of breaths.

3.1.2 Inhale vs. Exhale Lengths

Separate sites in the brain generate inhale and exhale activity [5]. The preBötzinger complex is known to provide inspiratory drive, while the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG) signals active expiration [5]. Thus, abnormalities in inspiration or expiration could indicate a problem from a different circuit.

As premature infants have undeveloped central nervous systems, they exhibit unique biphasic responses to both hypoxia (with hypoxic ventilatory depression) and hypercapnia. Unlike adults who increase respiratory frequency with hypercapnic conditions [21], premature infants only increase their ventilation within the first two minutes of hypercapnic conditions. After this time, their respiration rate *decreases* back to its original value due to increased expiration length. This is not due to the passive nature of expiration [22], but rather for the phenomena known as expiratory braking that is prevalent in premature infants [23], [22].

Infants increase expiratory time by either slowing down exhales or pausing them completely. This enables the maintenance of higher tidal lung volume, or the volume of air inhaled or exhaled in a normal breath [23]. An example of expiratory braking is shown in Fig. 3.1. Increased lung svolume allows infants to improve gas exchange [22], [24]. Additionally, larger lung volume activates the mechanoreceptor reflexes that signal expiration, further prolonging expiration length [22]. In a study of both premature and in term infants immediately after birth, premature infants engaged in expiratory braking more often than in term infants [23].

Therefore, premature infants alter their respiratory pattern in response to chemical concentrations. We investigate how their breathing changes right before an apnea, and if these patterns are different depending on apnea duration. Excessive exhale lengths or decreased respiration before an apnea could indicate hypercapnia or hypoxia, respectively [22], [3]. If the infant is breathing at an increased rate, carbon dioxide could also drop below apnea threshold, which is another potential cause for apnea [3]. We consider all of these separate factors for our analysis.

3.2 Methods

We calculate respiration rates for our analyses using the filtered and renormalized chest impedance signal. Since inhales increase and exhales lower chest impedance, positive and negative fluctuations from zero indicate inhales and exhales, respectively.

We construct a code in Matlab to read each chest impedance signal and identify zero crossings. Between each zero crossing, the code identifies the maxima and minima of the chest impedance oscillations, or the amplitudes. We will interpret the inhale length as
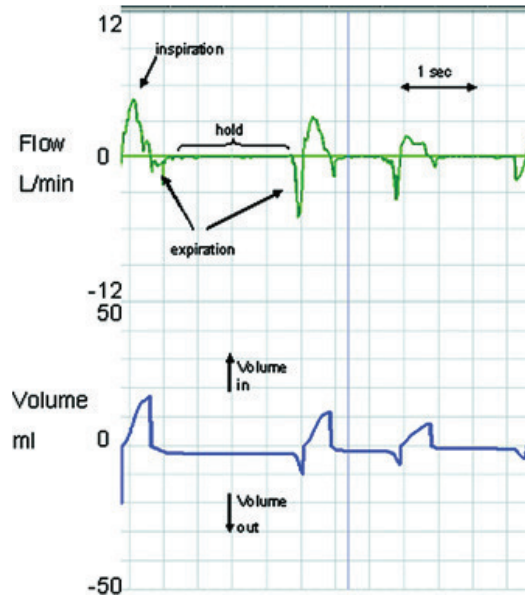
FIGURE 3.1: This figure displays expiratory patterns common in preterm infants. The green trace shows the flow of air through their lungs. Here, expiration is paused, followed by a quick exhale and immediate inhale. The bottom blue trace shows that the lungs expel less air than they inhale, allowing preterm infants to maintain lung volume. Reproduced from te Pas et al. in [23].

the time between a minimum and maximum, and the exhale length between a maximum and minimum. We record a breath length as the time between two consecutive minima. A visual representation of this procedure is shown in Fig. 3.2.

To prevent small fluctuations around zero to be mistakenly recorded as breaths, we include two checks for amplitudes. First, the probability of an apnea must be < 0.5 at the time of the amplitude. Second, two consecutive amplitudes must differ by at least $0.1 \cdot \sigma$ where σ is the standard deviation of the signal. We removed all amplitudes that did not meet these criteria to ensure that we were only recording actual breath lengths.

Following this algorithm, we recorded 100 inhales, 100 exhales, and 100 breaths for each case of apnea and time period. To test the effect of apnea, we compared two time groups: 5 minutes before an apnea vs. right before an apnea. We used two different sample sets of apnea durations for our VLA analysis. The first group contains apnea cases with durations between 10 - 20 s (N = 285). The VLA group includes apneas lasting longer than 60 s (N = 80).
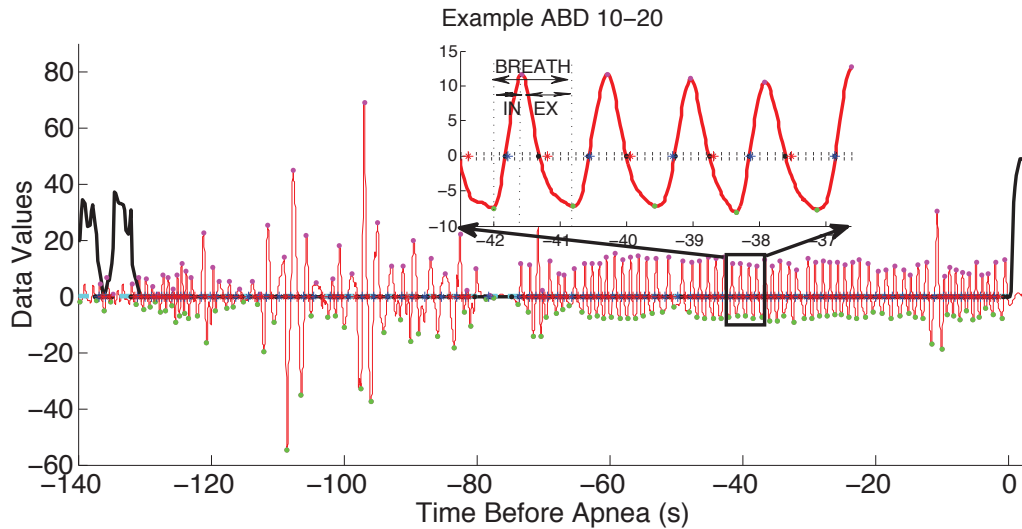
FIGURE 3.2: Here we show an example chest impedance signal from a single apnea case. Focusing on a small portion of the signal, we can see the method behind calculating breath lengths. We find minimum (green) and maximum (magenta) amplitudes, and calculate inhale, exhale, and breath times based on the relative differences between these amplitudes.

3.3 Results

3.3.1 Respiration Rate

After recording breath lengths, we organize our results into cumulative probability distributions of breaths. Instead of a histogram that displays the frequency of a particular breath length, a cumulative probability distribution reports the fraction of breaths in the data set below or equal to each given breath length. We then can take the derivative of the resulting cumulative probability distribution curves for a continuous histogram. This method allows us to see a continuous histogram distribution function, as opposed to typical histograms which only give discrete information and are dependent upon sample and bin size.

