Development and Analysis of a Simple Grey-Box Model of Central Sleep Apnea

by

Ali Kazerani

B.A.Sc., University of Waterloo (2010)

Submitted to the Department of Electrical Engineering and Computer Science

in partial fulfillment of the requirements for the degree of Master of Science in Electrical Engineering and Computer Science

at the MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2013

© Massachusetts Institute of Technology 2013. All rights reserved.

Author

Department of Electrical Engineering and Computer Science

May 22, 2013

Certified by

John N. Tsitsiklis
Professor
Thesis Supervisor

George C. Verghese
Professor
Thesis Supervisor

Accepted by

Leslie A. Kolodziejski
Chairman, Departmental Committee on Graduate Students
Development and Analysis of a Simple Grey-Box Model of Central Sleep Apnea

by

Ali Kazerani

Submitted to the Department of Electrical Engineering and Computer Science on May 23, 2013, in partial fulfillment of the requirements for the degree of Master of Science in Electrical Engineering and Computer Science

Abstract

In this thesis, we develop and analyze a simple grey-box model that describes the pathophysiology of central sleep apnea (CSA). We construct our model following a thorough survey of published approaches. Special attention is given to PNEUMA, a complex, comprehensive model of human respiratory and cardiovascular physiology that brings together many existing physiological models. We perform a sensitivity analysis, concluding that signals of interest in PNEUMA are insensitive to changes in all but approximately twenty parameters. This justifies our goal of developing a small, simple model that captures approximately the same behaviour among signals of interest. The simplicity of our model not only makes it accessible to analytical and intuitive exploration, but also opens up the possibility that its parameters could be reliably estimated from a patient’s data records. This could be of great value in developing patient-specific or state-specific treatments for CSA.

Our model describes the dynamics of the alveolar gas exchange, blood gas transport, and cerebral gas exchange processes, which together determine the cerebral and arterial partial pressures of carbon dioxide, given ventilation as input. Our model of the ventilatory controller senses both the cerebral and arterial carbon dioxide partial pressures and issues a ventilatory drive command from which the level of ventilation is determined, closing the loop. We develop a linearized small-signal model of our system and determine conditions for its stability. We conclude by comparing the stability predictions suggested by our linear analysis to the stability properties of our original nonlinear model, with promising results.

Thesis Supervisor: John N. Tsitsiklis
Title: Professor

Thesis Supervisor: George C. Verghese
Title: Professor
Acknowledgments

Mom (Parichehr) and Dad (Mehrdad), no words will ever be enough. Thank you, for absolutely everything. To my brother, Iman: thank you for, amongst so many other things, never failing to make me smile. I love you all so dearly.

To my research advisors, Professors John Tsitsiklis and George Verghese: I am remarkably fortunate to work with you. Thank you for demonstrating, without fail, every professional and personal virtue imaginable, along with something resembling omniscience. And of course, thank you in particular for all the guidance you offered as I wrote (and you read) this thesis.

Thanks also to Dr. Thomas Heldt, who taught me so much both in class and during research meetings.

I would like to thank the Periodic Breathing Foundation for a generous gift to MIT, which made this work possible. I offer my sincere thanks also to Robert Daly, for the inspiration he provided and for sharing his experience and expertise with us in discussions, meetings, and tours.

I am incredibly grateful to all those who guided and helped me while, not so very long ago, I was searching for a research home. My thanks in particular to Professors Leslie Kolodziejski and Alan Oppenheim, for looking after me through the tumult. I would also like to thank Janet Fischer for all her help and apparently inexhaustible patience. And I will forever owe a great debt to Professor Terry Orlando, who spent a great many hours over many months helping me find and make my way in this place. My journey would have been very, very different if I had not met him.

PNEUMA, a physiological model implementation that I explore in this thesis, is supported and distributed by the University of Southern California Biomedical Simulations Resource.
# Contents

1 Introduction 13
   1.1 Background .................................................. 13
   1.2 Literature Survey ............................................. 15
   1.3 Contributions and Outline .................................... 17

2 PNEUMA 21
   2.1 Introduction to PNEUMA ........................................ 21
   2.2 Simulating Stable and Unstable Breathing in PNEUMA .......... 23
   2.3 Issues with PNEUMA ............................................ 26
   2.4 Preparing PNEUMA for Numerical Experiments .................. 29
   2.5 Sensitivity Analysis .......................................... 30
      2.5.1 Our Procedure ............................................ 31
      2.5.2 Some Additional Details .................................. 34
      2.5.3 Results ................................................... 36
      2.5.4 Conclusions .............................................. 41

3 A New, Simple Model 43
   3.1 Overview ..................................................... 43
      3.1.1 Pulmonary Gas Exchange Plant, $P_A$ ..................... 44
      3.1.2 Lung-to-Carotid Transport Plant, $P_a$ ................. 45
      3.1.3 Cerebral Gas Exchange Plant, $P_b$ ...................... 46
      3.1.4 Chemoreflex Controller ................................... 47
      3.1.5 Ventilation Plant ........................................ 47
CONTENTS

3.2 Model Properties .......................................................... 48
  3.2.1 Requirements .......................................................... 48
  3.2.2 Simplifications .......................................................... 48

3.3 Model Details .............................................................. 49
  3.3.1 Pulmonary Gas Exchange Model ..................................... 49
    3.3.1.1 Linearization .................................................... 53
  3.3.2 Cerebral Gas Exchange Model ....................................... 55
  3.3.3 Lung-to-Carotid Transport Model ................................... 61
  3.3.4 Chemoreflex Control of Ventilation ............................... 74

3.4 Model Parameters ........................................................ 85
  3.4.1 The System Operating Point ......................................... 89

3.5 Simulation Results ........................................................ 93
  3.5.1 Incorporating Padé Approximants .................................... 94
  3.5.2 Using Linearized Plant Models ...................................... 96

4 Stability Analysis ......................................................... 101
  4.1 Linear Stability Analysis .............................................. 101
    4.1.1 The Linearized Model ............................................ 101
    4.1.2 Stability of the Linear Model System ............................ 104
  4.2 Influence of Central and Peripheral Gains on Stability .......... 111
  4.3 Stability of our Nonlinear Model System ............................ 116

5 Conclusion ................................................................. 121
  5.1 Future Work ............................................................ 122

References ................................................................. 125
List of Figures

1.1 Lung volume waveforms for normal breathing and CSA. ......................... 15

2.1 PNEUMA’s top-level block diagram. .............................................. 23
2.2 PNEUMA-simulated waveforms representing normal, steady conditions in sleep. . 24
2.3 PNEUMA-simulated waveforms representing CSA. ........................... 25
2.4 The continuous tidal volume and arterial carbon dioxide tension waveforms. .... 31
2.5 $p_a$ and $v_T$. ........................................................................... 33
2.6 Sensitivity versus parameter rank, for $v_T$. ..................................... 36
2.7 Sensitivity versus parameter rank, for $p_a$. .................................... 37
2.8 Sensitivity versus parameter rank, for $T$. ....................................... 37
2.9 Baseline and perturbed $v_T$ waveforms for the six highest-ranked parameters. .. 39
2.10 Baseline and perturbed $p_a$ waveforms for the six highest-ranked parameters. .. 40

3.1 Block diagram of our new, simple model. ........................................ 44
3.2 Autoregulation of cerebral blood flow. ............................................ 57
3.3 Step response of Lange model. ...................................................... 65
3.4 Step responses of D1M and D0M models best fitting the D2M step response. ... 67
3.5 Responses of D2M, D1M, and D0M models to sinusoidal input. .............. 69
3.6 Responses of Padé-approximated transport models to sinusoidal input. .......... 71
3.7 Phase delay versus period, for adjusted and unadjusted Padé-approximated transport models. ................................................................. 73
3.8 Filtered $p_a,CO_2$ and $s_a,O_2$ waveforms from PNEUMA simulation of CSA. .... 79
3.9 \([p_a,CO_2 - P_a,CO_2,TH]^+ [S_a,O_2,TH - s_a,O_2]^+\), and \([p_a,CO_2 - P_a,CO_2,TH]^+ [S_a,O_2,TH - s_a,O_2]^+\) waveforms. .......................................................... 80

3.10 \(G_{PNEUMA,a}[p_a,CO_2 - P_a,CO_2,TH]^+ [S_a,O_2,TH - s_a,O_2]^+\) and \(G_a[p_a,CO_2 - P_a,CO_2,TH]^+\) waveforms. .......................................................... 80

3.11 Ventilation, tidal volume, and respiratory rate versus chemical drive, in PNEUMA. . 82

3.12 The subsystem made up of the gas exchange and transport model systems. .......... 91

3.13 Steady-state CSA simulation results from our model (black) and PNEUMA (red). . 94

3.14 Simulation results from our model when Padé-approximated transport models are used. 95

3.15 Simulation results from our model when linearized gas exchange models are used. . 96

4.1 Our large-signal linearized model. .......................................................... 103

4.2 Our small-signal linearized model. .......................................................... 103

4.3 The \(\chi_\Delta = 0\) hyperbola in the first quadrant of the \((G'_a, G'_b)\) plane. ........... 115

4.4 Stable and unstable regions in the \((G'_a, G'_b)\) plane. ................................. 116

4.5 Stability boundary, along with numerically-determined stability of points in the \((G'_a, G'_b)\) plane, using \(m = n = 1\). .......................................................... 117

4.6 Stability boundary using \(m = n = 1\), along with numerically-determined stability of points in the \((G'_a, G'_b)\) plane, using \(m = n = 2\) and \(m = n = 3\). ......................... 118

4.7 Stability of the nonlinear and linearized models. ........................................ 119
List of Tables

3.1 Parameter values for our pulmonary gas exchange plant ($P_A$) model. .................. 85
3.2 Parameter values for our lung-to-carotid transport plant ($P_a$) model. .................. 86
3.3 Parameter values for our cerebral gas exchange plant ($P_b$) model. ...................... 87
3.4 Parameter values for our chemoreflex controller model. .................................. 88
3.5 Parameter values for our ventilation plant model. ...................................... 89
3.6 Equilibrium operating points for our model. ................................................. 93
4.1 The Routh array. ............................................................................. 106
4.2 Four possible sign sequences for the second column of the Routh array. ............. 107
4.3 Characteristics of zeros implied by signs of Routh array elements. .................... 109
Chapter 1

Introduction

In this thesis, we develop and simulate a simple grey-box physiological model of central sleep apnea, following a review of existing models. We then develop a linear approximation of the behaviour of our model system in the vicinity of its equilibrium operating point, and describe the regimes in which this linear system is stable. Finally, we compare the predictions of our linear stability analysis to the behaviour of the original model.

We begin with an introduction to the pathophysiology of central sleep apnea.

1.1 Background

In a normal, healthy individual, respiration is under tight control, ensuring that oxygen \((O_2)\) is brought into the body at a rate that meets tissue demand, and carbon dioxide \((CO_2)\) is expelled at a rate matching that of \(CO_2\) production by the tissues. The dominant mechanism of control is the respiratory chemoreflex: chemosensors\(^1\) detect the levels of \(O_2\) and \(CO_2\) in the oxygenated blood leaving the lungs and direct adjustments in ventilation that tend to normalize blood gas levels. For instance, if the level of carbon dioxide in the blood is elevated (depressed), the chemoreflex directs an increase (decrease) in ventilation to return the blood \(CO_2\) level to some setpoint.

Ventilation determines the rate at which fresh air enters the alveoli (the gas exchange regions of the lungs). Oxygen and carbon dioxide are exchanged between the air in the alveoli and the blood in the pulmonary capillaries that perfuse them. Ventilation therefore directly influences the

\(^1\)We use the terms "chemosensor" and "chemoreceptor" interchangeably.
gas content of the pulmonary capillary blood leaving the alveoli. The chemosensors, however, are not situated in the lungs, so they do not measure the levels of gases in the alveolar air or the pulmonary end-capillary blood (with which the alveolar air is in equilibrium). Let $p_A$ denote the partial pressure$^2$ of carbon dioxide in the alveolar air and pulmonary end-capillary blood.

Once blood from the pulmonary capillaries merges in the pulmonary vein, it enters the heart, is pumped out into the aorta, and there encounters the first set of peripheral (arterial) chemosensors: the aortic chemosensors. Further downstream, the blood encounters the carotid chemosensors, which make up the second set of peripheral (arterial) chemosensors. Even further along, $\mathrm{CO}_2$ in the arterial blood influences the pH of cerebrospinal fluid, which is detected by the central chemoreceptors in the brainstem. Each cluster of chemosensors therefore detects a version of $p_A$ delayed by a length of time determined by its location and by the rate of blood flow. Furthermore, even correcting for delays, the time course of $p_A$ differs from the time course of $\mathrm{CO}_2$ tension at each set of chemoreceptors, since the blood in which the gas is transported undergoes mixing, and the central chemoreceptors do not directly measure the carbon dioxide content of the blood. Finally, the contribution of each set of chemoreceptors to the overall ventilatory drive exhibits its own characteristic gain and dynamics.

In some individuals, irregularities in the chemoreflex (such as prolonged transport delay and elevated chemoreflex gain) render the closed-loop system unstable, resulting in oscillations in ventilatory drive. If the oscillations are sufficiently severe, ventilation is sometimes excessive (hyperpnea), sometimes present but insufficient to remove carbon dioxide from the blood at an appropriate rate (hypopnea), and sometimes completely absent (apnea). Figure 1.1 shows ventilation patterns in computer-simulated cases of stable and unstable breathing. The closed-loop system is especially vulnerable during sleep, leading in extreme cases to central sleep apnea (CSA), a disorder whose sufferers experience frequent apneas in their sleep. These periods of zero ventilation are associated with a number of acute disruptions (such as arousals and cardiovascular shocks) and chronic health problems (such as chronic hypertension). One particularly regular form of unstable breathing caused by chemoreflex instability is Cheyne-Stokes respiration (CSR), which is especially prevalent in individuals suffering from congestive heart failure (CHF).

$^2$We use the terms “partial pressure” and “tension” interchangeably.
1.2 Literature Survey

A Simple Toy Model

Very simple models have been proposed that, when simulated, generate periodic ventilation patterns similar to those that are characteristic of CSR. The earliest of these is the model of Mackey and Glass, which consists of a single equation in which the rate of carbon dioxide buildup in the blood is determined by ventilation – the volume flow rate of air into (or out of) the lungs, averaged over each inspiration (expiration) [KS09]. To model the chemoreflex, ventilation is described as a sigmoidal function of the delayed alveolar carbon dioxide partial pressure. A stability analysis shows that sufficiently high chemoreflex gains and transport delays will lead to instability. With parameters thus selected, time domain simulations show oscillatory ventilation and carbon dioxide tension. While the model’s simplicity makes it accessible to analysis and intuitive understanding, it is rather removed from real physiology, and we would not expect it to be able to capture very many patterns relevant to treatment or diagnosis, nor would we expect it to reproduce real ventilation waveforms.
with any fidelity.

A Complex Model

Near the opposite end of the spectrum is the early and very complex model of Grodins et al. [GBB67]. It describes, amongst other things, the dynamics of oxygen, carbon dioxide, and nitrogen levels in the compartments representing the lungs, the brain, and the remaining body tissues. Air flows into and out of the lung compartment, and blood carries gases from the lungs to the brain and tissues, then back to the lungs. Ventilation is determined in response to both peripheral and central cues, and cardiac output is changed in response to changes in arterial gas levels. Cardiac output-dependent delays represent the time needed for blood to carry gases between pairs of compartments. The model equations are numerous and complex, and there are many state variables and parameters.

Intermediate-Complexity Models

The significantly more tame model of Khoo et al. [KKSS82] is still very faithful to the physiology of the controlled system. It too describes gas levels in the three compartments and provides models of the peripheral and central components of chemoreflex control. It accounts for mixing in the vasculature but treats the blood gas transport times as constant parameters. Much of the complexity of the Grodins model is absent.

Khoo et al. also linearized their model equations about an equilibrium state, then developed expressions for the loop gain of the linear system and produced Nyquist plots demonstrating the effects of changing conditions (e.g., wakefulness vs. sleep and changing altitude) on respiratory stability.