Figure 3.3 shows these two distribution types for breath lengths immediately preceding an apnea. With shorter apneas and VLAs on the same graph, we can see their different distributions. VLAs have a peak around 0.7 s, whereas shorter apneas have a smaller peak with more breaths that are longer. This is consistent with the cumulative distribution in that both show VLA breaths to be shorter. To test the significance of the differences of the two breath length distributions (shorter apneas vs. VLAs), we employ the Kalmogorov-Smirnov two-sample test in Matlab. This resulted in significant ($p \ll 0.01$) differences between shorter apnea and VLA breath length distributions. It is clear that VLAs tend to have shorter breaths right before apnea. VLAs are associated
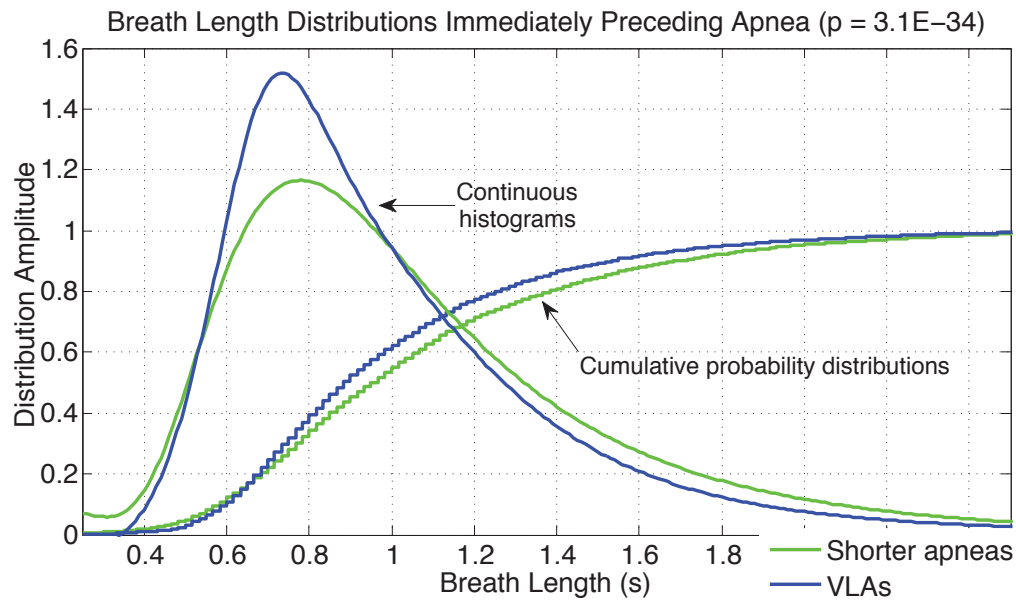
FIGURE 3.3: Here we show two different distributions of 100 breaths right before an apnea: continuous histograms and cumulative probability distributions. Both shorter apneas and VLAs are included. We can see a very clear distribution peak at 0.7 s associated with VLAs. Shorter apneas, however, have more breaths that are longer. These results are consistent with the cumulative probability distribution. We see a significant difference between distributions ($p \ll 0.01$). Thus, VLAs are associated with shorter breaths right before an apnea.

with an average breath that is 6.8% faster than for shorter apneas. Additionally, they have a median breath length that is 7.6% faster than that for shorter apneas. Thus, hyperventilation seems to precede VLAs.

As each case could involve many different factors, the different distributions right before an apnea do not alone prove a link between respiration rate and length of apnea. To control for other variables like different patients, we also looked at breath lengths during normal breathing, which we consider as 5 minutes before an apnea. Figure 3.4 shows our result.

While the distributions still pass the Kalmogorov-Smirnov significance test, ($p \ll 0.01$), it is clear that there is a smaller difference between respiration rates of shorter vs. longer apneas. The similarity in breath lengths is apparent in both the continuous histogram and cumulative probability distribution shown in Fig. 3.4. Breaths during normal conditions before a VLA are on average 3.0% faster than for shorter apneas, with a median breath length 3.3% faster than for shorter apneas. This decrease in average and median percent differences is consistent with our more similar distributions. The differences in respiration rates are amplified right before an apnea, when hyperventilation is present before VLAs.
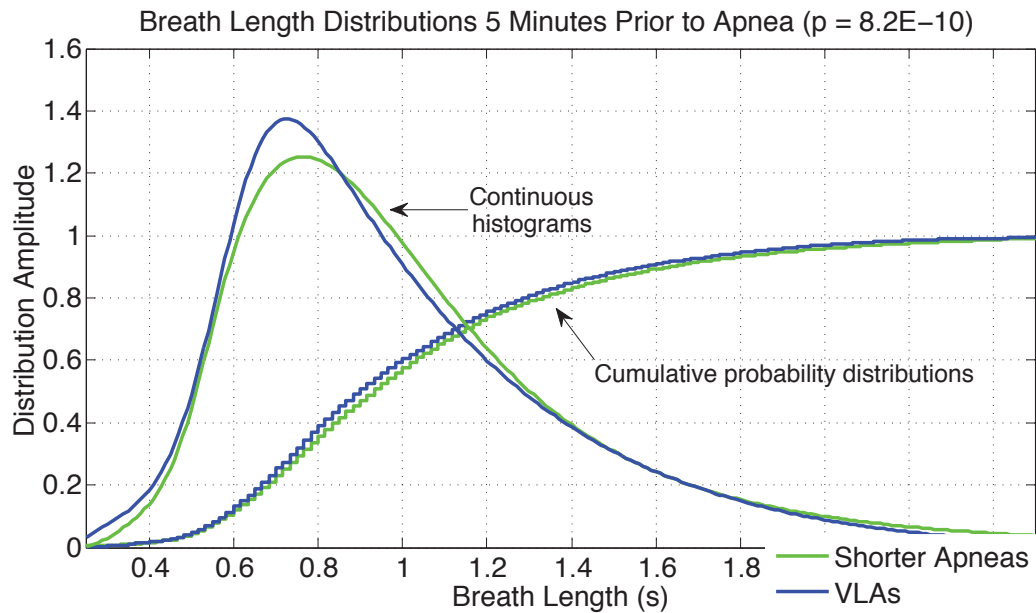
FIGURE 3.4: Here we show two different distributions of 100 breaths five minutes before an apnea: continuous histograms and cumulative probability distributions. Both shorter apneas and VLAs are included. Unlike the distributions right before an apnea, we do not see such a distinctive difference in distributions between apnea groups. While there is a significant difference between distributions ($p \ll 0.01$), it is not as distinctive as for breaths directly preceding an apnea event.

3.3.2 Inhale vs. Exhale Lengths

Consistent with previous research noted above in [22] and [24], we find exhale lengths significantly greater ($p < 0.05$) than inhale lengths. We report similar results for all apnea duration and time groups, so we include one plot as a representative in Fig. 3.5.

We next examine how inhale/exhale lengths change five minutes before an apnea vs. right before an apnea. This way, we can see if inhales or exhales before VLAs are changing independently of one another, accounting for the total increase in respiration that we observe. We include shorter apneas as a control.

First, we focus on inhales and exhales associated with VLAs. Figure 3.6 shows that *both* inhales and exhale lengths decrease right before an apnea. Thus, inhales and exhales change together. Applying the same method to shorter apnea cases, we can see that inhales and exhales lengths both seem to increase right before an apnea (Fig. 3.7).

In both cases, we see that inhale/exhale lengths change together right before an apnea. There is no observable trend in inhales/exhale lengths that could indicate properties of VLAs or associated chemical concentrations.

In summary, we have shown that VLAs are associated with hyperventilation right before an apnea. We are unable at this point to make an assumption of O_2 or CO_2 levels
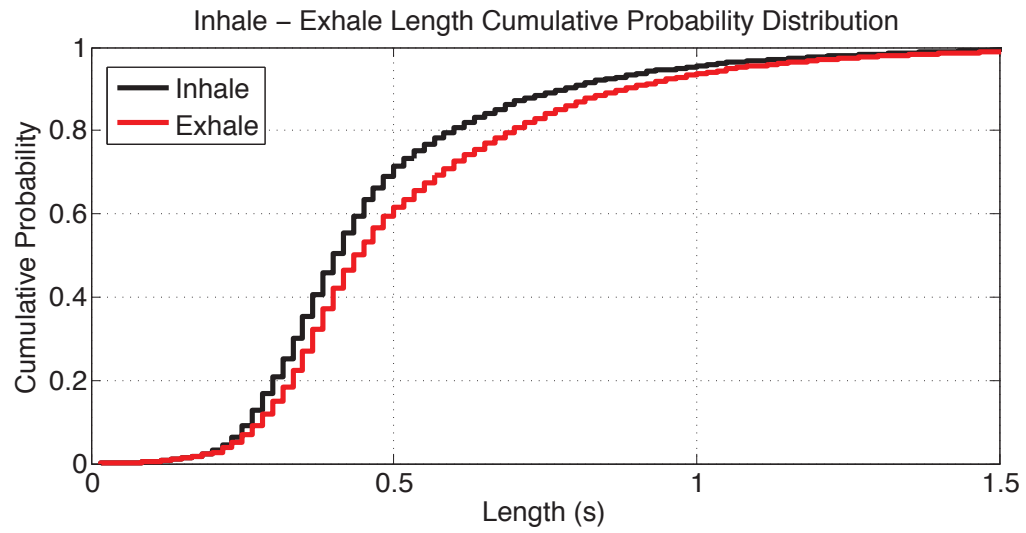
FIGURE 3.5: Cumulative distribution plot of 100 inhales and exhales right before apnea. All cases show a significant difference (p<0.05) between inhale and exhale distributions. Exhales are consistently longer in all cases (VLAs vs. shorter apneas and right before apnea vs. five minutes before). This pattern is independent of the apnea event.