Keener and Sneyd present a simplified version of the Grodins and Khoo models [KS09]. It describes only carbon dioxide dynamics in the three compartments. Only the central chemoreflex component is modelled. Increasing the associated gain sufficiently can render the system unstable and capable of producing sustained oscillations.

In [BT00a] and [BT00b], Batzel and Tran found it reasonable to simplify the Khoo model by neglecting tissue compartment dynamics. They then carried out a very involved stability analysis of the simplified model system. One of their conclusions was that the system was less prone to instability with both the central and peripheral control branches intact than with just the peripheral
Francis et al. propose a simple small-signal model describing the dynamics of alveolar carbon dioxide tension [FWD+00]. This one-compartment model includes a transport delay and a single chemoreflex gain. The authors estimate the model's parameters more or less one at a time, through experimental procedures. Using the model, they propose a classification of individuals based on such characteristics as mean ventilation and carbon dioxide tension, chemoreflex delay, and chemoreflex gain; the classification is shown to accurately discriminate between awake periodic breathers and stable breathers.

In [NES+11], Nemati et al. characterize the transfer functions relating gas tensions and ventilation in the closed-loop system from measured spontaneous breathing patterns. However, their model is nearly a black box model; no low-level physiology is represented.

**A Large, Comprehensive Model**

The models discussed so far are essentially descriptions of gas exchange processes, blood gas transport processes, and ventilatory control. On the other hand, the most complex and comprehensive model we have come across, “PNEUMA”, described in [CIFK10], incorporates previously-proposed models (usually along with the associated parameter values) for respiratory muscle mechanics, gas flow through the upper airways, sympathetic and parasympathetic responses to cardiopulmonary stimuli, gas exchange, cardiovascular fluid mechanics, and sleep-wake regulation. When the values of its parameters are set appropriately, PNEUMA can model several pathological states (CSA, for instance).

**1.3 Contributions and Outline**

We begin, in Chapter 2, with an exploration of PNEUMA. We see how, under different parameter configurations, it may be used to simulate normal breathing and CSA. We then describe some drawbacks of using a model of such great complexity as a model of CSA. Not only does this complexity make it very difficult to intuitively or analytically explore, discern, and explain patterns and phenomena of interest in CSA, but it also presents a significant identifiability problem. There are so many parameters in the model that it is impossible to estimate all of them robustly from
any reasonable collection of patient-specific output data. In light of this issue, we determine the sensitivities of a pair of model waveforms to perturbations in parameter values. We find that in the vicinity of a parameter configuration that represents CSA conditions, the model's behaviour on intermediate timescales is insensitive to all but a few model parameters. This finding motivates us to develop a model that has few state variables and few parameters (and which therefore stands a chance of being identifiable from data collected from a single subject), yet is able to produce physiologically-accurate output waveforms and capture fundamental phenomena of interest in CSA. Such a model could then be used to discover or explain patterns (the stabilizing influence of certain interventions, for instance) and even allow therapies and interventions to be titrated according to individual patients' conditions. We continue to use PNEUMA to help us determine which subsystems should be included in a reduced model, to guide the development of its components, and to provide data that (in lieu of real clinical data) may be used to configure and test it.

We develop our new simple model in Chapter 3. Our model features three dynamic subsystems: one representing the effect of ventilation on blood gas content, another representing the transport of gas in the blood from the lungs to the peripheral chemosensors, and a third describing the dynamics of the cerebral carbon dioxide tension that is measured by the central chemosensors. We formulate our nonlinear dynamic models of the first and third subsystems (the alveolar and cerebral gas exchange plants) according to the conservation of mass, following models established in the literature. For each of these models, we develop a linearized version that approximates its behaviour in the vicinity of an equilibrium operating point. (These linear models are used in our later analysis of the local stability of the model system.) We construct a pure-delay model of gas transport, following a consideration of the relevant physiology, published models, and the results of PNEUMA simulations. We use Padé approximants to describe approximations to our pure-delay model, then explore the properties of these alternatives.

Drawing again from published results, physiological considerations, and PNEUMA experiments, we then construct a model of the chemoreflex controller. Given the carbon dioxide tensions measured by the chemosensors, it generates a ventilatory drive signal. The ventilation is then modelled as an affine function of the ventilatory drive. In our model, central and peripheral drive components add to produce the total ventilatory drive. Each component is proportional to the amount by which the associated measured CO₂ tension exceeds the corresponding apneic threshold. With justification,
we do not include blood oxygen levels explicitly in our model.

Using PNEUMA parameter values and simulation results in normal and CSA configurations, we estimate corresponding parameter values, including operating points, for our model. We then show that in simulation our model produces waveforms that for the most part exhibit good agreement with their PNEUMA analogues. We briefly explore the consequences of replacing nonlinear elements of our model with their linearized versions, and of using our Padé-based gas transport models instead of our pure delay model.

In Chapter 4, we construct a linear small-signal version of our model, using our linearized gas exchange plant models and our Padé-based blood gas transport models. We determine the linear system's characteristic polynomial, then apply the Routh-Hurwitz stability criterion to describe the conditions in which the system is stable and those in which it is unstable. Applying this result, we determine how the gains of the peripheral and central chemoreflex branches influence the stability of the linear system. We conclude by comparing our analytically-determined stability boundary both to stability boundaries obtained numerically using higher-order (improved) Padé approximants, and to the stability boundaries we deduce by simulating nonlinear versions of the model system. We find that using only a low-order Padé approximant, our linear analysis provides a rather good approximation of the stability boundary (in chemoreflex gain space) for our full nonlinear system.

Finally, in Chapter 5, we summarize the main points of this thesis and suggest directions for future work.
Chapter 2

PNEUMA

2.1 Introduction to PNEUMA

PNEUMA is a complex model of human cardiovascular and respiratory physiology, implemented in SIMULINK. It was developed to allow simulation of these interacting systems subject to clinical interventions, variable sleep-wake states, and pathological conditions. PNEUMA’s high-level sub-models describe:

1. the cardiovascular system, including the beating heart and the pulmonary and systemic vasculature;

2. the respiratory system, including the upper airways, respiratory mechanics, and gas exchange dynamics;

3. the sleep mechanism, governing the circadian rhythm and changes in sleep state; and

4. components of the central nervous (or neural) system that integrate afferent signals from the cardiovascular, respiratory, and sleep systems and generate efferent signals controlling the behaviour of the cardiovascular and respiratory systems.

In addition to these four domains, which model the physiology of the body in its natural environment, PNEUMA also features components that may be used to simulate the application of clinical interventions and maneuvers, such as mechanical ventilation, continuous positive airway pressure, and the Valsalva maneuver. These additional components lie beyond the scope of our study.
The sub-models are interconnected, as is clear from Figure 2.1, which shows part of PNEUMA’s top-level block diagram. For instance, blood flow, a key variable of the cardiovascular system model, contributes significantly to the dynamics of gas exchange (at both the lungs and other tissues) modelled in the respiratory block. In a blurring of boundaries, the respiratory system block also uses blood flow information to model the transport (convection and mixing) of carbon dioxide and oxygen in the blood, from the lungs to the chemosensors. As the respiratory system block determines the partial pressures of carbon dioxide and oxygen in the blood, it relays this information to the central neural block, mimicking the activities of the chemosensors and the signals they transmit via afferent nerve fibers. The central neural block integrates the sensory input it receives to generate control signals that are sent to the cardiovascular and respiratory blocks. The signals sent to the cardiovascular system represent the intensities of α-sympathetic, β-sympathetic, and parasympathetic outflows that direct changes in cardiac contractility, heart rate, arteriolar tone, and venous unstressed volumes. Efferent signals to the respiratory system include the pulsating ventilatory drive signal that causes the breathing muscles to rhythmically contract and relax, and hence the lungs to fill and empty. The sleep mechanism block (curiously) resides in the respiratory system block, and so is not visible in the figure. Its key output is an index indicating sleep-wake state. (As sleep takes over, this index rises from 0 to 1.) Its behaviour is driven by its internal circadian and ultradian rhythms and modulated by its input: an arousal index, which rises when ventilatory drive grows too large. This can happen in sleep apnea, when inadequate ventilation results in escalating blood carbon dioxide levels, leading the ventilatory controller in the central neural block to signal a rising demand for ventilation. The sleep-wake state index influences metabolism and the control of ventilation, vascular tone, heart rate, and contractility, amongst other things.
The model is hierarchical. With the exception of the most elemental blocks, each block encapsulates an underlying network of interconnected blocks that determines its overall behaviour. At the highest levels, blocks often represent models of physiological systems and components, and connections between blocks represent physiologically-meaningful state variables whose values are determined by one block and influence the behaviour of others. In only a few cases, interconnections correspond directly to nerve fibers, and the quantities transmitted through those interconnections correspond to nerve impulse rates. At lower levels, networks often simply represent basic implementations of mathematical models and individual blocks and elements have little clear physiological significance.

PNEUMA is largely an aggregate of implementations of subsystem models from the literature. The nominal values of many of the parameters in PNEUMA are set equal to the nominal values listed alongside the corresponding published model descriptions. Some of PNEUMA's structure, and a good number of parameter values, are set independently by PNEUMA’s developers.

### 2.2 Simulating Stable and Unstable Breathing in PNEUMA

PNEUMA’s default parameter values are intended to reflect normal physiology and normal environmental conditions in wakefulness. Obviously, the characteristic symptoms of CSA manifest
themselves in sleep, so it helps to consider how the simulation behaves when sleep is enabled and all other parameters are left at their default values. The generated waveforms should be roughly consistent with the time courses of physiological state variables in a normal individual exposed to a normal environment. Figure 2.2 shows the time courses of a few of PNEUMA’s variables, under these conditions, during sleep.

Figure 2.2: PNEUMA-simulated waveforms representing normal, steady conditions in sleep.

Now, with sleep enabled, [CIFK10] sets up its most extreme simulation of CSA as follows:

- Reduce $\text{Base}_E_{\text{max}}$ – the parameter representing the basal maximum end-systolic elastance of the left ventricle – by 90%, reflecting the severely diminished contractility of the left ventricle in a chronic heart failure sufferer. This results in severely diminished cardiac output. 

- Increase $T_p_{\text{delay Const}}$ – the parameter representing the effective lung-to-carotid transport volume$^1$ – by 50%, ostensibly to represent cardiomegaly, which is common among CHF

$^1$The amount of time it takes for a change in blood gas levels in the pulmonary capillaries to begin to influence
2.2. SIMULATING STABLE AND UNSTABLE BREATHING IN PNEUMA


- Increase $G_p$ – the parameter representing the peripheral chemoreflex gain – by 600%, reflecting the elevation in hypercapnic ventilatory response that seems to be necessary for CHF sufferers to develop CSA.

The reduction in cardiac output and the increase in effective lung-to-carotid volume together increase the time delay that separates a change in blood gas levels at the pulmonary capillaries from the detection of the resulting change in blood gas levels at the carotid chemosensor site. Figure 2.3 shows the waveforms that result (once sleep has taken over) from simulating under these conditions.

Figure 2.3: PNEUMA-simulated waveforms representing CSA.

Blood gas levels at the carotid bifurcation is taken equal to the effective lung-to-carotid transport volume divided by the instantaneous blood flow.
2.3 Issues with PNEUMA

PNEUMA is a very complex model with many parameters. The nominal values of many of these parameters have been drawn from published estimates that are interpreted as representing an “average” subject. The remainder have been set by PNEUMA’s developers, with the aim of generating behaviour in simulation that is “realistic” and “internally consistent”. They judge the model’s realism by comparing its responses under a variety of conditions to published empirical results that are taken to reflect “average” physiological behaviour in the population of interest. These comparisons are almost entirely qualitative and generally examine only fairly coarse features of waveforms corresponding to a limited set of the model’s state variables. The developers claim that a quantitative goodness-of-fit approach was not possible because no “single complete experimental dataset” is available for model validation.

In light of this, there are four principal issues with using PNEUMA as a model of CSA:

1. **Validation:** While its responses under the set of conditions studied may indeed look reasonable and the behaviours of its state variables may appear to be consistent with one another, PNEUMA has not been quantitatively validated against real data. It could hypothetically be the case that the developers’ choices of parameter values result in a poor quantitative fit to real data, whether patient-specific or population-averaged, at baseline or in pathological conditions. Even if the subsystem models were each assigned parameter values that produced an acceptable fit to data used in the respective studies that developed these models, the interconnection of such models may not yield an acceptable fit to new system-level data. It may be that, to obtain an acceptable fit, parameter values must be chosen outside the plausible ranges of the quantities they purportedly represent, or perhaps no choice of parameter values can give an acceptable fit. Such departures would indicate structural flaws in the model, such as missing or incorrectly-implemented components.

2. **Minimalism:** PNEUMA is in principle intended for the simulation of physiological behaviour under a wide variety of conditions. It may well be that much of its complexity is unnecessary for any specific purpose. For instance, the dynamics of very slow and very fast processes may not contribute to any of the phenomena of interest in CSA. The influence of fast dynamics (such as those associated with the beating heart and pulsatile blood flow) may be imperceptible in
2.3. ISSUES WITH PNEUMA

real data records, considering the influence of noise and the intermediate timescales associated with measured outputs (such as tidal volume or end-tidal carbon dioxide fraction). The influence of slow dynamics (those corresponding to circadian and ultradian rhythms, say) may be imperceptible over short recordings. It may be that a model that applies quasi-steady-state assumptions to fast-changing state variables and constancy assumptions to slow-changing variables would be perfectly adequate for explaining the phenomena that are of interest or manifest themselves in real data records. Some of PNEUMA’s components may only significantly influence outputs that are neither measured in data records nor of interest in our study of CSA. Finally, some components (some of the branches of the ventilatory controller, for instance) may simply appear to be inactive in CSA (and perhaps in other conditions as well), possibly because their contributions to the response are small or change little relative to components that dominate the large- or small-signal response in this regime. PNEUMA’s possibly-unnecessary complexity contributes significantly to the two items that follow.

3. Insight: By running simulations under a variety of conditions, patterns can be observed. For instance, the relative contributions of various parameters to system stability may be suggested. Because PNEUMA is so complex, each simulation takes a long time to run. Many simulations would need to be run to first propose and then confirm with some confidence any interesting patterns. No general conclusions may even be drawn in this manner, since parameter space cannot be explored exhaustively in simulation. Proposed patterns would need to be explained either analytically or intuitively, considering the model structure. However, the complexity of PNEUMA (many components, many interconnections, many nonlinearities, many parameters) renders analytical approaches and rigorous logical explanations all but impossible.

4. Identifiability: Consider some assignment of parameter values and the resulting “measured” output vector, obtained by concatenating the various measured outputs. Then there exists a region of parameter space for which the corresponding model output vector is very close (in a weighted sum of squares sense, say) to the measured output vector. If this region is just a fairly small neighbourhood in the parameter space, then there is hope of estimating the values of all parameters within some reasonable uncertainty. Otherwise, it is not possible to identify
the system in practice (using as a fitting cost function the same measure of output vector
closeness as before). It may be, however, that some subset of the parameters can be selected
such that the projection of the region mentioned before onto the corresponding restricted
parameter space is just a fairly small neighbourhood. This restricted set of parameters could
be estimated with some confidence. The remaining parameters do not contribute strongly
enough to the output for their values to be estimable in practice; these could be set at their
nominal values. Such non-identifiable parameters might, for example, be associated with the
sorts of fast, slow, inactive, or unmeasured dynamics discussed previously.

Of these four issues, we now focus on the last: PNEUMA's identifiability. Ideally, we would want to
answer the following questions for physiological data recorded as a single human subject experiences
episodes of CSA:

1. Is it possible to assign values to parameters in PNEUMA so that the resulting simulated
waveforms agree closely with their analogues in the real data record?

2. Can the parameter set be partitioned successfully into an identifiable subset and a non-
identifiable subset? The non-identifiable parameters would all be assigned predetermined
nominal or arbitrary values and we would only attempt to estimate the identifiable param-
eters to fit the model output to real data. A partition would be considered successful if

(a) demanding the best possible fit between simulated and real data restricted the iden-
tifiable parameters to a tight region of the corresponding parameter space, which the
implemented estimator would approach in reasonable time (i.e., the estimated param-
eters were in fact uniquely identifiable within acceptable uncertainty);

(b) the resulting identifiable parameter estimates would change little if the given real data
were perturbed slightly, say through measurement noise (i.e., the estimator was robust);

(c) simulated data generated using the estimated parameters would agree well with the given
data (i.e., if, despite fixing a subset of the parameters at nominal values, bias was low).

In the absence of real data, we resort to inspecting PNEUMA on its own. For if PNEUMA, with
its parameters set to produce output data exhibiting episodes of CSA, cannot be identified accept-
ably from noise-corrupted versions of its own output, then there is surely little hope of identifying
2.4 Preparing PNEUMA for Numerical Experiments

PNEUMA version 2.0 is a software package at whose heart lies the PNEUMA Simulink model. However, for user-friendliness, the model is not normally accessed directly. Instead, the user accesses the PNEUMA “control panel” and its children, which together form a graphical user interface (GUI) through which the user may adjust aspects of PNEUMA’s configuration (essentially, this provides access to some of PNEUMA’s parameters) and run simulations. This interface also provides access to displays of simulation progress and graphs of selected simulated waveforms.

While possibly acceptable for a rather limited exploration of the model, PNEUMA 2.0’s native form is not suitable for our purposes. To investigate the model’s identifiability as well as for other numerical explorations, we require the ability to automatically run a large number of simulations – one simulation for each desired assignment of values to parameters – and collect the results. To this end, the following steps were taken:

1. The graphical user interface was no longer used.

2. Parameter values, previously set and adjusted through a number of MATLAB scripts and GUI-linked functions that directly modified the properties of model blocks, are now all assigned their nominal values in a single script. The model uses the parameter values that are in place at the beginning of the simulation.

3. Simulations are now configured and run directly by the scripts that need them, not through the control panel.

4. Data-logging blocks have been added to the model, capturing the full simulated time courses of many signals of interest. (Some were being tracked less directly in the original implementation and were plotted as the simulation executed.) The data thus collected can be processed, stored, and analyzed by scripts.
2.5 Sensitivity Analysis

To shed some light on the issues raised in Section 2.3, we will now examine how much influence each of PNEUMA’s parameters has on the behaviour of the model system in the CSA regime. For our investigation, we probe this behaviour via two “output signals”:

1. **The continuous tidal volume waveform, \( v_T (t) \):**

   The *functional residual capacity (FRC)* is the volume of air that remains in the lungs at the end of each expiration during unforced breathing. Let \( \Delta v_L (t) \) denote the lung volume in excess of FRC. This excess volume increases from FRC during inspiration, reaches a maximum value – the *tidal volume* – at the end of inspiration, then decreases back to FRC as air leaves the lungs during expiration. At steady state in the CSA regime, we may construct a continuous periodic waveform, with period equal to the time between the beginnings of successive apneas, that fits the maxima of the \( \Delta v_L \) waveform and lies at zero during apneas. We call this waveform the continuous tidal volume waveform and denote it by \( v_T (t) \). It represents the periodic envelope of the steady-state \( \Delta v_L \) waveform, and at the end of each inspiration, it approximates the tidal volume for that breath.

2. **The arterial carbon dioxide tension, \( p_a (t) \):**

   At steady state in the CSA regime, the partial pressure of carbon dioxide in the blood at the peripheral chemosensor site is very well approximated by a smooth periodic waveform, \( p_a (t) \), having the same period as \( v_T (t) \). We will refer to the common period of oscillation of \( v_T (t) \) and \( p_a (t) \) as the *CSA period, T*.

Figure 2.4 shows \( v_T (t) \) and \( p_a (t) \) over a few CSA periods for our prototypical PNEUMA CSA simulation.
Recall that we are interested in those aspects of the model system’s behaviour that are associated with the key phenomena that manifest themselves in typical data records of CSA cases. We have therefore chosen to observe the system’s behaviour through quantities that exhibit neither high-frequency activity (associated with dynamics occurring on timescales shorter than the duration of one breath)\(^2\) nor very low-frequency activity (associated with phenomena that become apparent only over many cycles of CSA). Furthermore, note that we consider the model system’s behaviour in steady-state.

\subsection{2.5.1 Our Procedure}

Our goal is to determine how strongly each model parameter influences \(v_T\) and \(p_a\) at steady state in the CSA regime. We will do this by measuring how much these two waveforms change as a result of a small perturbation in each parameter.

\(^2\)For instance, we selected the tidal volume waveform rather than the lung volume waveform, and the arterial carbon dioxide tension rather than the alveolar tension.
We must therefore meaningfully quantify the difference between periodic waveforms that may have different periods. To this end, we now define finite-duration signals, \( \tilde{p}_a \) and \( \tilde{v}_T \), representing one period of \( p_a \) and \( v_T \), respectively. Let \( t_{\text{min}} \) denote the time at one of the minima of the \( p_a (t) \) waveform. We then extract a segment of the \( p_a (t) \) waveform spanning one CSA period, bounded by a pair of adjacent minima, and we transform its time axis so that this segment spans the normalized time interval \( [-\frac{1}{2}, \frac{1}{2}] \):

\[
\tilde{p}_a (\xi) = \begin{cases} 
  p_a (T (\xi + \frac{1}{2}) + t_{\text{min}}) & \text{for } -\frac{1}{2} \leq \xi < \frac{1}{2} \\
  0 & \text{elsewhere}
\end{cases}
\]

Similarly,

\[
\tilde{v}_T (\xi) = \begin{cases} 
  v_T (T (\xi + \frac{1}{2}) + t_{\text{min}}) & \text{for } -\frac{1}{2} \leq \xi < \frac{1}{2} \\
  0 & \text{elsewhere}
\end{cases}
\]

To compare \( p_a \) and \( v_T \) waveforms obtained under different parameter configurations, we may directly compare the corresponding \( \tilde{p}_a \) and \( \tilde{v}_T \) waveforms and CSA periods. Figure 2.5 shows the \( \tilde{p}_a \) and \( \tilde{v}_T \) waveforms corresponding to the \( p_a \) and \( v_T \) waveforms shown in Figure 2.4.
2.5. SENSITIVITY ANALYSIS

Figure 2.5: The \( \hat{\rho}_a \) and \( \hat{\nu}_T \) waveforms corresponding to the \( p_a \) and \( \nu_T \) waveforms shown in Figure 2.4.

We now describe the steps of our sensitivity analysis:

1. We first simulate the model system under our prototypical “baseline” CSA parameter values.

   From the resulting output waveforms, we determine \( T_0 = T, \ \hat{\nu}_{T,0}(\xi) = \hat{\nu}_T(\xi) \) and \( \hat{\rho}_{a,0}(\xi) = \hat{\rho}_a(\xi) \), which represent the steady-state behaviour of the model at baseline.

2. We compile a list of \( M \) model parameters of interest: \( \theta_1, \theta_2, \ldots, \theta_M \), whose baseline values are \( \theta_{1,0}, \theta_{2,0}, \ldots, \theta_{M,0} \), respectively.

3. For each parameter, \( \theta_k, \ k = 1, 2, \ldots, M \), in our list, we run a pair of simulations in which we perturb \( \theta_k \) first 5 % downward (−), then 5 % upward (+):

   \(-\) \quad We set \( \theta_k = 0.95\theta_{k,0} \) and leave all other parameters (including those not in our list) at their baseline values, then simulate the model system. From the resulting output waveforms, we determine \( T_k^- = T, \ \hat{\nu}_{T,k^-}(\xi) = \hat{\nu}_T(\xi) \) and \( \hat{\rho}_{a,k^-}(\xi) = \hat{\rho}_a(\xi) \).

   \(+\) \quad We set \( \theta_k = 1.05\theta_{k,0} \) and leave all other parameters (including those not in our list) at their baseline values, then simulate the model system. From the resulting output waveforms, we determine \( T_k^+ = T, \ \hat{\nu}_{T,k^+}(\xi) = \hat{\nu}_T(\xi) \) and \( \hat{\rho}_{a,k^+}(\xi) = \hat{\rho}_a(\xi) \).
4. To quantify the changes in the continuous tidal volume waveform resulting from the perturbations in $\theta_k$, we compute the RMS (root mean square) value of the difference between $\bar{v}_{T,k \pm} (\xi)$ and $\bar{v}_{T,0} (\xi)$, and divide it by the total swing in the baseline continuous tidal volume waveform to obtain the dimensionless quantity:

$$S_{v,k \pm} = \frac{\sqrt{\int_{-\frac{1}{2}}^{\frac{1}{2}} [\bar{v}_{T,k \pm} (\xi) - \bar{v}_{T,0} (\xi)]^2 d\xi}}{\max_{-\frac{1}{2} \leq \xi < \frac{1}{2}} \bar{v}_{T,0} (\xi) - \min_{-\frac{1}{2} \leq \xi < \frac{1}{2}} \bar{v}_{T,0} (\xi)}.$$

Similarly, we define

$$S_{p,k \pm} = \frac{\sqrt{\int_{-\frac{1}{2}}^{\frac{1}{2}} [\bar{p}_{a,k \pm} (\xi) - \bar{p}_{a,0} (\xi)]^2 d\xi}}{\max_{-\frac{1}{2} \leq \xi < \frac{1}{2}} \bar{p}_{a,0} (\xi) - \min_{-\frac{1}{2} \leq \xi < \frac{1}{2}} \bar{p}_{a,0} (\xi)}.$$

$S_{v,k -}$ and $S_{v,k +}$ provide measures of the magnitude of the sensitivity of the continuous tidal volume to $\theta_k$, while $S_{p,k -}$ and $S_{p,k +}$ provide measures of the magnitude of the sensitivity of the arterial carbon dioxide tension to $\theta_k$. Since these sensitivities quantify changes in the single-period-normalized waveforms $\bar{v}_{T,k \pm} (\xi)$ and $\bar{p}_{a,k \pm} (\xi)$ relative to baseline, we must consider the change in CSA period separately. We therefore introduce a third sensitivity measure:

$$S_{T,k \pm} = \frac{|T_{k \pm} - T_0|}{T_0}.$$

For each $k = 1, 2, \ldots, M$, we take the sensitivities $S_{v,k} = \max (S_{v,k -}, S_{v,k +})$, $S_{p,k} = \max (S_{p,k -}, S_{p,k +})$, and $S_{T,k} = \max (S_{T,k -}, S_{T,k +})$ to measure the influence $\theta_k$ exerts on the behaviour of model system components of interest, on the timescales of interest, in the regime of interest.

### 2.5.2 Some Additional Details

**Disabling the Sleep Mechanism**

To perform our sensitivity analysis, we found it necessary to modify PNEUMA beyond the alterations described in Section 2.4: we disabled the sleep mechanism. The sleep state variables were instead held constant at values consistent with sleep. We took this step for two reasons:
1. It significantly reduces the length of the transient period at the beginning of each simulation, allowing us to complete the necessary suite of simulations with a reasonable amount of computation time. If we leave the sleep mechanism in place with sleep enabled, unless we set the initial state of the system to represent a subject who is already very nearly asleep\(^3\), the process of sleep onset takes some considerable time, with the sleep state variables changing significantly before finally reaching values that represent a sleeping subject.

2. The intact sleep mechanism causes the sleep state variables to change during sleep. We would then be unable to clearly identify a "typical" cycle of CSA for each parameter configuration, and the slow-timescale processes involved lie outside the scope of our study.

**Excluded Parameters**

We start with a candidate pool of parameters, made up of all the named quantities that are initialized in preparation for a PNEUMA simulation. (We therefore miss any initial conditions, saturation limits, gains, and other model component properties whose values are hardcoded in the PNEUMA Simulink implementation.) We will not investigate sensitivity to changes in all these parameters. In particular, we exclude the following from further consideration:

- all quantities that do not appear in the PNEUMA model (a very small minority of these are parameters rendered inert by our removal of the sleep mechanism);
- parameters associated with interventions such as Valsalva maneuvers or applied airway pressure;
- one parameter that represented a physical constant;
- parameters that control properties of the simulator, or data logging;
- binary-valued parameters; and
- parameters whose baseline values are zero, since we perturb each parameter in proportion to its baseline value.\(^4\)

\(^3\)This does not appear to be a straightforward task.

\(^4\)We can recommend reasonable scales for some of these parameters, but for consistency, we do not include those results here.
In the end, we are left with $M = 264$ parameters, including those that specify initial conditions.

**Baseline Configuration**

The baseline parameter configuration we used differs somewhat from the prototypical CSA configuration discussed in Section 2.2: we reduced $\text{Base}_\text{Emaxlv}$ by 70% (instead of 90%), and we increased $Gp$ by 400% (instead of 600%). This milder configuration represents another of the cases mentioned in [CIFK10].

### 2.5.3 Results

We now present a summary of the results of our sensitivity study.

Having determined $S_{v,k,\pm}$ and $S_{v,k}$ for $k = 1, 2, \ldots, M$, we rank the parameters according to $S_{v,k}$. The parameter with the largest $S_{v,k}$ is assigned rank $R_{v,k} = 1$, the parameter with the second-largest $S_{v,k}$ is assigned rank $R_{v,k} = 2$, and so on. Similarly, we assign ranks $R_{p,k}$ according to the values of $S_{p,k}$, and $R_{T,k}$ according to $S_{T,k}$. Figure 2.6 plots the sensitivities $S_{v,k,\pm}$ and $S_{v,k}$ against the rank $R_{v,k}$ for each parameter $\theta_k$. Figures 2.7 and 2.8 show sensitivity-versus-rank plots for $\bar{p}_a$ and $T$, respectively.

Figure 2.6: Sensitivity versus parameter rank, for $\bar{v}_T$. 
2.5. SENSITIVITY ANALYSIS

Figure 2.7: Sensitivity versus parameter rank, for $\hat{p}_a$.

Figure 2.8: Sensitivity versus parameter rank, for $T$.

Witness that there are two parameters for which a 5% perturbation leads to quite a significant
change in $\dot{v}_T$. There are three parameters like this for $\dot{p}_a$. Notice also that there is a clear gap separating the eleven highest $S_{v,k}$ values from the rest, with no comparable gaps among these lower 253 $S_{v,k}$ values. We will refer to the corresponding set of eleven parameters as the $\dot{v}_T$-influential cluster. We see a similar gap separating the nine highest $S_{p,k}$ values and the lower 255, among which no comparable gaps appear. We will refer to the corresponding set of nine parameters as the $\dot{p}_a$-influential cluster. Note that the gaps in $S_{v,k}$ and $S_{p,k}$ appear at similar values of these roughly normalized sensitivities. It is less easy to identify a cluster of most influential parameters in Figure 2.8, but one reasonable possibility is the set of parameters with the six highest $S_{T,k}$ values.

The twenty-six data points we have identified correspond to sixteen distinct parameters. Unsurprisingly, some parameters appear in more than one of the three clusters we have identified. The following parameters appear in both the $\dot{v}_T$-influential cluster and the $\dot{p}_a$-influential cluster:

- all three gas level thresholds of the chemoreflex controller;

- the total blood volume;

- the effective lung-to-carotid volume; and

- one of the parameters that characterizes the (dissociation) mapping from oxygen and carbon dioxide partial pressures in the blood to blood oxygen concentration.

The sensitivities associated with the remaining parameters are very small indeed.

To better illustrate just how much or how little $\dot{v}_T$ and $\dot{p}_a$ change as a result of a 5% change in each of the highest-ranked parameters, we show in Figure 2.9 the $\dot{v}_{T,0}$, $\dot{v}_{T,k-}$, and $\dot{v}_{T,k+}$ waveforms for the parameters with the six highest $S_{v,k}$ values, and in Figure 2.10 the $\dot{p}_{a,0}$, $\dot{p}_{a,k-}$, and $\dot{p}_{a,k+}$ waveforms for the parameters with the six highest $S_{p,k}$ values.
2.5. SENSITIVITY ANALYSIS

Figure 2.9: Baseline and perturbed $\hat{\varphi}_T$ waveforms for the six highest-ranked parameters.
Figure 2.10: Baseline and perturbed $\bar{p}_a$ waveforms for the six highest-ranked parameters.