that may cause this increased respiration. In addition, exhale times are typically longer than inhale times, but inhale/exhale proportions appear to be unrelated to the onset of apnea.
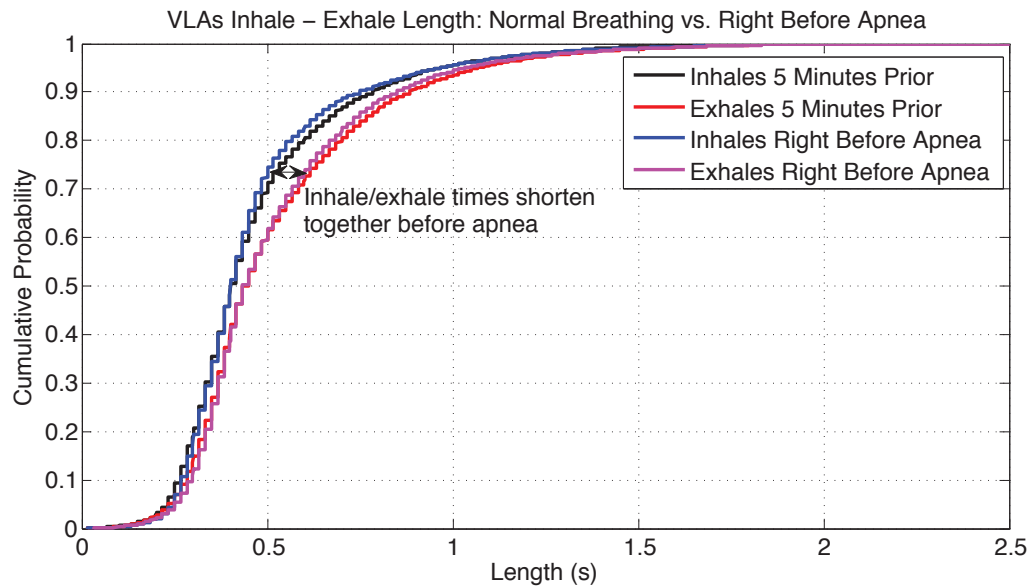
FIGURE 3.6: Cumulative distribution plots of 100 inhales and exhales five minutes before and right before a VLA. We observe that right before apneas, *both* inhales and exhales shorten, instead of one remaining constant while the other changes.
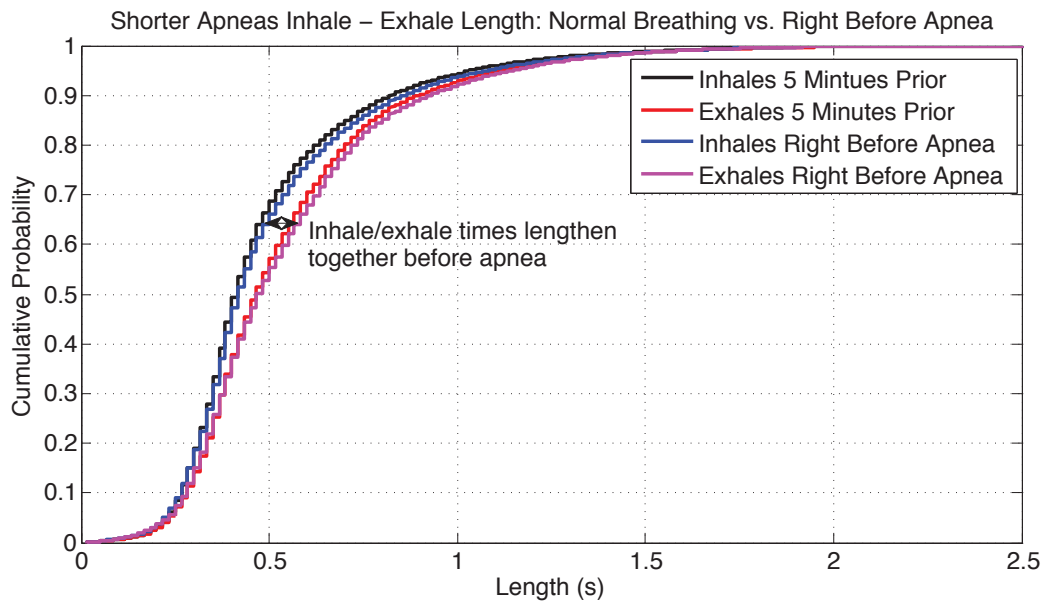

FIGURE 3.7: Cumulative distribution plots of 100 inhales and exhales five minutes before and right before a shorter apnea. We observe that right before apneas, *both* inhales and exhales lengthen, instead of one remaining constant while the other changes.

Chapter 4

Apnea Theory

In order to improve our understanding of O_2 decreases during apnea, we now examine a theory of the rate of oxygen desaturation associated with apneas. We test its ability to describe individual apnea cases. This theory was developed in a paper by Sands et al. in [2]. Upon application to actual data, determining relevant parameters in the model would provide important information on how oxygen saturation and O_2 consumption change during an apnea event.

4.1 Physiology of Breathing

4.1.1 Stage One

Respiration involves exchanges of O_2 and CO_2 between the alveoli and capillaries. Oxygen molecules inside the lungs follow concentration and pressure gradients to diffuse across the surface of alveoli and into the blood [25]. Carbon dioxide follows its own opposite gradient to exit the capillaries and leave the body through the lungs.

Figure 4.1 simplifies the respiration process. Lungs fill with air and oxygen diffuses into capillaries. Blood transporting the inhaled oxygen from the lungs to the body will be referred to as "arterial" blood. From here, oxygen is used by the body at a rate dependent on metabolic output that we will refer to as constant e. Blood containing less oxygen then returns from the different parts of the body back to the lungs to receive more oxygen. We call this less oxygenated blood "venous" blood, with its corresponding oxygen saturation $S_v O_2$. Both oxygen saturation levels are important for modeling arterial oxygen saturation.

Assuming equilibrium conditions hold between the alveoli and arteries, an increase in partial pressure (PO_2) of O_2 in the lungs immediately increases $S_a O_2$. Likewise, a
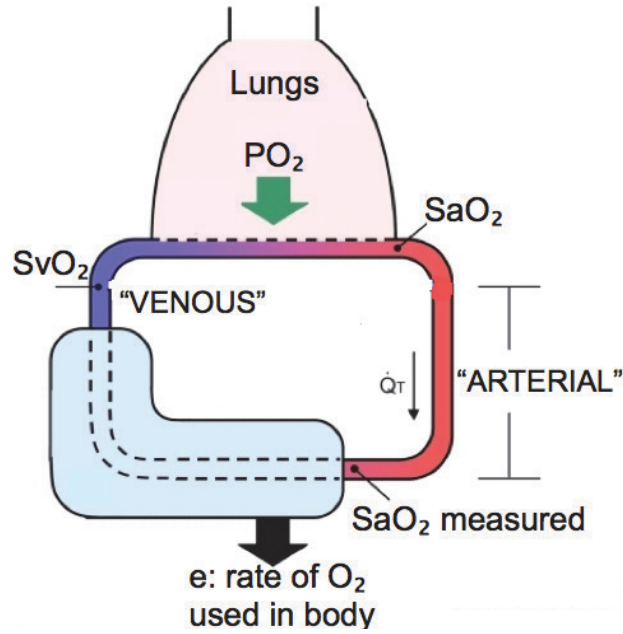
FIGURE 4.1: Simplified diagram of the ventilatory process. After a breath, oxygen diffuses from the alveoli into "arterial" blood. Oxygen is then circulated throughout the body. "Venous" blood then takes the less oxygenated blood back to the lungs to receive more oxygen. Modified from Sands et al. in [2].

cessation in breathing will result in an immediate decrease in arterial oxygen saturation. However, because of the location of measurement, there is a delay for the apnea to affect measured S_aO_2. We can observe a time delay of varying duration in each case of apnea. As less-oxygenated blood circulates throughout the body, it still has not reached the "venous" blood supply. We refer to this early stage as *stage one* for when S_vO_2 is constant.

As the apnea continues, the less-oxygenated blood returns from the body to the veins. The subsequent decrease of S_vO_2 marks the start of *stage two*. Because the infant is not breathing, no additional oxygen is inhaled. Thus, S_aO_2 will approach S_vO_2, and the two values will fall together at the same rate. The behavior of both of these stages will determine our approach to model arterial oxygen saturation.

We use the mathematical model in Sands et al. to describe the decrease in oxygen saturation during an apnea. Oxygen saturation is a percentage of oxygenated hemoglobin in the blood. Thus, we can begin to derive a formula for oxygen saturation by beginning with the moles of oxygen entering the blood. Since the total amount of oxygen is conserved, we can say the moles of oxygen lost in the lungs is equal to the number of moles gained in the blood, or

$$\frac{dn_{blood}^{O_2}}{dt} = \text{rate moles } O_2 \text{ entering blood} = -\text{rate moles } O_2 \text{ leaving lungs} \qquad (4.1)$$

The rate of change of oxygen concentration will be equal to the change in oxygen concentration multiplied by the total blood flowing per unit time. This is modeled by the equation:

$$\frac{dn_{blood}^{O_2}}{dt} = \dot{Q} \times \left([O_2]^{arteries} - [O_2]^{veins}\right) \tag{4.2}$$

where $\dot{Q}$ is the cardiac output, or the rate of blood flow and $[O_2]$ is the oxygen concentration. From here, we can convert from concentration to oxygen saturation using Equations 2.4 to 2.6 and get:

$$\frac{dn_{lungs}^{O_2}}{dt} = -\dot{Q}([Hb] \cdot 4)\left(S_aO_2 - S_vO_2\right) \tag{4.3}$$

where [Hb] is the concentration of hemoglobin, and SO_2 is the oxygen saturation. The negative sign comes from our transition from modeling O_2 gain in blood to O_2 lost in the lungs. (We focus on O_2 changes in the lungs to solve for arterial saturation by using the relationship between partial pressure of O_2 in the lungs and percent saturation.) The ideal gas law states

$$PV = nRT \tag{4.4}$$

Taking the derivative of both sides gives us

$$\frac{dn_{lungs}^{O_2}}{dt} = \frac{V}{RT}\left(\frac{dP_{lungs}^{O_2}}{dt}\right) \tag{4.5}$$

Solving for the partial pressure of oxygen, we rearrange Eq. 4.5 to get

$$\frac{dP_{lungs}^{O_2}}{dt} = -\left(\frac{RT}{V}\right)\dot{Q}([Hb] \cdot 4)\left(S_aO_2 - S_vO_2\right) \tag{4.6}$$

We need to convert partial pressure of oxygen in the lungs to arterial oxygen saturation. We begin with the chain rule, which gives

$$\frac{dP_{lungs}^{O_2}}{dt} = \frac{dP_{lungs}^{O_2}}{dS_{blood}} \cdot \frac{dS_{blood}^{O_2}}{dt} \Rightarrow \frac{dS_{blood}^{O_2}}{dt} = \frac{dP_{lungs}^{O_2}}{dt} \cdot \frac{dS_{blood}}{dP_{lungs}} \tag{4.7}$$

We know dP/dt from Eq. 4.6, so we now need dS/dP. Oxygen saturation is defined as the fraction of oxygenated hemoglobin molecules out of the total hemoglobin molecules, or

$$S_aO_2 = \frac{[HbO_2]}{[Hb] + [HbO_2]} \tag{4.8}$$

Through experimental observation, it is found that partial pressure and oxygen saturation are related by [2]

$$S_aO_2 \simeq \frac{(kP^{O_2})^n}{1 + (kP^{O_2})^n} \tag{4.9}$$

where k and n are constants and P is the partial pressure of oxygen in the lungs.

Thus, taking the derivative of Eq. 4.9 with respect to pressure allows us to solve for the rate of change of oxygen saturation to resolve the final version of the formula

$$\frac{dS_a^{O_2}}{dt} = -\underbrace{\frac{dS}{dP}(S)}_{D(S)} \cdot \underbrace{\left(\frac{RT}{V}\right) \dot{Q}_T([Hb] \cdot 4)}_{C} \left(\underbrace{S_aO_2}_{S_a} - \underbrace{S_vO_2}_{S_v}\right) \tag{4.10}$$

or

$$\frac{dS_a}{dt} = -D(S) \cdot C \left(S_a(t) - S_v(t)\right) \tag{4.11}$$

Early in the apnea, there are reasons to believe that the cardiac output and S_v remain constant. We can calculate these constants using the value and rate of change of measured S_aO_2 at two points. This model's fit to average oxygen saturation curves is shown in Fig. 4.2. The models fit the average curve reasonably well, which prompted further investigation on an individual basis.

The next step is to compare theory with individual saturation curves. As shown in Fig. 4.3, the theory applies to the data for a limited amount of time. The differential equation for arterial oxygen saturation fits the data until it begins to reach a constant asymptote, S_v. This point of divergence occurs at a circulation time, τ_c, after the onset of desaturation. At this moment, oxygenated blood has cycled through the body and reaches "venous" blood. We now incorporate stage two in our model.
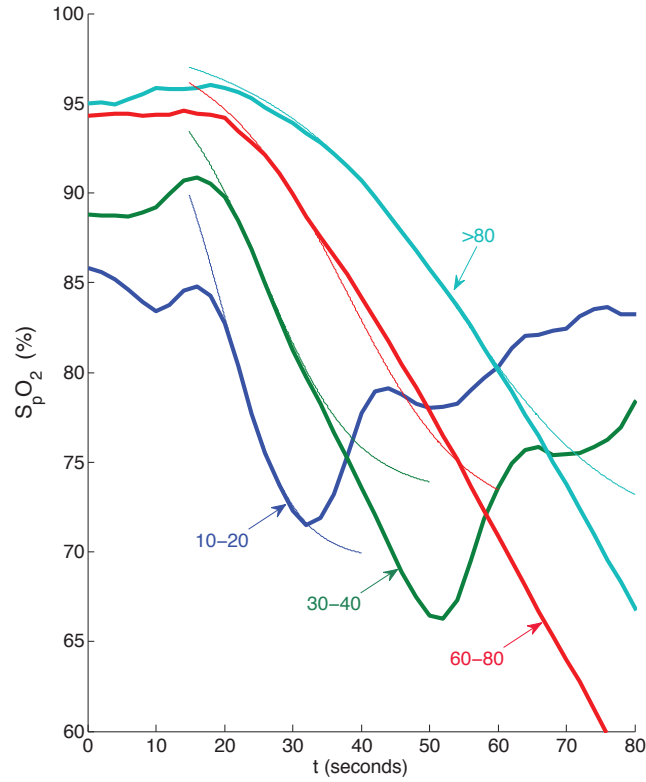
FIGURE 4.2: Mohr et al. in [19] applied stage one modeling theory to average oxygen saturation levels. Divided into groups based on apnea duration, we can see a reasonably good fit until the theory curves deviate from observed data.

4.1.2 Stage Two

We must first understand what happens as deoxygenated blood circulates to different areas of the body. Once the infant first stops breathing, the veins still carry the same amount of oxygen as before. Thus, there is a delay in the time from the patient's last breath to when the veins experience the deficit. After the apnea persists and the deoxygenated blood circulates back to the lungs without additional oxygen, S_aO_2 approaches S_vO_2. The derivation for stage two begins in a similar manner as with stage one [2].