Note the peculiar and extreme results of downward perturbations for the parameters with $R_{v,k} = 1$, $R_{v,k} = 2$, and $R_{p,k} = 1$. The parameter corresponding to $R_{v,k} = R_{p,k} = 1$ is the peripheral (arterial) chemoreflex threshold for oxygen. By decreasing its value by 5 %, we moved the system out of the CSA regime and into the stable regime, where $v_T$ and $p_a$ do not oscillate appreciably. The parameter ranked second in terms of its influence on $\bar{v}_T$ represents the central chemoreflex threshold (for carbon dioxide). Once we decreased its value, breathing continued to be periodic, but apneas no longer appeared.

It is certainly possible that among the lower-ranked parameters, numerical factors can account for much of the difference observed between $\bar{v}_{T,0}$ and $\bar{v}_{T,k\pm}$ and between $\bar{p}_{a,0}$ and $\bar{p}_{a,k\pm}$. Performing longer simulations might allow us to generate more accurate $\bar{v}_T$ and $\bar{p}_a$ waveforms, and this may reduce the computed sensitivities. It is also important to note that PNEUMA includes few if any sources of non-numerical noise. Many of the output waveform changes we have observed would be
negligible compared to the noise present in real measurements or noisy simulated data.

2.5.4 Conclusions

In the vicinity of the parameter configuration we selected to represent CSA conditions, the tidal volume and arterial carbon dioxide tension waveforms appear to be insensitive to changes in the values of all but a few parameters. This lends support to the following hypotheses:

1. If, given only continuous tidal volume and arterial carbon dioxide tension waveforms collected in the CSA regime at steady state, we are able to successfully partition PNEUMA's parameters into an identifiable subset and a non-identifiable subset, the non-identifiable subset will be much larger than the identifiable subset.\textsuperscript{5}

2. It is possible to construct a small model (one with few parameters and state variables) that can, in simulation, approximately reproduce the steady-state tidal volume and arterial carbon dioxide tension waveforms generated by PNEUMA in the CSA regime.

(\textit{It seems reasonable to expect that the role played here by the continuous tidal volume and arterial carbon dioxide tension waveforms would be similarly well played by any small set of waveforms representing intermediate-frequency activity of physiological state variables.})

The remainder of this thesis is dedicated to the development and analysis of a small grey-box model of central sleep apnea.

\textsuperscript{5}We use the terminology of Section 2.3.
Chapter 3

A New, Simple Model

3.1 Overview

A block diagram representing our model is presented in Figure 3.1.

Unlike PNEUMA, we will not be modelling processes that occur on timescales shorter than one breath. For example, we do not model the rise and fall of lung volume over the course of each breath. We instead propose a model that provides a plausible picture of system behaviour down to a resolution of around two to four breaths. We shall refer to this as our “multibreath” timescale. Our model also does not include processes on timescales longer than a few minutes – processes associated with changing sleep state or metabolism, for instance. If the model parameters (non-signal quantities) are treated as constants, then the model is applicable at most over intervals of time during which the general physiological state of the subject is approximately constant. Of course, it should be possible to separately model system behaviour in a number of general states (different sleep or metabolic states, say), by setting the model parameters appropriately in each case. If the parameters are instead viewed as slowly-varying exogenous variables whose waveforms may be supplied to the model, then longer simulations may become meaningful.
3.1.1 Pulmonary Gas Exchange Plant, $P_A$

We model the pulmonary (or alveolar) gas exchange process as a single-input single-output (SISO) dynamic plant, $P_A^1$. The input to the plant is alveolar ventilation, denoted by $\phi_A$. It represents the rate at which fresh air is brought into the alveoli for gas exchange. The plant’s output is $p_A$, the partial pressure of carbon dioxide in the alveolar spaces and in the pulmonary end-capillary blood.

---

1. The "A" stands for "Alveolar".
(i.e., the blood leaving the alveoli). The behaviour of $P_A$ in our model is governed by

$$V_A \frac{dp_A}{dt} = P_{BS} Q [C_v - f_d (p_A)] + \phi_A (P_I - p_A),$$

where

- $V_A$ represents the time-averaged carbon dioxide storage volume of the alveoli;
- $P_{BS} = 863$ mmHg;
- $Q$ represents cardiac output;
- $C_v$ represents the concentration of carbon dioxide in mixed venous blood;
- $f_d (\cdot)$ is a function mapping the partial pressure of carbon dioxide in alveolar air to the concentration of carbon dioxide in the pulmonary end-capillary blood with which it is in equilibrium;
- $P_I$ represents the partial pressure of carbon dioxide in inspired air.

We obtain this model equation by applying a conservation of mass argument to the alveoli. Carbon dioxide is added by inspired air and by incoming high-CO$_2$ pulmonary arterial blood; it is removed by expired air and by outgoing pulmonary venous blood.

The pulmonary gas exchange plant model is described in detail in Section 3.3.1.

### 3.1.2 Lung-to-Carotid Transport Plant, $P_a$

A second plant, $P_a^2$, models the transport of carbon dioxide in the blood from the alveoli to the peripheral chemosensors. We take this plant’s output $- p_a$, the CO$_2$ partial pressure at the peripheral chemosensor site $- p_A$. Denoting the magnitude of the delay by $D_a$, we have:

$$p_a (t) = p_A (t - D_a)$$

The system function representing this plant is then

$$H_a (s) = e^{-D_a s}$$

$^2$The “a” stands for “arterial”. 
To facilitate analysis, we may consider using the Padé approximant

\[ H_{a,1/1}(s) = \frac{-\frac{1}{2}D_{a,1/1}s + 1}{\frac{1}{2}D_{a,1/1}s + 1}, \]

where \( D_{a,1/1} \) may be set equal to \( D_a \). A more accurate but higher-order Padé approximation is provided by

\[ H_{a,2/2}(s) = \frac{\frac{1}{12}D_{a,2/2}^2s^2 - \frac{1}{2}D_{a,2/2}s + 1}{\frac{1}{12}D_{a,2/2}^2s^2 + \frac{1}{2}D_{a,2/2}s + 1}, \]

where \( D_{a,2/2} \) may be set equal to \( D_a \).

We describe our model of \( \mathcal{P}_a \) in detail in Section 3.3.3.

### 3.1.3 Cerebral Gas Exchange Plant, \( \mathcal{P}_b \)

The plant \( \mathcal{P}_b \)\(^3\) represents gas exchange in the brain. The input here is \( p_a \), and the output is \( p_b \): the partial pressure of carbon dioxide in the brain tissue housing the central chemosensors. The variable \( p_b \) is the most "downstream" quantity whose dynamics we model. Our dynamical model for \( \mathcal{P}_b \) is:

\[ S_b \frac{dp_b}{dt} = M_b + q_bS(p_a - p_b) - H, \]

where:

- \( S_b \) and \( S \) represent the slopes of the dissociation (concentration versus partial pressure) curves for carbon dioxide in the brain tissue and arterial blood, respectively (the curves are approximated by straight lines over the partial pressure ranges of interest);
- \( q_b \) represents the flow rate of the blood feeding the brain tissue;
- \( M_b \) represents the rate of carbon dioxide production by metabolic processes in the brain;
- \( H \) is associated with the degree of separation between the carbon dioxide dissociation curves for oxygen-rich arterial blood and oxygen-poor cerebral venous blood.

We obtain this model equation by applying a conservation of mass argument to the brain tissue housing the chemosensors. Carbon dioxide is added by metabolism and by incoming low-CO\(_2\) arterial blood; it is removed by outgoing cerebral venous blood.

\(^3\)The "b" stands for "brain".
3.1. OVERVIEW

Cerebral blood flow has been observed to increase with $p_b$, as a consequence of cerebral autoregulation. We employ a straight-line approximation of this effect:

$$q_b = F_{q,b}p_b + Q_{b0},$$

where $F_{q,b}$ and $Q_{b0}$ are constants. Note that this results in the model being nonlinear.

Details of the cerebral gas exchange plant model are presented in Section 3.3.2.

3.1.4 Chemoreflex Controller

Our chemoreflex controller model accepts as inputs the “measured” carbon dioxide tensions at the peripheral and central chemosensor sites. Its output is chemical “drive”, $d$, a signal that reflects the perceived need to ventilate. The total drive is taken to consist of two additive components: the peripheral component, $d_a$ — which is a function of $p_a$ — and a central component, $d_b$ — a function of $p_b$. If $p_a$ is below the associated threshold, $P_{a,TH}$, the corresponding chemoreflex control branch contributes nothing to the drive signal: $d_a = 0$. Above the threshold, $d_a$ increases with $p_a$: $d_a = G_a(p_a - P_{a,TH})$, where $G_a$ denotes the peripheral chemoreflex gain. We model the central chemoreflex branch similarly.

Section 3.3.4 addresses the details and origins of our controller model.

3.1.5 Ventilation Plant

In our model, the chemical drive, $d$, determines alveolar ventilation, $\phi_A$, via a static “ventilation plant” model. Very weak drive signals do not produce any ventilation or are too shallow to bring any fresh air past the conducting airways and into the alveoli. Hence $\phi_A = 0$ until $d > D_{TH,A}$, after which alveolar ventilation increases with $d$: $\phi_A = K_{\phi,A}(d - D_{TH,A})$, where $K_{\phi,A}$ denotes the constant gain associated with the ventilation plant.

The details of our ventilation plant model are best described in conjunction with the chemoreflex controller (in Section 3.3.4).
CHAPTER 3. A NEW, SIMPLE MODEL

3.2 Model Properties

3.2.1 Requirements

We are interested in developing a model with the following properties:

- It includes grey-box descriptions of the physiological elements and processes fundamental to the pathophysiology of CSA.

- It is identifiable, given data (e.g., polysomnogram) records for a patient (or, say, the PNEUMAsimulated equivalent). That is, it must be possible to determine, within reasonable uncertainty bounds, physiologically-reasonable values for a large, known subset of the model parameters such that the resulting simulated waveforms agree well with the corresponding patient data. (Thus, the set of points in the restricted parameter space that produce acceptable fits to the data must be small.)

- It is simple, nearly minimal (not only to help identifiability, but also to provide a clear picture of the relevant physiology that is amenable to analysis).

- It explains the efficacy or inefficacy of basic clinical interventions commonly applied to CSA patients. (The identified model, complete with patient-specific parameter values, may then be used to personalize the patient’s therapy. General observations of the model, on the other hand, may suggest new interventions.)

3.2.2 Simplifications

Our model presents a very simplified representation of reality. In particular:

- The temporal resolution of the model is limited to our multibreath timescale.

- The dynamics and effects of blood oxygen levels are not explicitly represented.

- A number of quantities are represented in the model by constant parameters (or, really, exogenous variables), though they are in reality non-constant and may be influenced (even if not overwhelmingly) by certain model variables (e.g., blood carbon dioxide levels). Examples include cardiac output, venous carbon dioxide concentration, and the rate of metabolism in brain tissue.
• The chemoreflex controller and ventilation plant models represent a static map from sensed carbon dioxide levels to alveolar ventilation, and sharp thresholds present the only nonlinearities in this part of the model.

3.3 Model Details

3.3.1 Pulmonary Gas Exchange Model

We begin by developing a dynamical description of our pulmonary gas exchange plant model, \( P_A \).

Consider an expiration followed by an inspiration. Assume the following:

• The volume of air expelled during the expiration is equal to the volume of air drawn in during the inspiration. This is the *tidal volume*, \( V_T \).

• The carbon dioxide content of inspired air is constant; denote its partial pressure by \( P_l \).

• Air does not exchange gases with blood while in the conducting airways. This *anatomic dead space* has a fixed volume, \( V_D \). Air moves through the anatomic dead space only by bulk transport; there is no mixing.

• The tidal volume exceeds \( V_D \).

• The regions of the airways (including, of course, the respiratory zone) in which gas exchange does occur can be modelled as a single *superalveolus* whose air is of uniform composition (the chamber is well-mixed). Gases are exchanged so rapidly between the superalveolus and pulmonary capillaries that the partial pressure of carbon dioxide in the superalveolus – \( p_A \), the alveolar partial pressure of \( CO_2 \) – is always equal to that in the departing pulmonary capillary blood. Since we will not be modelling dynamics on shorter timescales, we represent by \( p_A \) the alveolar partial pressure of \( CO_2 \) viewed on our multibreath timescale.

We do not explicitly model:

• The *shunt* effect: the (normally very small) fraction of the total blood flow that passes from the venous system to the arterial system without traversing the walls of ventilated alveoli.
Any physiologic dead space that is not part of the anatomic dead space. (The former consists of all regions of the conducting, transitional, and respiratory airways whose contents do not exchange gases with blood. The latter includes only the conducting airways. The difference between the two is normally very small [Wes12].)

- Other alveolar ventilation or perfusion inhomogeneities.

So:

- During expiration, the superalveolus loses a volume $v_T$ of air whose carbon dioxide partial pressure is $p_A$.
  - The first $v_T - V_D$ that leaves the superalveolus passes through the dead space, then leaves the body.
  - The final $V_D$ to leave the superalveolus fills up the dead space.

- During inspiration, the superalveolus gains a volume $v_T$ of air.
  - The first $V_D$ that enters the superalveolus empties the dead space of all the “old” air that it contained at the beginning of the inspiration. This is just the last air that left the superalveolus during the previous expiration; its carbon dioxide partial pressure is $p_A$.
  - The final $v_T - V_D$ is inspired “new” air that traverses the dead space, then enters the superalveolus; its carbon dioxide partial pressure is $P_I$.

Therefore, from the beginning of the expiration to the end of the inspiration, the superalveolus loses a net volume $v_T - V_D$ of air at CO$_2$ partial pressure $p_A$ ("$p_A$ air") and gains the same volume of air at CO$_2$ partial pressure $P_I$ ("$P_I$ air").

Let $T_R$ denote the respiratory period: the amount of time that passes from the beginning of the expiration to the end of the inspiration. Then, over a number of identical respiratory cycles (expirations and inspirations), $\frac{v_T - V_D}{T_R}$ is the net (volume) flow rate, appropriate on our multibreath timescale, of $p_A$ air exiting and $P_I$ air entering the superalveolus. This quantity is the alveolar ventilation, and we denote it by $\phi_A$. 
This definition allows us to proceed without henceforth explicitly accounting for behaviour on sub-breath timescales. Thus, in what follows, all variables represent behaviour on our multibreath timescale.

Consider a control volume that encloses only the superalveolus and the pulmonary capillaries participating in gas exchange.

- The (volume) flow rate of blood into and out of the control volume is equal to the cardiac output, \( Q \), which is the volume of blood pumped by each side of the heart per unit time (on our multibreath timescale).

  - The blood entering the control volume is (mixed) venous blood whose carbon dioxide concentration (volume ratio of carbon dioxide to blood) we denote by \( C_v \). We take this quantity to be effectively constant on our multibreath timescale. Carbon dioxide therefore enters the control volume via blood flow at a volumetric rate \( QC_v \). Since gas volumes in blood are specified under “standard temperature and pressure, dry” (STPD) conditions, therefore the molar rate of entry of carbon dioxide into the control volume via blood flow is given by the ideal gas law to be \( \frac{P_{STPD}QC_v}{R_{STPD}} \). Here, \( P_{STPD} = 760 \text{ mmHg} \) and \( T_{STPD} = 273.15 \text{ K} \) define STPD, and \( R \) is the ideal gas constant.

  - The blood leaving the control volume has (as was previously explained) a carbon dioxide partial pressure (nearly) equal to the alveolar partial pressure of CO\(_2\): \( p_A \). Letting \( f_d(\cdot) \) represent the dissociation function for CO\(_2\) in end-capillary blood, the CO\(_2\) concentration of the blood leaving the control volume is \( f_d(p_A) \). Carbon dioxide therefore leaves the control volume via blood flow at a volumetric rate \( Qf_d(p_A) \). The corresponding molar rate is \( \frac{P_{STPD}Qf_d(p_A)}{R_{STPD}} \).

- Air carrying carbon dioxide at partial pressure \( P_l \) enters the superalveolus at volumetric flow rate \( \phi_A \), and air carrying carbon dioxide at partial pressure \( p_A \) leaves the superalveolus at the same rate. Gas volumes in inspired and alveolar air are specified under “body temperature and pressure, saturated” (BTPS) conditions, so \( \phi_A \) is specified at BTPS. Thus, the molar rates at which carbon dioxide is added to and removed from the control volume via air flow are given by the ideal gas law to be \( \frac{P_l\phi_A}{R_{BTPS}} \) and \( \frac{p_A\phi_A}{R_{BTPS}} \), respectively. Here, \( T_{BTPS} \) denotes
Since carbon dioxide is only added to or removed from the control volume by blood and air flows, the rate of change of the (molar) amount of carbon dioxide in the control volume is given by

\[ \frac{d n_{CV}}{dt} = \frac{P_{STPD} Q C_v}{RT_{STPD}} - \frac{P_{STPD} Q f_d(p_A)}{RT_{STPD}} + \frac{P_I \phi_A}{RT_{BTPS}} - \frac{p_A \phi_A}{RT_{BTPS}} \]

\[ = \frac{P_{STPD} Q}{RT_{STPD}} [C_v - f_d(p_A)] + \frac{\phi_A}{RT_{BTPS}} (P_I - p_A) \]  

(3.1)

Let \( v_A \) denote the effective BTPS carbon dioxide storage volume associated with the control volume. (That is, let \( v_A \) denote the volume of an imaginary container, filled entirely with dry ideal gases at body temperature, that would hold \( n_{CV} \) moles of carbon dioxide at partial pressure \( p_A \). This \( v_A \) is a little larger than the volume of the superalveolar space because the lung tissues and capillary blood also store CO\(_2\).) Hence

\[ n_{CV} = \frac{p_A v_A}{RT_{BTPS}} \Rightarrow \frac{d n_{CV}}{dt} = \frac{1}{RT_{BTPS}} \left( v_A \frac{dp_A}{dt} + p_A \frac{dv_A}{dt} \right) \]

If the superalveolar volume changes little enough or slowly enough on our multibreath timescale that \( \frac{1}{v_A} \frac{dv_A}{dt} \ll \frac{1}{p_A} \frac{dp_A}{dt} \), then approximately:

\[ \frac{d n_{CV}}{dt} = \frac{v_A}{RT_{BTPS}} \frac{dp_A}{dt} \]  

(3.2)

Now, (3.1) and (3.2) together give an ordinary differential equation (ODE) describing the dynamics of pulmonary gas exchange on our multibreath timescale:

\[ \frac{v_A}{RT_{BTPS}} \frac{dp_A}{dt} = \frac{P_{STPD} Q}{RT_{STPD}} [C_v - f_d(p_A)] + \frac{\phi_A}{RT_{BTPS}} (P_I - p_A) \]

\[ v_A \frac{dp_A}{dt} = P_{BS} Q [C_v - f_d(p_A)] + \phi_A (P_I - p_A) \]  

(3.3)

where we define \( P_{BS} = \frac{T_{BTPS}}{T_{STPD}} P_{STPD} \). With \( T_{STPD} = 273.15 \) K and \( P_{STPD} = 760 \) mmHg, taking \( T_{BTPS} = 310 \) K gives \( P_{BS} \approx 863 \) mmHg.
3.3. MODEL DETAILS

3.3.1.1 Linearization

We now consider the behaviour of $P_A$ in the vicinity of any given equilibrium operating point.

Define

$$g_1(p_A, \phi_A) = \frac{P_{BSQ} [C_v - f_d(p_A)] + \phi_A (P_I - p_A)}{v_A}$$

so that $\frac{dp_A}{dt} = g_1(p_A, \phi_A)$, by (3.3).

Suppose we are interested in the behaviour of $P_A$ in the vicinity of some operating point described by $(p_A, \phi_A) = (P_{A,OP}, \Phi_{A,OP})$ where $P_A$ is at equilibrium. That is:

$$g_1(P_{A,OP}, \Phi_{A,OP}) = 0 \Leftrightarrow \frac{P_{BSQ} [C_v - f_d(P_{A,OP})] + \Phi_{A,OP} (P_I - P_{A,OP})}{v_A} = 0$$

$$\Leftrightarrow \Phi_{A,OP} = \frac{P_{BSQ} [C_v - f_d(P_{A,OP})]}{P_{A,OP} - P_I}$$

(\(v_A\) is always positive.)

Witness:

$$\frac{\partial g_1}{\partial p_A} (P_{A,OP}, \Phi_{A,OP}) \bigg|_{P_{A,OP}} = \frac{P_{BSQ} F_{d,OP} + \Phi_{A,OP}}{v_A}$$

$$\frac{\partial g_1}{\partial \phi_A} (P_{A,OP}, \Phi_{A,OP}) \bigg|_{P_{A,OP}} = \frac{P_I - P_{A,OP}}{v_A}$$

where $F_{d,OP} = \frac{\partial f_d}{\partial p_A} \bigg|_{P_{A,OP}}$. Both partial derivatives are finite. So $g_1$ may be approximated by its linearization about $(P_{A,OP}, \Phi_{A,OP})$ for sufficiently small excursions $\tilde{p}_A = p_A - P_{A,OP}$ and $\tilde{\phi}_A = \phi_A - \Phi_{A,OP}$:

$$g_1(p_A, \phi_A) \approx g_1(P_{A,OP}, \Phi_{A,OP}) + \frac{\partial g_1}{\partial p_A} (P_{A,OP}, \Phi_{A,OP}) \tilde{p}_A + \frac{\partial g_1}{\partial \phi_A} (P_{A,OP}, \Phi_{A,OP}) \tilde{\phi}_A$$

$$= 0 - \frac{P_{BSQ} F_{d,OP} + \Phi_{A,OP}}{v_A} \tilde{p}_A + \frac{P_I - P_{A,OP}}{v_A} \tilde{\phi}_A$$

$$= -\frac{(P_{BSQ} F_{d,OP} + \Phi_{A,OP}) \tilde{p}_A + (P_{A,OP} - P_I) \tilde{\phi}_A}{v_A}$$
Since \( \frac{d\hat{p}_A}{dt} = \frac{d}{dt} (p_A - P_{A,OP}) = \frac{d\phi_A}{dt} = g_1(p_A, \phi_A), \)

\[
\frac{d\hat{p}_A}{dt} \approx - \frac{(P_{BSQF_d,OP} + \Phi_{A,OP}) \hat{p}_A + (P_{A,OP} - P_I) \hat{\phi}_A}{v_A}
\]  

(3.5)

This is the linearized description of \( P_A \). Let \( \hat{P}_A \) and \( \hat{\phi}_A \) denote the bilateral Laplace transforms of \( \hat{p}_A \) and \( \hat{\phi}_A \), respectively. Taking Laplace transforms in (3.5) gives:

\[
\hat{P}_A \left[ s + \frac{P_{BSQF_d,OP} + \Phi_{A,OP}}{v_A} \right] \approx - \frac{P_{A,OP} - P_I}{v_A} \hat{\phi}_A
\]

\[
\hat{P}_A \approx \frac{P_{A,OP} - P_I}{P_{BSQF_d,OP} + \Phi_{A,OP}} \frac{v_A}{s + 1}
\]

(3.6)

Thus, the transfer function describing the linearized pulmonary gas exchange plant model is

\[
H_A(s) = -\frac{K_A}{\tau_A s + 1},
\]

(3.7)

where

\[
K_A = \frac{P_{A,OP} - P_I}{P_{BSQF_d,OP} + \Phi_{A,OP}}
\]

(3.8)

\[
\tau_A = \frac{v_A}{P_{BSQF_d,OP} + \Phi_{A,OP}}
\]

(3.9)

Note that \( K_A > 0 \) (provided \( P_{A,OP} > P_I \)) and \( \tau_A > 0 \).

Clearly, (3.5) may be rewritten in terms of \( K_A \) and \( \tau_A \):

\[
\frac{d\hat{p}_A}{dt} \approx - \frac{1}{\tau_A} \hat{P}_A - \frac{K_A}{\tau_A} \hat{\phi}_A
\]

(3.10)

Hence a suitable state-space representation of the linearized model of \( P_A \) with input \( u = \hat{\phi}_A \) and...
output \( y = \tilde{p}_A \) has state variable \( x = \tilde{p}_A \) and governing equations:

\[
\frac{dx}{dt} = -\frac{1}{\tau_A} x - \frac{K_A}{\tau_A} u
\]  

(3.11)

\[ y = x \]  

(3.12)

\[ x(0) = \tilde{p}_A(0) \]  

(3.13)

### 3.3.2 Cerebral Gas Exchange Model

Our cerebral gas exchange plant model, \( P_b \), is identical to the analogous model implemented in PNEUMA.

At its core is a basic model proposed in [RL67]. Referring to the superficial medullar brain tissue housing the central chemoreceptors as “receptor tissue”, we let:

- \( c_b \) denote the carbon dioxide concentration of the receptor tissue – more precisely, the volumetric carbon dioxide content of the receptor tissue per unit mass of tissue;

- \( c_a \) and \( c_v \) denote the carbon dioxide concentrations of, respectively, the receptor arterial blood supplying and the receptor venous blood leaving the receptor tissue – more precisely, the volumetric carbon dioxide content of the blood per unit volume of blood;

- \( p_b, p_a, \) and \( p_v \) denote the partial pressures of carbon dioxide in the receptor tissue, receptor arterial blood, and receptor venous blood, respectively;

- \( \dot{M}_b \) denote the metabolic rate of carbon dioxide production – the volume of CO\(_2\) evolved per unit time per unit mass of tissue – in the receptor tissue;

- the carbon dioxide dissociation relations in the receptor tissue, receptor arterial blood, and receptor venous blood be approximated in the regimes of interest by \( c_b = S_b p_b + R_b \), \( c_a = S_a p_a + R_a \), and \( c_v = S_v p_v + R_v \), respectively;

- \( q_b \) denote the receptor arterial and venous blood flow;

- \( m_b \) denote the receptor tissue mass.

The rate of change of the volume of carbon dioxide in the receptor tissue is then \( \frac{d}{dt}(m_b c_b) \). Metabolism adds to this volume at a rate \( m_b \dot{M}_b \), arterial blood flow adds CO\(_2\) at a rate \( q_b m_b c_a \),
and venous blood removes CO₂ at a rate \( q_b m_b c_v \). Ergo:

\[
\frac{d}{dt} (m_b c_b) = m_b M_b + q_b m_b c_a - q_b m_b c_v \\
\frac{d c_b}{dt} = M_b + q_b (c_a - c_v) \\
S_b \frac{dp_b}{dt} = M_b + q_b \left[ (S_a p_a + R_a) - (S_v p_v + R_v) \right] \\
S_b \frac{dp_b}{dt} = M_b + q_b \left[ (S_a p_a - S_v p_v) + (R_a - R_v) \right]
\]

Now, the receptor venous blood is assumed to leave the receptor tissue having fully equilibrated with it – that is, \( p_v = p_b \). Furthermore, the difference between the arterial and venous dissociation curves is taken to be primarily the result of the Haldane effect: the CO₂ dissociation curve shifts to the left as oxygen saturation falls. [RL67] approximates the result in the regime of interest through a pure shift of size inversely proportional to receptor blood flow. Hence, \( S_v = S_a \) – henceforth denoted simply by \( S \) – and \( R_v = R_a + \frac{H}{q_b} \), with \( H \) the constant of (inverse) proportionality having dimensions of carbon dioxide volume per unit time per unit receptor tissue mass. Therefore:

\[
S_b \frac{dp_b}{dt} = M_b + q_b \left[ (S_a p_a - S_p_b) + \left( -\frac{H}{q_b} \right) \right] \\
\frac{dp_b}{dt} = \frac{M_b + q_b S (p_a - p_b) - H}{S_b}
\] (3.14)

**Autoregulation of Cerebral Blood Flow**

[RL67] also models the increase in receptor blood flow effected in response to an elevation in the local carbon dioxide level. (The stimulus is taken, with some justification, to be tissue or venous carbon dioxide, not arterial carbon dioxide.) PNEUMA includes this effect, but using the formulation provided in [Kho90]. In this latter model, \( q_b \) is related to \( p_b \) via

\[
q_b^2 - \left( 1 + 0.03 (p_b - 40) \right) Q'_{d0} q_b + \frac{0.03 (M'_{d0} - H) Q'_{d0}}{S} = 0
\] (3.15)

where \( Q'_{d0} \) is a constant parameter, and \( M'_{d0} \) represents the value of \( M_d \) in wakefulness. For any given value of \( p_b \), the corresponding \( q_b \) is the larger of the two roots of the equation. Figure 3.2 shows the
3.3. MODEL DETAILS

$q_b$-$p_b$ relationship for $42 \text{ mmHg} \leq p_b \leq 60 \text{ mmHg}$.

Figure 3.2: The dependence of cerebral blood flow (in units of litres of blood per second per kilogram of brain tissue) upon cerebral carbon dioxide tension (in mmHg), as published in [Kho90] and used in PNEUMA.

Now, in our PNEUMA CSA simulation, $p_b$ oscillates between 47.3 mmHg and 48.1 mmHg. (Without the parameter adjustments that were made to destabilize breathing, $p_b$ would remain nearly steady at 51.1 mmHg. The corresponding figure in wakefulness is 48.5 mmHg.) It seems that for a (PNEUMA-simulated) subject in a given constant general physiological state, $p_b$ varies sufficiently little that we may take $q_b$ to vary almost exactly linearly with $p_b$. Indeed, the $q_b$-$p_b$ characteristic used in [Kho90] and PNEUMA exhibits so little curvature that we can safely approximate it by a single straight line for the range of $p_b$ values in which we are interested:

$$q_b = F_{q,b}p_b + Q_{b0}$$

where $F_{q,b}$ and $Q_{b0}$ are constants. [RL67] also proposes a straight-line relationship.

Linearization

We now consider the behaviour of the cerebral gas exchange plant ($P_b$) in the vicinity of any given equilibrium operating point.

From (3.14), we have $\frac{dp_b}{dt} = g_2 (p_b, p_a)$, where

$$g_2 (p_b, p_a) = \frac{M_b + q_b S (p_a - p_b) - H}{S_b}$$

Note that [Kho90] does not give a domain of validity for the relationship, but with the parameter values given, (3.15) has no real roots for $0 \leq p_b < 41.92 \text{ mmHg}$. 

---

\[\text{Note that [Kho90] does not give a domain of validity for the relationship, but with the parameter values given, (3.15) has no real roots for } 0 \leq p_b < 41.92 \text{ mmHg}.\]
and \(q_b\) is understood to be related to \(p_b\) via (3.15).

Suppose we are interested in the behaviour of \(P_b\) in the vicinity of some operating point described by \((p_b, p_a) = (P_{b,OP}, P_{a,OP})\) where \(P_b\) is at equilibrium. That is:

\[
g_2 (P_{b,OP}, P_{a,OP}) = 0 \Leftrightarrow \frac{M_b + Q_{b,OP} S (P_{a,OP} - P_{b,OP}) - H}{S_b} = 0
\]

\[
\Leftrightarrow P_{a,OP} = P_{b,OP} + \frac{H - M_b}{Q_{b,OP} S}
\]

(3.16)

where \(Q_{b,OP} = F_{q,b} P_{b,OP} + Q_{b0}\) is the value \(q_b\) takes when \(p_b = P_{b,OP}\).