We seek an expression describing the rate of change of S_vO_2. We again begin with the premise that the rate of change of O_2 moles in the veins is equal the difference in rates of O_2 entering vs. leaving the veins. Put in symbolic form,

$$\frac{dn_v^{O_2}}{dt} = (\text{rate moles } O_2 \text{ entering veins} - \text{rate moles } O_2 \text{ leaving veins}) \qquad (4.12)$$
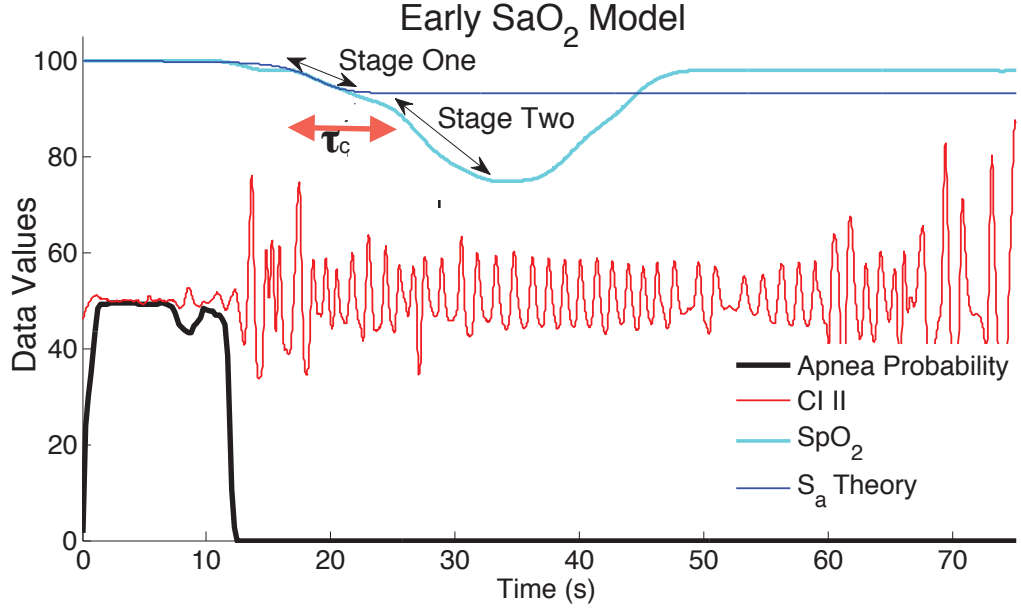
In terms of oxygen concentrations, Eq. 4.12 is equal to

FIGURE 4.3: Here we show signals from a specific case of apnea. The light blue curve is the measured S_aO_2, while the dark blue curve is our modeled S_a. Considering stage one only, our theory curve deviates from the observed oxygen saturation. There is a clear point of inflection in the curve, which marks the beginning of stage two. We define the circulation time, τ_c, as the time from the beginning of oxygen desaturation to the onset of stage two. We must include stage to improve the model's accuracy.

$$\frac{dn_v^{O_2}}{dt} = \dot{Q}([O_2]_{in} - [O_2]_{out}) - \frac{[O_2]_{body}}{\text{unit time}} \qquad (4.13)$$

Here, $[O_2]_{in}$ refers to oxygen entering capillaries, while $[O_2]_{out}$ refers to oxygen leaving the veins. We must also include $[O_2]_{body}$ or the oxygen concentration used for metabolic processes in the body now that oxygenated blood has circulated throughout the body. This accounts for oxygen lost to metabolic processes. Again, $\dot{Q}$ is the cardiac output.

As done previously, we can convert from oxygen concentration to oxygen saturation to get:

$$\frac{dn_v^{O_2}}{dt} = \dot{Q}([Hb] \cdot 4)(S_a(t - \tau_c) - S_v(t)) - \frac{[O_2]_{body}}{\text{unit time}} \qquad (4.14)$$

where τ_c is the blood circulation time from arterial to venous locations. We incorporate this time lag because our differential equation depends on the net gain of arterial minus venous oxygen supply. The same blood supply at these two sties is separated by the time it takes to travel throughout the body.

Additionally, we know that

$$n_v^{O_2} = (\text{vol}_{veins})([Hb] \cdot 4) \cdot S_v \tag{4.15}$$

Where vol_{veins} is the volume of blood circulating in the veins. After differentiating Eq. 4.15, and solving for dS_v/dt, we get the final result of

$$\frac{dS_v^{O_2}}{dt} = \underbrace{\frac{\dot{Q}}{\text{vol}_{veins}}}_{d}(S_a(t - \tau_c) - S_v(t)) - \underbrace{\frac{[O_2]_{body}}{\text{unit time} \cdot 4 \cdot [Hb] \cdot \text{vol}_{veins}}}_{e} \tag{4.16}$$

Simplifying the expression with constants d and e, we get

$$\frac{dS_v}{dt} = d\left(S_a(t - \tau_c) - S_v(t)\right) - e \tag{4.17}$$

Here, d is proportional to cardiac output, τ_c is the time constant that determines the lag, and e is related to the metabolic rate.

In summary, our two equations for arterial and venous oxygen saturation are

$$\frac{dS_a}{dt} = -D(S) \cdot C\left(S_a(t) - S_v(t)\right) \tag{4.18}$$

with

$$S_v(t) = \begin{cases} Sv_{const}, \text{Stage One} \\ S_v(t), \quad \text{Stage Two} \end{cases}$$

and

$$\frac{dS_v}{dt} = \begin{cases} 0, & \text{Stage One} \\ d\left(S_a(t - \tau_c) - S_v(t)\right) - e, \text{Stage Two} \end{cases}$$

We apply solutions for these two coupled equations in two different ways. First, we test this model with individual cases of apnea. To apply to each data set, we must solve for the two unknown constants, d and e. We use given values of S_a to approximate dS_a/dt. We then employ two assumptions to solve for d and e. The first is that early in the apnea,

$$\frac{dS_v}{dt} = 0 \approx d(Sa_{early} - Sv_{const}) - e \quad \text{[Stage One]} \tag{4.19}$$

which provides a constraint to solve for one variable from the other. Our second assumption is that once S_a approaches S_v, the two levels fall at the same rate, or
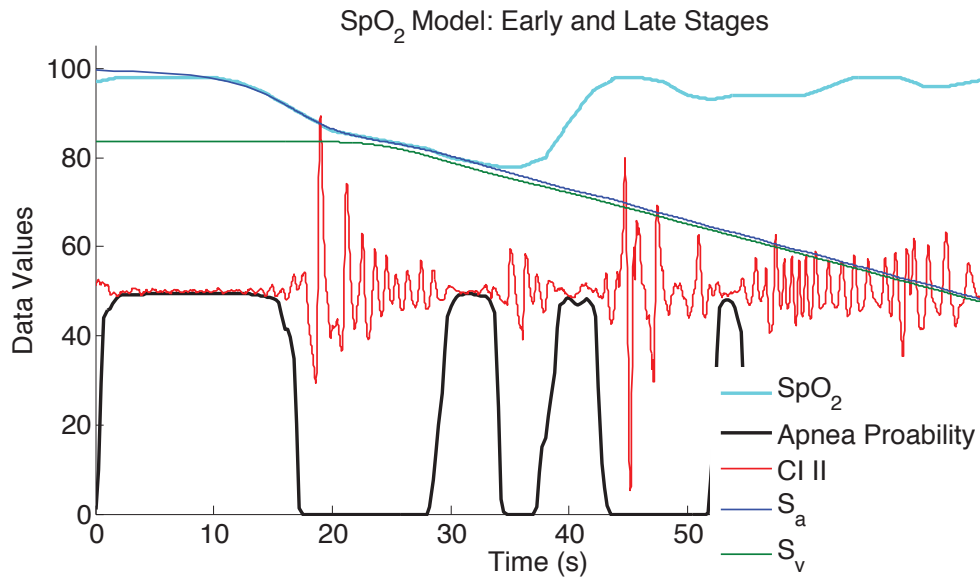
FIGURE 4.4: Here we show the model that incorporates changes in both S_aO_2 and S_vO_2 (dark blue and green lines, respectively). We can see that this complete approach results in more agreement between theoretical and observed S_aO_2 levels

$$\frac{dS_v}{dt} \simeq \frac{dS_a}{dt} \quad \text{[Stage Two]} \tag{4.20}$$

Thus, in later stages, we can use the given S_a curve to approximate dS_v/dt to find d and e.