Now,

\[
\left. \frac{\partial g_2}{\partial p_b} \right|_{(P_{b,OP}, P_{a,OP})} = \frac{S}{S_b} \left[ \left. \frac{d q_b}{d p_b} \right|_{P_{b,OP}} (P_{a,OP} - P_{b,OP}) - Q_{b,OP} \right]
\]

\[
= \frac{S}{S_b} [F_{q,b} (P_{a,OP} - P_{b,OP}) - (F_{q,b} P_{b,OP} + Q_{b0})]
\]

\[
= \frac{S}{S_b} [F_{q,b} (P_{a,OP} - 2P_{b,OP}) - Q_{b0}]
\]

(3.17)

\[
\left. \frac{\partial g_2}{\partial p_a} \right|_{(P_{b,OP}, P_{a,OP})} = \frac{S Q_{b,OP}}{S_b}
\]

\[
= \frac{S}{S_b} (F_{q,b} P_{b,OP} + Q_{b0})
\]

(3.18)

These partial derivatives are finite, so \(g_2\) may be approximated by its linearization about \((P_{b,OP}, P_{a,OP})\) for sufficiently small excursions \(\tilde{p}_b = p_b - P_{b,OP}\) and \(\tilde{p}_a = p_a - P_{a,OP}\):

\[
g_2 (p_b, p_a) \approx g_2 (P_{b,OP}, P_{a,OP}) + \left. \frac{\partial g_2}{\partial p_b} \right|_{(P_{b,OP}, P_{a,OP})} \tilde{p}_b + \left. \frac{\partial g_2}{\partial p_a} \right|_{(P_{b,OP}, P_{a,OP})} \tilde{p}_a
\]

\[
= 0 + \frac{S}{S_b} [F_{q,b} (P_{a,OP} - 2P_{b,OP}) - Q_{b0}] \tilde{p}_b + \frac{S}{S_b} (F_{q,b} P_{b,OP} + Q_{b0}) \tilde{p}_a
\]

\[
= \frac{S}{S_b} [F_{q,b} (P_{a,OP} - 2P_{b,OP}) - Q_{b0}] \tilde{p}_b + \frac{S}{S_b} (F_{q,b} P_{b,OP} + Q_{b0}) \tilde{p}_a
\]

(3.19)

Since \(\frac{d \tilde{p}_b}{dt} = \frac{d}{dt} (p_b - P_{b,OP}) = \frac{dp_b}{dt} = g_2 (p_b, p_a)\), therefore:

\[
\frac{d \tilde{p}_b}{dt} \approx \frac{S}{S_b} [F_{q,b} (P_{a,OP} - 2P_{b,OP}) - Q_{b0}] \tilde{p}_b + \frac{S}{S_b} (F_{q,b} P_{b,OP} + Q_{b0}) \tilde{p}_a
\]

(3.19)

This is the linearized description of \(P_b\). Let \(\tilde{P}_b\) and \(\tilde{P}_a\) denote the bilateral Laplace transforms of
3.3. MODEL DETAILS

\( \tilde{p}_b \) and \( \tilde{p}_a \), respectively. Taking Laplace transforms in (3.19) gives:

\[
\begin{align*}
\tilde{\mathcal{S}} \tilde{P}_b &= \frac{S}{S_b} [F_{q,b}(P_{a,OP} - 2P_{b,OP}) - Q_{b0}] \tilde{P}_b + \frac{S}{S_b} (F_{q,b}P_{b,OP} + Q_{b0}) \tilde{P}_a \\
\frac{\tilde{P}_b}{\tilde{P}_a} &= \frac{\frac{S}{S_b} (F_{q,b}P_{b,OP} + Q_{b0})}{s + \frac{S}{S_b} [F_{q,b}(2P_{b,OP} - P_{a,OP}) + Q_{b0}]} \\
&= \frac{F_{q,b}P_{b,OP} + Q_{b0}}{F_{q,b}(2P_{b,OP} - P_{a,OP}) + Q_{b0}} \frac{S}{S} \left[ F_{q,b}(2P_{b,OP} - P_{a,OP}) + Q_{b0} \right] s + 1
\end{align*}
\]

Thus, the transfer function describing the linearized cerebral gas exchange plant model is

\[
H_b(s) = \frac{K_b}{\tau_b s + 1},
\]

where

\[
K_b = \frac{F_{q,b}P_{b,OP} + Q_{b0}}{F_{q,b}(2P_{b,OP} - P_{a,OP}) + Q_{b0}}
\]

\[
\tau_b = \frac{S_b}{S} \left[ F_{q,b}(2P_{b,OP} - P_{a,OP}) + Q_{b0} \right]
\]

Clearly, (3.19) may be rewritten in terms of \( K_b \) and \( \tau_b \):

\[
\frac{d\tilde{p}_b}{dt} \approx -\frac{1}{\tau_b} \tilde{p}_b + \frac{K_b}{\tau_b} \tilde{p}_a
\]

Hence a suitable state-space representation of the linearized model of \( P_b \) with input \( u = \tilde{p}_a \) and output \( y = \tilde{p}_b \) has state variable \( x = \tilde{p}_b \) and governing equations:

\[
\begin{align*}
\frac{dx}{dt} &= -\frac{1}{\tau_b} x + \frac{K_b}{\tau_b} u \\
y &= x \\
x(0) &= \tilde{p}_b(0)
\end{align*}
\]

**Linearization Assuming Constant \( q_b \)**

Had we instead assumed that \( q_b \) maintains some constant value, \( Q_b \), independent of changes in \( p_b \), we would have obtained in place of (3.16) the equilibrium condition
\[ P_{a,OP} = P_{b,OP} + \frac{H - M_b}{Q_b S}, \]  

in place of (3.17) and (3.18) the partial derivatives

\[ \left. \frac{\partial g_2}{\partial p_b} \right|_{(P_{b,OP}, P_{a,OP})} = -\frac{SQ_b}{S_b} \]  
\[ \left. \frac{\partial g_2}{\partial p_a} \right|_{(P_{b,OP}, P_{a,OP})} = \frac{SQ_b}{S_b}, \]

and in place of (3.19) the linearized model ODE

\[ \frac{d\tilde{p}_b}{dt} = g_2(p_b, p_a) \approx g_2(P_{b,OP}, P_{a,OP}) + \left. \frac{\partial g_2}{\partial p_b} \right|_{(P_{b,OP}, P_{a,OP})} \tilde{p}_b + \left. \frac{\partial g_2}{\partial p_a} \right|_{(P_{b,OP}, P_{a,OP})} \tilde{p}_a \]

\[ = \frac{SQ_b}{S_b} (-\tilde{p}_b + \tilde{p}_a), \]

which gives in place of (3.20) the transfer function

\[ s\tilde{P}_b = \frac{SQ_b}{S_b} (-\tilde{P}_b + \tilde{P}_a) \]

\[ \tilde{P}_b \left( s + \frac{SQ_b}{S_b} \right) = \frac{SQ_b}{S_b} \tilde{P}_a \]

\[ \frac{\tilde{P}_b}{\tilde{P}_a} = \frac{1}{\frac{S_b}{SQ_b} s + 1} \]

This is again of the form (3.21) (and (3.24)-(3.27) still apply), but now

\[ K_b = 1 \]  
\[ \tau_b = \frac{S_b}{SQ_b} \]
3.3. MODEL DETAILS

3.3.3 Lung-to-Carotid Transport Model

We assumed in Section 3.3.1 that blood in the pulmonary capillaries, having fully equilibrated with alveolar air, leaves the alveoli bearing carbon dioxide at partial pressure $p_A$. Blood from all the pulmonary capillaries converges to flow through the pulmonary vein into the left atrium of the heart, then into the left ventricle, whence it is pumped into the aorta. The two common carotid arteries branch off the aorta, conducting a portion of the blood flow toward the head. At the level of the neck, each of the carotid arteries divides into an external branch and an internal branch. The latter supplies the brain. Blood perfuses the carotid body, which houses the peripheral chemosensors, at the point of the bifurcation. Let $p_a$ denote the partial pressure of carbon dioxide in the (arterial) blood perfusing the carotid body.

Pure Transport Delay

A change in alveolar carbon dioxide level will obviously not be detected immediately by the peripheral chemosensors. There is always a significant delay between a change in $p_A$ and the arrival at the carotid bifurcation of any of the blood that had been subjected to this change while in the pulmonary capillaries.

Mixing in the Heart

In each contraction, the left ventricle only pumps out a fraction – the left ventricular ejection fraction, $r_{lv}$ – of the blood it contains. Between ventricular contractions, blood from the pulmonary vein is added to the ventricle via the left atrium. Denote the CO₂ concentration of the blood remaining in the left ventricle at the end of the $k$th ventricular contraction by $c_{lv}[k]$, and suppose that the blood added to it prior to the beginning of the $(k+1)$th contraction has carbon dioxide concentration $c_{pv}$. If we suppose that ventricular filling and contraction mix left-over and freshly-added blood together perfectly, then both the blood pumped out by the left heart in the $(k+1)$th contraction and the blood remaining in the ventricle just after that contraction will have CO₂ concentration $c_{lv}[k+1] = (1 - r_{lv})c_{lv}[k] + r_{lv}c_{pv}$, intermediate between $c_{lv}[k]$ and $c_{pv}$. So $c_{lv}[k+1] - c_{lv}[k] = -r_{lv}(c_{lv}[k] - c_{pv})$. On our slow multibreath timescale, we see $c_{lv}$ changing at
the rate

\[ \frac{dc_{lv}}{dt} = -\frac{r_{lv}(c_{lv} - c_{pv})}{T_H}, \]  

(3.35)

where \( T_H \) denotes the duration of each cardiac cycle (this is just the reciprocal of the heart rate). Suppose that in the regime we consider, the \( \text{CO}_2 \) concentration and partial pressure of blood between the pulmonary vein and aorta can be fairly approximated by a straight-line dissociation characteristic, \( c = Sp + R \). Then (3.35) simply implies

\[ \frac{dp_{lv}}{dt} = -\frac{r_{lv}}{T_H} (p_{lv} - p_{pv}) \]  

(3.36)

The corresponding transfer function from \( p_{pv} \) to \( p_{lv} \) is thus

\[ \frac{1}{\frac{T_u}{r_{lv}} s + 1} \]  

(3.37)

Since the left heart pumps out in each contraction only some of blood with which it has filled, and since left-over and freshly-added blood mix in the left heart, the \( \text{CO}_2 \) partial pressure waveform that leaves the heart is a smeared (and very slightly delayed) version of the waveform that enters it. This smearing may be approximated by the action of a first-order system with unity gain and time constant equal to the reciprocal of the product of the left ventricular ejection fraction and the heart rate.

Mixing in the Vasculature

Consider two cross-sections of a blood vessel. Blood that passes through the upstream cross-section at any given time will almost certainly not arrive all at once at the downstream cross-section. This is because the velocity profile across any cross-section of the vessel is non-uniform (and under turbulent conditions, chaotic), an effect intensified by the pulsatile nature of arterial blood flow and the elasticity of arterial walls. The result is progressive blurring of the \( \text{CO}_2 \) partial pressure waveform as we look downstream along a blood vessel. Further mixing of old and new blood, adding to this blurring, is caused by especially turbulent flow through and near heart valves and branch points in the vasculature. The overall effect is similar to that of mixing of older and newer blood in the heart as described in the preceding subsection.
3.3. MODEL DETAILS

Overall Effect

To model the dynamic relationship between alveolar gas partial pressures and gas tensions in arterial blood at the carotid bifurcation, PNEUMA’s developers closely followed the model presented in [LHB+66]. There, Lange et al. propose a transfer function of the following form:

\[ H_{a,D2M}(s) = \frac{e^{-sD_{a,D2M}}}{(\tau_{a,D2M,1}s + 1)(\tau_{a,D2M,2}s + 1)} \]  

(3.38)

This represents the action of a pure transport delay \( D_{a,D2M} \) and two first-order systems with unity gain and time constants \( \tau_{a,D2M,1} \) and \( \tau_{a,D2M,2} \), all placed in series. (“D2M” stands for “Delay and 2 Mixers.”) Essentially, the pure delay and first-order systems correspond, respectively, to the pure transport delay and mixing effects we discussed in the preceding three subsections. ([KKSS82] claims that one time constant is associated with mixing in the heart, and the other with mixing in the vasculature.)

In PNEUMA, \( D_{a,D2M} \) is replaced by a variable delay that is inversely proportional to instantaneous systemic blood flow; the constant of proportionality is interpreted as the “effective” lung-to-carotid volume. (Really, the transport time would be influenced by the flow rate throughout the journey, not just at one end.) The two mixing elements are also implemented, with the nominal values of the time constants \( \tau_{a,D2M,1} \) and \( \tau_{a,D2M,2} \) – drawn directly from [LHB+66]. (The particular subset of experiments in [LHB+66] that produced these estimates actually examined the effect of transport from the pulmonary artery to the femoral artery on the concentration waveform of an injected dye.) They are both implemented as constant parameters, though our earlier discussion suggests that at least one time “constant” does depend upon time-varying system state variables.

Imagine that \( P_a \) (the lung-to-carotid transport plant) is stable, governed by some system function \( H_a(s) \), and that it is operating in an open-loop configuration with input \( p_A \) and output \( p_a \). Suppose that \( p_A(t) = P_{A0} + \Delta P_A u(t - t_0) \), with \( t_0, P_{A0}, \) and \( \Delta P_A \) all positive constants and \( u(t) \) representing the unit step:

\[ u(t) = \begin{cases} 0 & t < 0 \\ 1 & t \geq 0 \end{cases} \]

Had the input to \( P_a \) simply been \( P_{A0} \) (for all time), its output would have been \( H_a(j0)P_{A0} \) (for all
CHAPTER 3. A NEW, SIMPLE MODEL

time). Had its input been \( \Delta P_A u(t - t_0) \), its output would have been \( \mathcal{L}^{-1}\{H_a(s) \mathcal{L}\{\Delta P_A u(t - t_0)\}\} \).

Thus, by linearity, given input \( p_A(t) = P_A^0 + \Delta P_A u(t - t_0) \), \( P_a \) would have produced as output

\[
P_a(t) = H_a(j0) P_A^0 + \mathcal{L}^{-1}\{H_a(s) \mathcal{L}\{\Delta P_A u(t - t_0)\}\}.
\]

Now, suppose \( H_a(s) = H_a,D2M(s) \) with \( \tau_{a,D2M,1} \neq \tau_{a,D2M,2} \). Then the output generated by \( P_a \) is:

\[
p_{a,D2M}(t) = H_{a,D2M}(j0) P_A^0 + \mathcal{L}^{-1}\{H_{a,D2M}(s) \mathcal{L}\{\Delta P_A u(t - t_0)\}\}
\]

\[
= P_A^0 + \mathcal{L}^{-1}\left\{e^{-s\tau_{a,D2M}} \frac{1}{(\tau_{a,D2M,1}s + 1)(\tau_{a,D2M,2}s + 1)} \Delta P_A e^{-s\tau_0} \frac{1}{s}\right\}
\]

\[
= P_A^0 + \mathcal{L}^{-1}\left\{\Delta P_A e^{-s(t_0 + \tau_{a,D2M})} \frac{1}{s(\tau_{a,D2M,1}s + 1)(\tau_{a,D2M,2}s + 1)}\right\}
\]

\[
= P_A^0 + \mathcal{L}^{-1}\left\{\Delta P_A e^{-s(t_0 + \tau_{a,D2M})} \left(\frac{1}{s} + \frac{1}{\tau_{a,D2M,2}} - \frac{1}{s + \tau_{a,D2M,1}^{-1}} + \frac{1}{\tau_{a,D2M,2}} - \frac{1}{s + \tau_{a,D2M,2}^{-1}}\right)\right\}
\]

\[
= P_A^0 + \Delta P_A u(t - t_0 - D_{a,D2M}) \cdot \left[1 - \frac{1}{\tau_{a,D2M,2}} \exp\left(-\frac{t - t_0 - D_{a,D2M}}{\tau_{a,D2M,1}}\right) + \frac{1}{\tau_{a,D2M,1}} \exp\left(-\frac{t - t_0 - D_{a,D2M}}{\tau_{a,D2M,2}}\right)\right]
\]

Under our usual settings for simulating CSA in PNEUMA, \( \tau_{a,D2M,1} = 1 \) s, \( \tau_{a,D2M,2} = 2 \) s, the effective lung-to-carotid volume is 882 mL, and the cardiac output (systemic blood flow, viewed on our multibreath timescale) oscillates, once initial transients have subsided, between 3.96 L/min (corresponding to \( D_{a,D2M} = 13.4 \) s) and 5.09 L/min (corresponding to \( D_{a,D2M} = 10.4 \) s), about a mean value of 4.37 L/min (corresponding to \( D_{a,D2M} = 12.1 \) s). Figure 3.3 shows the resulting step responses.
Figure 3.3: The step response of $P_a$ when governed by $H_{a,D2M}(s)$, with the values of the mixing time constants drawn directly from PNEUMA. The input, $p_A$, is shown in black. The output, $p_{a,D2M}$, is shown in red. The solid red curve shows the response when the delay time is computed from the effective lung-to-carotid volume and mean cardiac output in our usual PNEUMA simulation of CSA. The dashed curve on the left (right) uses the delay time associated with the maximum (minimum) observed cardiac output.

Until just before the step in $p_A$ at time $t_0$, the left heart and all the vasculature from the alveoli to the carotid bifurcation contain only $P_{A0}$ blood. Then, $p_A$ suddenly increases by $\Delta P_A$. It takes a length of time equal to $D_{a,D2M}$ for any of the post-step blood to reach the carotid bifurcation. Thus, at $t_0 + D_{a,D2M}$, the carbon dioxide tension of blood at the carotid bifurcation ($p_{a,D2M}$) begins to rise, as $P_{A0} + \Delta P_A$ blood washes progressively more of the old $P_{A0}$ blood out of the left heart and vasculature. Eventually, all of the old blood between the alveoli and the carotid bifurcation gets replaced; that is, $p_{a,D2M} \rightarrow P_{A0} + \Delta P_A$ as $t \rightarrow \infty$. The rise in $p_{a,D2M}$ is not purely exponential; it is governed by the two time constants of our mixing model.

The contribution of the pure delay to shaping the step response (rightward shift) is clearly distinguishable from the contribution of the mixing elements (smearing or stretching). The length of the delay is considerable: a 12.1-second delay is 2.6 times the mean respiratory period observed in our CSA simulation. Compared to the delay, mixing appears to occur quite quickly. This suggests that while our model of $P_a$ should certainly include a pure delay, we may not need to incorporate two first-
order mixing elements. Of course, should key phenomena only appear or the fit to data significantly improve with the inclusion of both mixing elements, we ought to keep them in our model. If including them confers no such benefit, then doing so would unnecessarily complicate analysis by increasing the order of the model and would hurt identifiability by unnecessarily increasing the number of parameters to be estimated.

Consider a model that describes a pure time delay (of length \( D_{a,D1M} \)) in series with just one first-order mixing element (with unity gain and time constant \( \tau_{a,D1M} \)),

\[
H_{a,D1M}(s) = \frac{e^{-sD_{a,D1M}}}{\tau_{a,D1M}s + 1},
\]

and another model that describes only a pure delay (of length \( D_{a,D0M} \)):

\[
H_{a,D0M}(s) = e^{-sD_{a,D0M}}
\]

Suppose again that \( \mathcal{P}_a \) is operating in an open-loop configuration with input \( p_A(t) = P_{A0} + \Delta P_A u(t - t_0) \), but this time let \( \mathcal{P}_a \) be governed by \( H_a(s) = H_{a,D1M}(s) \). Then the output, \( p_{a,D1M} \), simply exhibits a delayed exponential increase, starting at \( P_{A0} \) and approaching \( P_{A0} + \Delta P_A \):

\[
p_{a,D1M}(t) = H_{a,D1M}(j0)P_{A0} + \mathcal{L}^{-1}\{H_{a,D1M}(s) \mathcal{L}\{\Delta P_A u(t - t_0)\}\}
\]

\[
= P_{A0} + \mathcal{L}^{-1}\left\{\frac{e^{-sD_{a,D1M}}}{\tau_{a,D1M}s + 1} \Delta P_A \frac{e^{-st_0}}{s}\right\}
\]

\[
= P_{A0} + \mathcal{L}^{-1}\left\{\Delta P_A e^{-s(t_0 + D_{a,D1M})} \frac{1}{s(\tau_{a,D1M}s + 1)}\right\}
\]

\[
= P_{A0} + \mathcal{L}^{-1}\left\{\Delta P_A e^{-s(t_0 + D_{a,D1M})} \left(\frac{1}{s} - \frac{1}{s + \tau_{a,D1M}^{-1}}\right)\right\}
\]

\[
= P_{A0} + \Delta P_A \left[1 - \exp\left(-\frac{t - t_0 - D_{a,D1M}}{\tau_{a,D1M}}\right)\right] u(t - t_0 - D_{a,D1M})
\]

Had we instead had \( H_a(s) = H_{a,D0M}(s) \), then the output, \( p_{a,D0M} \), would just have been a delayed
3.3. MODEL DETAILS

Step:

\[ p_{a,D0M}(t) = H_{a,D0M}(j0) P_{A0} + \mathcal{L}^{-1}\{H_{a,D0M}(s) \mathcal{L}\{\Delta P_A u(t-t_0)\}\} \]

\[ = P_{A0} + \mathcal{L}^{-1}\left\{e^{-sD_{a,D0M}} \frac{\Delta P_A e^{-st_0}}{s}\right\} \]

\[ = P_{A0} + \mathcal{L}^{-1}\left\{\Delta P_A \frac{e^{-s(t_0+D_{a,D0M})}}{s}\right\} \]

\[ = P_{A0} + \Delta P_A u(t-t_0-D_{a,D0M}) \]

Again assuming \(\tau_{a,D2M,1} = 1\) s and \(\tau_{a,D2M,2} = 2\) s, we find numerically that \(p_{a,D1M}(t)\) best approximates \(p_{a,D2M}(t)\) – in the sense that \(\int_{-\infty}^{\infty} [p_{a,D1M}(t) - p_{a,D2M}(t)]^2 dt\) is minimized – when \(D_{a,D1M} = D_{a,D2M} + 0.65\) s and \(\tau_{a,D1M} = 2.43\) s. \(p_{a,D0M}(t)\) best approximates \(p_{a,D2M}(t)\) when \(D_{a,D0M} = D_{a,D2M} + 2.46\) s. All three step responses are shown in Figure 3.4.

Figure 3.4: If \(P_a\) is governed by \(H_{a,D2M}(s)\) with \(\tau_{a,D2M,1} = 1\) s, \(\tau_{a,D2M,2} = 2\) s, and \(D_{a,D2M} = 12.1\) s, then its response to a step in its input (\(P_A\), shown in black) would be \(p_{a,D2M}\), plotted in red. If \(P_a\) were instead governed by \(H_{a,D1M}(s)\) or \(H_{a,D0M}(s)\), then its response would be \(p_{a,D1M}\) (green) or \(p_{a,D0M}\) (blue), respectively. The values of the parameters in \(H_{a,D1M}(s)\) and \(H_{a,D0M}(s)\) have been set to produce the best possible agreement between their responses and \(p_{a,D2M}\).

Notice that \(p_{a,D1M}(t)\) approximates \(p_{a,D2M}(t)\) extremely well, supporting our conjecture that at least one of the mixing elements in the Lange (D2M) model is superfluous. Using this excellent fit,
we may also quantify how fast the mixing really is relative to the delay length. With \( \tau_{a,D2M,1} = 1 \) s, \( \tau_{a,D2M,2} = 2 \) s, and \( D_{a,D2M} = 12.1 \) s, \( p_{a,D1M} \) best approximates \( p_{a,D2M} \) when \( D_{a,D1M} = 12.1 \) s + 0.65 s = 12.8 s and \( \tau_{a,D1M} = 2.43 \) s. Thus the ratio between the mixing time constant and the delay is \( \frac{\tau_{a,D1M}}{D_{a,D1M}} = \frac{2.43 \text{ s}}{12.8 \text{ s}} = 0.19 \). This confirms our claim that in \( p_{a,D2M} \), the mixing timescale seems significantly shorter than the delay time. This suggests that \( H_{a,D0M}(s) \) may be perfectly adequate for our model of \( P_a \). Admittedly, its step response does not agree closely with \( p_{a,D2M} \) (as we expect, since \( \frac{\tau_{a,D1M}}{D_{a,D1M}} \) is not very small). However, note that the spectrum of a true step is nonzero at all frequencies, whereas our CSA simulation results (viewed on our multibreath timescale) show a smooth \( p_A \) waveform in steady state, oscillating with period 42.5 s.

In light of this, suppose that instead of a step input to \( P_a \), we have a sinusoid with period \( T \):
\[
p_{A}(t) = \Delta P_A \cos \left( \frac{2\pi t}{T} \right) + P_{A0}.
\]
The output would then be
\[
p_{a}(t) = \left| H_a \left( j \frac{2\pi}{T} \right) \right| \Delta P_A \cos \left( \frac{2\pi}{T} \left[ t + \frac{T}{2\pi} \angle H_a \left( j \frac{2\pi}{T} \right) \right] \right) + H_a(j0) P_{A0}.
\]
Witness that:
\[
\left| H_{a,D2M} \left( j \frac{2\pi}{T} \right) \right| = \frac{1}{\sqrt{\left( 1 + \frac{4\pi^2 \tau_{a,D2M,1}^2}{T^2} \right) \left( 1 + \frac{4\pi^2 \tau_{a,D2M,2}^2}{T^2} \right)}} \quad (3.41)
\]
\[
-\frac{T}{2\pi} \angle H_{a,D2M} \left( j \frac{2\pi}{T} \right) = D_{a,D2M} + \frac{T}{2\pi} \left[ \arctan \left( \frac{2\pi}{T} \tau_{a,D2M,1} \right) + \arctan \left( \frac{2\pi}{T} \tau_{a,D2M,2} \right) \right] \quad (3.42)
\]
\[
\left| H_{a,D1M} \left( j \frac{2\pi}{T} \right) \right| = \frac{1}{\sqrt{1 + \frac{4\pi^2 \tau_{a,D1M}^2}{T^2}}} \quad (3.43)
\]
\[
-\frac{T}{2\pi} \angle H_{a,D1M} \left( j \frac{2\pi}{T} \right) = D_{a,D1M} + \frac{T}{2\pi} \arctan \left( \frac{2\pi}{T} \tau_{a,D1M} \right) \quad (3.44)
\]
\[
\left| H_{a,D0M} \left( j \frac{2\pi}{T} \right) \right| = 1 \quad (3.45)
\]
\[
-\frac{T}{2\pi} \angle H_{a,D0M} \left( j \frac{2\pi}{T} \right) = D_{a,D0M} \quad (3.46)
\]
In particular, \( H_{a,D2M}(j0) = H_{a,D1M}(j0) = H_{a,D0M}(j0) = 1 \). (We refer to \( H_a(j\omega), \left| H_a(j\omega) \right|, \angle H_a(j\omega), \) and \( -\frac{1}{\omega} \angle H_a(j\omega) \), where \( \omega = \frac{2\pi}{T} \), as the frequency response, magnitude response, phase response, and phase delay, respectively, of \( P_a \).

If we again assign values to the delays and time constants of the three system functions just
as we did for Figure 3.4, and if we take \( T = 42.5 \) s, then we obtain the responses shown in Figure 3.5. The outputs associated with \( H_{a,D2M}(s) \) and \( H_{a,D1M}(s) \) agree even more beautifully than their step responses did, and the \( H_{a,D0M}(s) \) response here really is quite similar to the other two; the difference between them is certainly far less pronounced than the disagreement between the corresponding step response plots.

![Figure 3.5: The response of \( P_a \) to the input \( p_A(t) = \Delta P_A \cos \left( \frac{2\pi t}{T} \right) + P_{A0} \) (black), where \( T = 42.5 \) s, if \( H_a(s) = H_{a,D2M}(s) \) (red), \( H_a(s) = H_{a,D1M}(s) \) (green), or \( H_a(s) = H_{a,D0M}(s) \) (blue). The delays and time constants in the system functions retain the values used in Figure 3.4.](image)

Note that given \( D_{a,D2M}, \tau_{a,D2M,1}, \) and \( \tau_{a,D2M,2} \), we selected values of \( D_{a,D1M}, \tau_{a,D1M}, \) and \( D_{a,D0M} \) that best fit the step responses of \( H_{a,D1M}(s) \) and \( H_{a,D0M}(s) \) to that of \( H_{a,D2M}(s) \). Our objective could instead be to minimize the differences between the responses to a sinusoidal input of some particular period, \( T_0 \). From (3.41)–(3.46), we see that this may be achieved by setting

\[
\tau_{a,D1M} = \sqrt{\frac{\tau_{a,D2M,1}^2 + \frac{4\pi^2}{T_0^2} \tau_{a,D2M,1} \tau_{a,D2M,2} + \tau_{a,D2M,2}^2}{2}}
\]

\[
D_{a,D1M} = D_{a,D2M} + \frac{T_0}{2\pi} \left[ \arctan \left( \frac{2\pi}{T_0} \tau_{a,D2M,1} \right) + \arctan \left( \frac{2\pi}{T_0} \tau_{a,D2M,2} \right) - \arctan \left( \frac{2\pi}{T_0} \tau_{a,D1M} \right) \right]
\]

\[
D_{a,D0M} = D_{a,D2M} + \frac{T_0}{2\pi} \left[ \arctan \left( \frac{2\pi}{T_0} \tau_{a,D2M,1} \right) + \arctan \left( \frac{2\pi}{T_0} \tau_{a,D2M,2} \right) \right]
\]

(3.47)

Then the phase responses of \( H_{a,D0M}(s), H_{a,D1M}(s), \) and \( H_{a,D2M}(s) \) would coincide at \( \omega = \omega_0 = \frac{2\pi}{T_0} \).
as would the magnitude responses of \( H_{a,D1M}(s) \) and \( H_{a,D2M}(s) \).

With \( \tau_{a,D1M} = 1 \text{ s}, \tau_{a,D2M} = 2 \text{ s}, \) \( D_{a,D2M} = 12.1 \text{ s}, \) and \( T_0 = 42.5 \text{ s}, \) we have \( \tau_{a,D1M} = 2.26 \text{ s}, \)
\( D_{a,D1M} = 12.9 \text{ s}, \) and \( D_{a,D0M} = 15.0 \text{ s}. \) These values are very close to those that produced the best agreement between step responses. Indeed, adopting these values would lead to step response plots very similar to those shown in Figure 3.4. The corresponding responses to a sinusoidal input of period 42.5 s are precisely as expected: the outputs of \( H_{a,D1M}(s) \) and \( H_{a,D2M}(s) \) match perfectly, while the \( H_{a,D0M}(s) \) response disagrees only (and slightly) in amplitude.

It now finally seems perfectly reasonable to adopt \( H_{a,D0M}(s) \) as the form of the system function for our model of \( P_a \):

\[
H_a(s) = e^{-sD_a}
\]

Should we later find this lacking, we may consider \( H_{a,D1M}(s) \). Moving up to the Lange model (which corresponds to \( H_{a,D2M}(s) \) and appears in PNEUMA) would likely do little beyond making analysis and parameter estimation more difficult.

### Padé Approximation

The stability of the model system depends upon the values of its parameters. We will explore the conditions for stability and instability in Chapter 4, starting with an examination of the fully linearized model system. But even in our linearized model, \( P_a \) includes a delay component, which complicates analysis. The Routh-Hurwitz stability criterion can be used to examine any system whose constituent blocks are governed only by rational transfer functions. We will therefore consider a further simplification of our model in which we employ a rational transfer function model of \( P_a \).

Given a suitable function \( f(z) \), we define its order \( m/n \) Padé approximant (where \( m \) and \( n \) are nonnegative integers) to be the rational function

\[
f_{m/n}(z) = \frac{\alpha_{m/n}(z)}{\beta_{m/n}(z)},
\]

where \( \alpha_{m/n}(z) = \sum_{k=0}^{m} a_k z^k \), \( \beta_{m/n}(z) = \sum_{k=0}^{n} b_k z^k \), \( b_0 = 1 \), \( \alpha_{m/n}(z) \) and \( \beta_{m/n}(z) \) have no common zeros, \( f_{m/n}(0) = f(0) \), and \( \frac{df_{m/n}}{dz^l} \bigg|_{z=0} = \frac{df}{dz^l} \bigg|_{z=0} \) for all \( l = 1, 2, \ldots, m+n \). The Maclaurin series of \( f(z) \) and \( f_{m/n}(z) \) thus agree up to the \( z^{m+n} \) term, so \( f_{m/n}(z) \) provides the best rational
approximation, with numerator degree \( m \) and denominator degree \( n \), of \( f(z) \) in the vicinity of \( z = 0 \).