Aside from studying individual cases, we make general models of S_aO_2 and S_vO_2 by choosing our own parameters. We then integrate the two coupled equations for plots of oxygen desaturation.

4.2   Results

Figures 4.4 and 4.5 show results for the model applied to three individual cases of apnea. These examples all have reasonably good agreement between theory and observed data. However, in the sample size of about 160 apneas lasting between 10 - 20 s, only 20 of them resulted in respectable fits with our model. While good fits are uncommon, this does not reflect the fact that the model is inaccurate, but rather that isolated apneas are rare. The theory behind the model only accounts for one apnea event at a time, so intermittent breathing and short apneas will prevent the theory from correctly describing observed data. We are currently seeking more isolated cases for further study.

Aside from trying to fit actual data, we also use the differential equations in Eq. 4.11
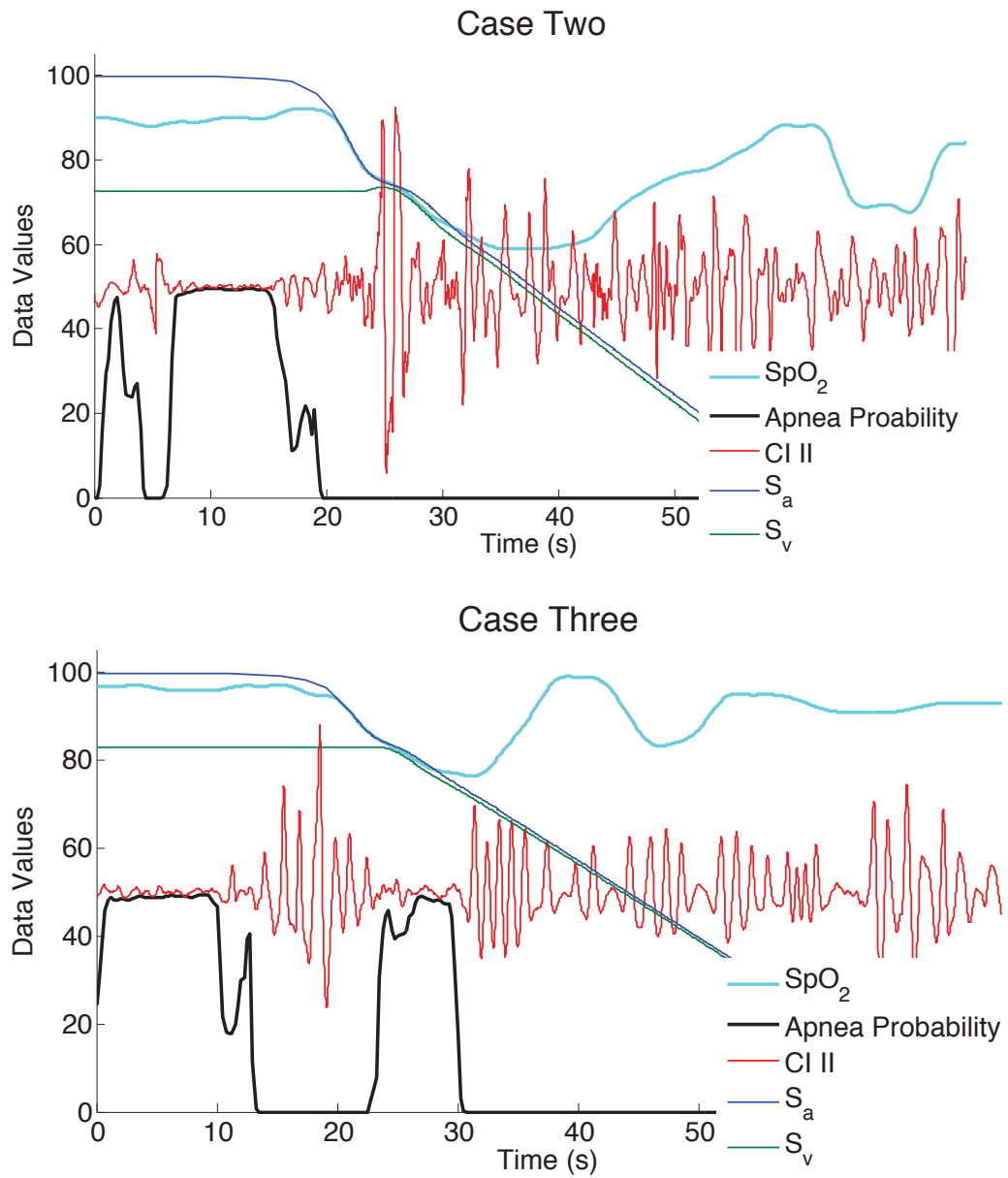
FIGURE 4.5: Further examples of good fits in which the modeled S_a agrees with measured values for a significant amount of time.
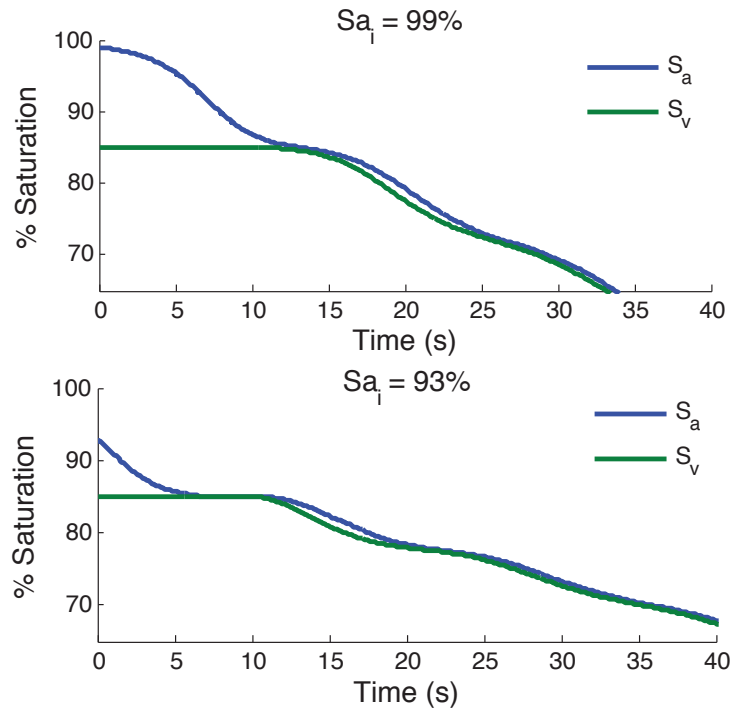
FIGURE 4.6: Shown are the S_a and S_v curves modeling oxygen saturation levels during an apnea. Top and bottom show 99% and 96% initial arterial oxygen saturations, respectively. Higher levels of initial arterial oxygen saturation results in slower decreases in S_aO_2.

and 4.17 to make simulations of oxygen desaturation by inputting our own parameters. This will allow us to observe the effects of different parameters levels. To expand on observations of initial arterial saturation levels, we first focus on this parameter and show results of different initial values. From the resulting plot in Fig. 4.6, we can see that the differential equations behave in the expected fashion: S_a converges to S_v from the initial start of apnea. Afterwards, the two values fall together.

We also observe that higher initial oxygen saturation levels result in slower decreases in oxygen saturation. This is consistent with our findings that average oxygen saturation levels begin at higher levels and take the longest to decrease.

Additional plots resulting from manipulation of other parameters and our method in detail is included in Appendix A.

Chapter 5

Conclusion

5.1   Summary of Results

We have used recorded data from the University of Virginia NICU to analyze signals taken surrounding apnea events in premature infants. Along with monitor data, we have expanded previous work by using the filtered chest impedance signal detailed in [1]. We have also tested the model for oxygen saturation during apnea presented in [2]. Each of our analyses aims to understand conditions unique to very long apneas.

Through integral approximation, we have calculated the deficit during an apnea in terms of heartbeats and oxygen transported. We have shown a positive relationship between duration of apnea and deficits in both these measures. The reduction in total number of heartbeats and moles of oxygen transported is approximately proportional to the duration of the apnea. This fact was not obvious because the heart rate and oxygen saturation fall slowly during VLAs.

We also observed that oxygen saturation levels are initially the highest for the longest apneas. We calculated respiration rates using the filtered chest impedance signal to confirm that VLAs are associated with hyperventilation immediately preceding apnea.

We have also tested a mathematical model from [2] for the rate of decrease of oxygen saturation during apnea. We computed the solution of the model for various input parameters, and we fit the parameters in the model to some of our apnea cases. The model provides an explanation as to why oxygen saturation falls slowly if the initial arterial saturation is high. We hope to collect more isolated apneas for further study and parameter fitting.

While there is still much more to be learned about VLAs, we have advanced our knowledge of them. We have continued previous research on apneas of prematurity to

work towards the eventual understanding of their causes, consequences, and associated conditions that could aid in their detection or prevention.

Appendix A

Additional Figures

Here we include plots of the apnea theory model detailed in [2] in which we vary one parameter at a time. This way, we can observe how changes in each variable affect the shape of the S_aO_2 curves.

We integrate our coupled differential equations presented in Chapter 4:

$$\frac{dS_a}{dt} = -D(S) \cdot C \left(S_a(t) - S_v(t) \right) \tag{A.1}$$

where $S_v(t)$ is a constant at times before the blood circulates through the body to reach the veins. In stage one, the constant S_v is a parameter that we must put into our model. We will refer to the constant S_v parameter as Sv_{const}. Our equation to model S_vO_2 is

$$\frac{dS_v}{dt} = d(S_a(t - \tau_c) - S_v) - e \tag{A.2}$$

where this is equal to 0 for $t \leq \tau_c$.

We choose parameters by observing their values that we calculated for each individual case. "Normal" parameter values we use for each model (unless otherwise specified) are:

- $Sa_i = 96\%$

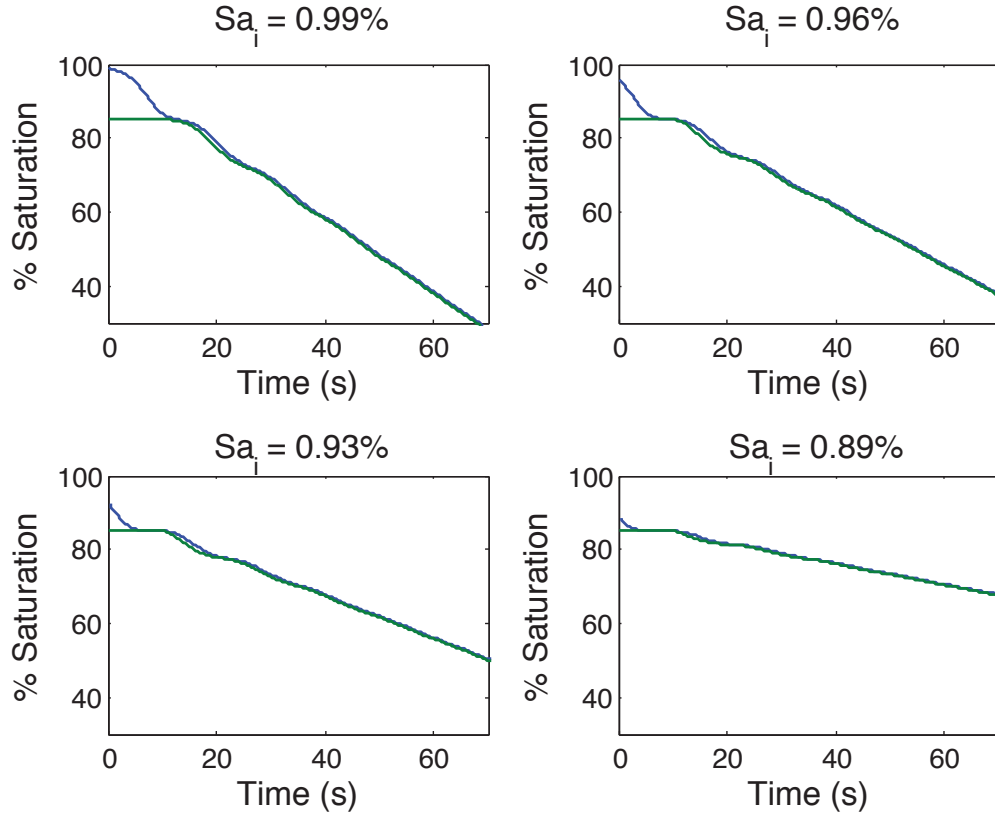- $Sv_{const} = 85\%$

- $C = 100$

- $d = 0.3$

- $\tau_c = 10$

FIGURE A.1: Results of the model with all parameters held constant except for Sa_i.

The parameter e is found with the condition for early stages:

$$\frac{dS_v}{dt} = 0 \approx d(Sa_i - Sv_{const}) - e \tag{A.3}$$

where Sa_i is the initial arterial oxygen saturation. This is the first variable that we vary. The resulting plots are shown in Fig. A.1. In all figures of our model, S_aO_2 is shown by the dark blue curve, while S_vO_2 is the green curve. As supported by previous discussion, our resulting model in Fig. A.1 shows that initial levels of oxygen saturation affect the rate of decrease in S_aO_2.

We now modify initial venous oxygen saturation, or Sv_{const}. From Fig. A.2, we can see that S_v values also affect the rate of decrease of S_aO_2 and S_vO_2. If Sv_{const} is low, it will take a long time for S_a to reach it, resulting in a more rapid and less linear drop of both values.

We then change the constant C. It is defined in Eq. 4.10, and is related to many relevant physical properties like cardiac output. Figure A.3 shows the resulting plots of different C values. We can see that C does not affect the rate of decline, but rather the
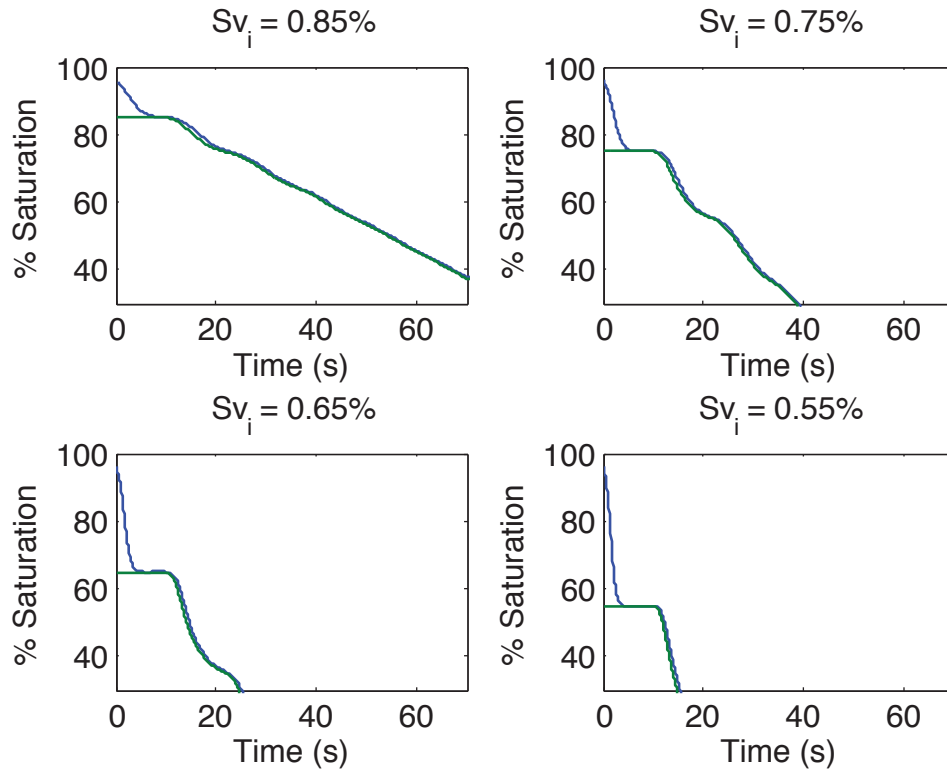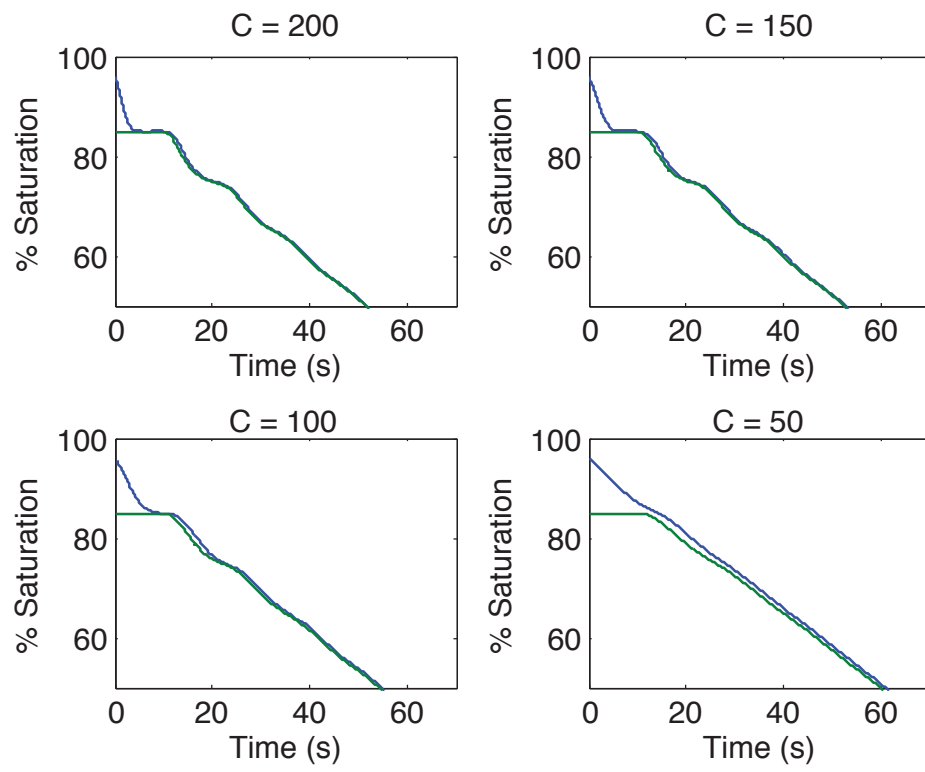
FIGURE A.2: Results of the model with all parameters held constant except for Sv_{const}, which we also refer to as Sv_i.

shape or linearity of the curves.

Like C, d also involves cardiac output (defined in Eq. 4.16). Thus, we expect analogous activity for parameter manipulates with C and d. Figure A.4 indeed shows similar properties to our modifications in C. The parameter d does not affect rate of change, but rather the linearity in both S_aO_2 and S_vO_2 curves.

We now change τ_c, or the amount of time it takes for the effect of apnea to reach S_vO_2 supply. In other words, this is the length of stage one or oxygen circulation in the body. Figure A.5 shows our results. It appears that the circulation time influences both rate of change and shape of the two curves. As the cycle time increases, the decline in S_aO_2 and S_vO_2 is slower and less linear.

We have not yet reached a conclusion for optimal values for our parameters. We will need to continue applying our model to individual isolated apneas and derive parameter values from these cases.

FIGURE A.3: Results of the model with all parameters held constant except for C.
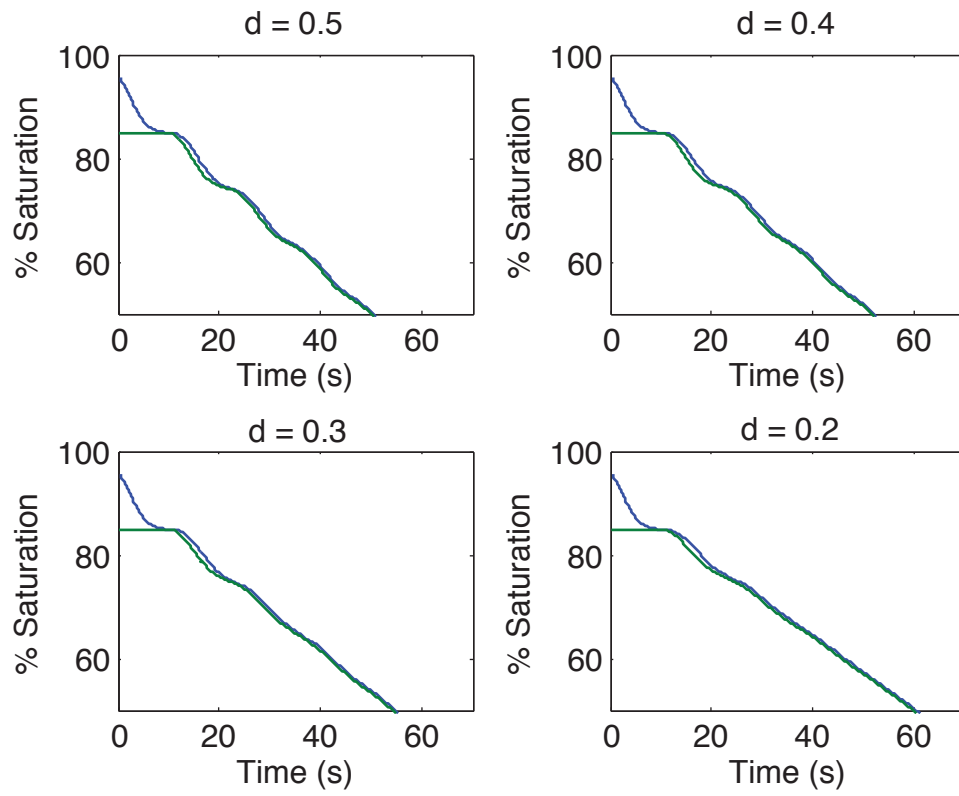
FIGURE A.4: Results of the model with all parameters held constant except for d.
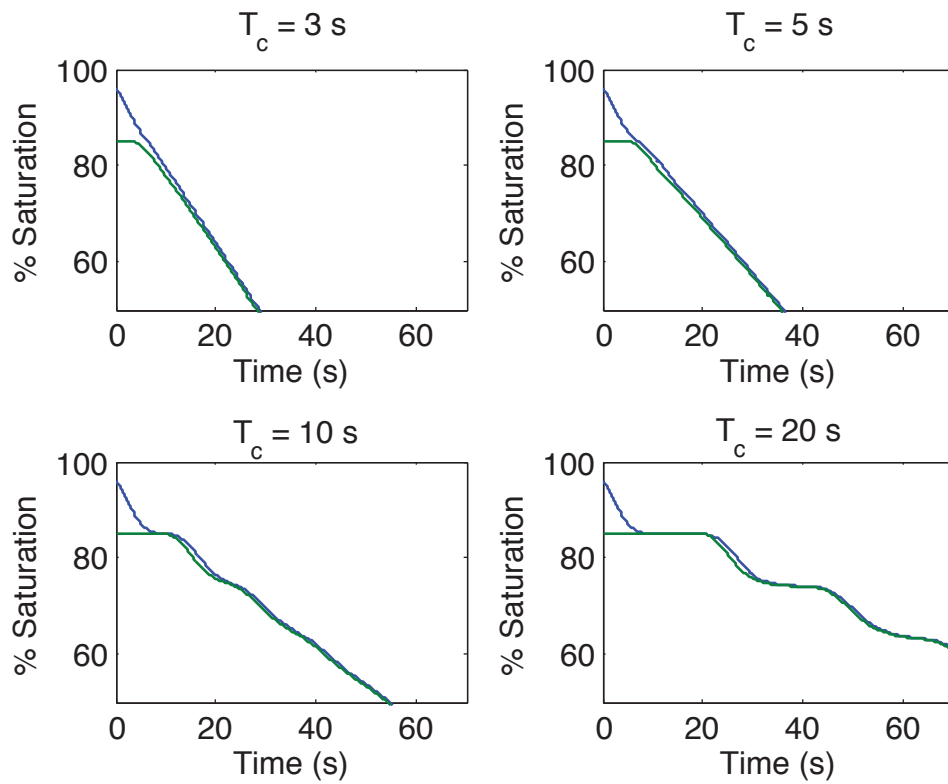
FIGURE A.5: Results of the model with all parameters held constant except for τ_c.

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