For \( H_a(s) = e^{-sD_a} \), the order 1/1 and 2/2 Padé approximants are \( H_{a,1/1}(s) = \frac{1}{2}D_a{s+1} \) and \( H_{a,2/2}(s) = \frac{1}{2}D_a{s^2} - \frac{1}{2}D_a{s+1} \). It can be verified that, for all \( T \),

\[
\left| H_a \left( \frac{2\pi}{T} \right) \right| = \left| H_{a,1/1} \left( \frac{2\pi}{T} \right) \right| = \left| H_{a,2/2} \left( \frac{2\pi}{T} \right) \right| = 1
\]

So a system governed by \( H_a(s) \), \( H_{a,1/1}(s) \), or \( H_{a,2/2}(s) \) would, in response to a sinusoidal input with period \( T \), produce a sinusoidal output of identical bias, period, and amplitude, but delayed in time by the associated phase delay:

\[
-\frac{T}{2\pi} \angle H_a \left( \frac{2\pi}{T} \right) = D_a
\]

\[
-\frac{T}{2\pi} \angle H_{a,1/1} \left( \frac{2\pi}{T} \right) = \frac{T}{\pi} \arctan \frac{\pi D_a}{T}
\]

\[
-\frac{T}{2\pi} \angle H_{a,2/2} \left( \frac{2\pi}{T} \right) = \begin{cases} 
T \left( 1 + \frac{1}{\pi} \arctan \frac{\pi D_a}{1 - \frac{\pi^2 D_a}{3T^2}} \right) & \text{if } T < \frac{\pi D_a}{\sqrt{3}} \\
\frac{T}{2} & \text{if } T = \frac{\pi D_a}{\sqrt{3}} \\
\frac{T}{\pi} \arctan \frac{\pi D_a}{1 - \frac{\pi^2 D_a}{3T^2}} & \text{if } T > \frac{\pi D_a}{\sqrt{3}}
\end{cases}
\]

With \( T = 42.5 \text{ s} \) and \( D_a = 15.0 \text{ s} \), the result is as shown in Figure 3.6.

Figure 3.6: The responses of systems governed by \( H_a(s) \) (red), \( H_{a,1/1}(s) \) (blue), and \( H_{a,2/2}(s) \) (green) to the input \( p_A(t) = \Delta P_A \cos \left( \frac{2\pi t}{T} \right) + P_{A0} \) (black), where \( T = 42.5 \text{ s} \) and \( D_a = 15.0 \text{ s} \).

The phase delay generated at this frequency by \( H_{a,1/1}(s) \) is very noticeably shorter than the "correct" delay produced by \( H_a(s) \). The order 2/2 approximant (unsurprisingly) comes much closer.
Since we do expect that the input \((p_A)\) will, at steady-state, be a smooth oscillation with a period near 42.5 s, we could adjust \(H_{a,1/1}(s)\) and \(H_{a,2/2}(s)\) so that their responses to a pure sinusoidal input of this particular period become identical to the response of the true delay system, \(H_a(s)\). Accordingly, redefine

\[
H_{a,1/1}(s) = \frac{-\frac{1}{2}D_{a,1/1}s + 1}{\frac{1}{2}D_{a,1/1}s + 1} \tag{3.48}
\]

\[
H_{a,2/2}(s) = \frac{\frac{1}{12}D_{a,2/2}^2s^2 - \frac{1}{2}D_{a,2/2}s + 1}{\frac{1}{12}D_{a,2/2}^2s^2 + \frac{1}{2}D_{a,2/2}s + 1} \tag{3.49}
\]

and denote the period of interest by \(T_0\), where \(T_0 > 2D_a\). Now, if instead of choosing \(D_{a,1/1} = D_{a,2/2} = D_a\), we take

\[
D_{a,1/1} = \frac{T_0}{\pi} \tan \frac{\pi D_a}{T_0}
\]

\[
D_{a,2/2} = \frac{3T_0}{2\pi} \sqrt{1 + \frac{4}{3} \tan^2 \frac{D_a\pi}{T_0} - 1} \tan \frac{D_a\pi}{T_0},
\]

then in response to a sinusoidal input of period \(T_0\), systems governed by \(H_{a,1/1}(s)\) and \(H_{a,2/2}(s)\) would each produce as output a \(D_a\)-delayed copy of the input sinusoid. (For \(D_a = 15.0\) s, \(T_0 = 42.5\) s, we would take \(D_{a,1/1} = 27.4\) s, \(D_{a,2/2} = 15.5\) s.)

Figure 3.7 shows how the phase delay varies with period for each of \(H_a(s)\), \(H_{a,1/1}(s)\), and \(H_{a,2/2}(s)\).
Figure 3.7: The relationship between period and phase delay for $H_a(s)$ (red), $H_{a,1/1}(s)$ (blue), and $H_{a,2/2}(s)$ (green). The solid lines correspond to $D_{a,1/1} = D_{a,2/2} = D = 15.0$ s. Setting $D_{a,1/1} = 27.4$ s and $D_{a,2/2} = 15.5$ s (the three systems would then respond identically to a sinusoidal input with period 42.5 s, marked by the dotted black line) produces the dashed lines.

Note that with $D_{a,1/1} = D_{a,2/2} = D = 15.0$ s, the Padé approximants (which are centred at $s = 0$) only produce the “correct” phase delay at infinite period (zero frequency). Everywhere else (including at $T = 42.5$ s, as both Figures 3.6 and 3.7 show), they produce less phase delay. Not surprisingly, the order 2/2 approximant fares better than the order 1/1 approximant, though both deviate further from the $H_a(s)$ response with decreasing period. (Note, however, that only the middle decade shown in the figure, 10 s to 100 s, corresponds to timescales that our model is expected to capture.) To have the three curves coincide at $T = 42.5$ s, we needed to set $D_{a,1/1}$ equal to nearly double $D$; the corresponding adjustment for $D_{a,2/2}$, on the other hand, was very slight. While the adjusted order 2/2 approximant does not do very well below $T = 42.5$ s, the adjusted 1/1 order approximant fares very badly on both sides of this particular period of interest (as would the order 2/2 approximant if $D_{a,2/2}$ were increased significantly).
3.3.4 Chemoreflex Control of Ventilation

Khoo Model

We begin by considering the following controller model, which captures the basic form of the controller model proposed by Khoo et al. in [KKSS82]:

\[
\phi_{Khoo} = G_{Khoo,a} \left( S_{a,O_2,TH} - s_{a,O_2} \right)^+ + G_{Khoo,b} \left( P_{b,CO_2} - P_{b,CO_2,TH} \right)^+ (3.50)
\]

For any real quantity \( x \), we use \([x]^+\) as shorthand notation for \( \max(0, x) \). In (3.50), \( G_{Khoo,a} \) and \( G_{Khoo,b} \) denote the peripheral and central chemoreflex gains, respectively; \( s_{a,O_2} \) denotes the oxygen saturation of blood at the peripheral chemosensor sites; \( p_{b,CO_2} \) and \( p_{a,CO_2} \) denote the partial pressures of carbon dioxide in the central chemosensor tissue and in the blood at the peripheral chemosensor sites, respectively. Finally, \( S_{a,O_2,TH}, P_{a,CO_2,TH}, \) and \( P_{b,CO_2,TH} \) denote "apneic" thresholds.

In this model, total ventilation is the sum of a peripheral component (determined entirely by gas levels sensed by the peripheral chemoreceptors) and a central component (determined entirely by the carbon dioxide level sensed by the central chemoreceptors). When \( p_{a,CO_2} \) is safely below \( P_{a,CO_2,TH} \) or \( s_{a,O_2} \) is safely above \( S_{a,O_2,TH} \), the controller becomes completely unresponsive to changes in gas levels at the carotid sites. Otherwise, the peripheral ventilation component is proportional to the product of the amounts by which the thresholds are transgressed, the constant of proportionality being the peripheral chemoreflex gain. Similarly, the central component is proportional to the amount by which \( p_{b,CO_2} \) exceeds \( P_{b,CO_2,TH} \); the sensitivity of total ventilation to changes in \( p_{b,CO_2} \) is given by the central gain. When \( p_{b,CO_2} \) is safely below \( P_{b,CO_2,TH} \), the controller is insensitive to changes in the level of carbon dioxide in brain tissue.

Note that (3.50) represents a purely static controller. To accept such a model, we must assume that all delays and other dynamic effects – in the detection of gas levels by the chemoreceptors, the action of the ventilatory controller, the communication of sensory information and control (motor) signals, and the responses of the respiratory muscles – either

- are so short and fast, respectively, that they are not significant on our multibreath timescale,
3.3. MODEL DETAILS

- may be accounted for by adjusting plant parameters (say, increasing $D_a$ to account for delays common to the peripheral and central chemoreceptors, and increasing $\tau_A$ to account for any sluggishness in the ventilatory controller.

Especially considering the coarseness of our model timescale, it seems almost certain that at least the first of these conditions will be met for our model.\(^5\)

PNEUMA Model

In PNEUMA, the ventilatory controller does not dictate ventilation directly. Rather, it produces (following the same form as (3.50)) a “chemical ventilatory drive” signal that reflects the total need for ventilation, given the measured gas levels:

$$d_{\text{PNEUMA}} = G_{\text{PNEUMA, a}} [s_{a,O_2,TH} - s_{a,O_2}]^+ [p_a,CO_2 - P_{a,CO_2,TH}]^+$$

Peripheral Component

$$+ G_{\text{PNEUMA, b}} [p_b,CO_2 - P_{b,CO_2,TH}]^+$$

Central Component

(3.51)

This chemical drive is modified according to the sleep state, so that the drive is weaker (through thresholding and scaling) during sleep than it is in wakefulness. The drive may then be processed by a network of nonlinear and dynamic elements that model “ventilatory afterdischarge” (though this part of the model is for some reason disabled by default). The modified drive dictates the respiratory rate according to the model presented in [DMV+00]. A train of ramp-like pulses is then generated, where the durations of the pulses and the intervals separating successive pulses are determined by the respiratory rate, and the slopes of the ramps are proportional to the size of the modified drive. This train represents the firing rate of the motor neurons that direct the contraction of the inspiratory muscles. This signal, together with the mechanical properties of the respiratory system, determines the lung volume waveform. Nonlinearities and dynamics in the mechanical (and

\(^5\)The model proposed by Grodins et al. in [GBB67], which is much more complex than the Khoo model, also uses a static controller. The authors claim that “certainly” for the “neural components” and “probably” for the “mechanical elements”, the delays associated with the controller are much shorter than those associated with the plant. Addressing the peripheral sensors in particular, [KKSS82] cites the work of Ponte and Purves, claiming that it is “generally accepted that the carotid chemoreceptors respond directly and very rapidly to changes in $P_{CO_2}$... and $P_{O_2}$ in the blood that perfuses them.” (According to [Nur05], the carotid body is “richly innervated” and is “supplied by an elaborate vascular network” that makes it “the tissue with the highest blood flow per unit weight”). While [KKSS82] implicitly assumes that the central chemoreceptors respond very rapidly to changes in receptor tissue gas levels, this is not stated or justified.
CHAPTER 3. A NEW, SIMPLE MODEL

possibly neural) subsystems imply a nonlinear, non-static relationship between $d_{PNEUMA}$ and tidal volume and ventilation.

**Duffin Model**

In the model of Duffin et al. [DMV+00], the ventilatory drive takes the form

$$d_{Duffin} = \frac{G_{Duffin,a} [p_{a,CO_2} - P_{CO_2,TH}^+]}{p_{a,O_2} - P_{a,O_2,asymptote} + G_{Duffin,b} [p_{b,CO_2} - P_{CO_2,TH}^+]}$$

(3.52)

where $P_{CO_2,TH}$ is a carbon dioxide tension threshold common to both drive components, $P_{a,O_2,asymptote}$ (a parameter with no genuine physiological significance) is given the value 30 mmHg, and $p_{a,O_2}$, the oxygen tension at the carotid sites, is at least 40 mmHg. The drive variable $d_{Duffin}$ has dimensions of volume, and its value places the controller in one of three regimes. While drive is below the fixed basal threshold, $v_T$ (tidal volume), $f_R$ (respiratory rate), and $\phi$ (ventilation) take their fixed, positive basal values. The model does not allow ventilation to drop below its basal level, no matter how low the ventilatory drive becomes. This reflects the “wakefulness drive” to breathe.

Between the basal threshold and some higher patterning threshold, $v_T$ and $f_R$ increase linearly with $d_{Duffin}$. Ventilation, $\phi = f_R v_T$, therefore increases quadratically with $d_{Duffin}$, but Duffin et al. show that over this range of drive values, the $\phi$-versus-$d_{Duffin}$ trend is fairly well approximated by a straight line. Once the drive exceeds the patterning threshold, the slope of the $v_T$-versus-$d_{Duffin}$ characteristic falls abruptly to a lower fixed value, and the $f_R$-versus-$d_{Duffin}$ characteristic steepens abruptly.

To develop their model and estimate “average” values of its parameters, Duffin et al. performed experiments in which subjects were fitted with a rebreathing bag. Through external control, $p_{a,O_2}$ was kept constant throughout each run of the experiment; the setpoint was varied across runs. Ostensibly, their rebreathing protocol also ensured that $p_{a,CO_2}$ and $p_{b,CO_2}$ rapidly equalized once rebreathing began, then rose together at a constant rate. Thus, they observed the ventilatory responses ($v_T$, $f_R$, and $\phi$) to $p_{a,O_2}$ and a single carbon dioxide tension variable, $pCO_2 = p_{a,CO_2} \approx$
Making this substitution in (3.52) gives, approximately,

\[ d_{\text{Duffin}} = \left( \frac{G_{\text{Duffin,a}}}{p_{a,O_2} - p_{a,O_2,\text{asymptote}}} + G_{\text{Duffin,b}} \right) [p_{CO_2} - P_{CO_2,TH}]^+ \]  

(3.53)

The average slopes of \( \nu_T, f_R, \) and \( \phi \) with respect to \( p_{CO_2} \) in the intermediate- and high-drive regimes, as well as the basal and patterning \( p_{CO_2} \) thresholds, were observed to change little as \( p_{a,O_2} \) was changed from 80 mmHg to 100 mmHg to 150 mmHg. In our PNEUMA simulation, we find that \( p_{a,O_2} \) never falls below 90 mmHg, so we are operating in the high-\( p_{a,O_2} \) regime. Here, the patterning threshold in terms of \( p_{CO_2} \) is approximately 55 mmHg. Neither our simulated \( p_{a,CO_2} \) nor our simulated \( p_{b,CO_2} \) rises this high. Looking at this from another perspective, the patterning threshold in terms of tidal volume is approximately 1.9 L, and our simulated tidal volume never rises above 1.2 L. Finally, PNEUMA maps the current chemical drive (\( d_{PNEUMA} \) as defined in (3.51)) to one of the three regimes. In our simulation, the high-drive regime is never reached. In our model, we may therefore safely ignore the highest of the three drive regimes.

Duffin et al. mention that in some of their earlier work, they had measured the response of \( \phi \), but not \( f_R \) and \( \nu_T \), to carbon dioxide levels. At that time, they associated the lower \( p_{CO_2} \) threshold with the peripheral component and the upper threshold with the central component. They had thought this reasonable because the lower threshold vanished in hyperoxia, when the peripheral chemosensor would be silenced. Having now observed how differently the \( f_R \)-versus-\( p_{CO_2} \) and \( \nu_T \)-versus-\( p_{CO_2} \) trends behave when each threshold is crossed, the authors have adopted their new interpretation: the peripheral and central thresholds coincide (\( P_{CO_2,TH} \)), and the basal and patterning thresholds are associated with abrupt changes in the behaviours of \( f_R \) and \( \nu_T \) as chemical drive increases.

---

6 Actually, they treated the measured end-tidal partial pressure of carbon dioxide as the observed variable represented by \( p_{CO_2} \). Now, \( p_{ET,CO_2} \) is essentially a sampled copy of \( p_{A,CO_2} \), and \( p_{A,CO_2} \) is a delayed, gently distorted copy of \( p_{A,CO_2} \). So their plots of \( \nu_T \), \( f_R \), and \( \phi \) against \( p_{ET,CO_2} \) are actually roughly right-shifted versions of the response plots against the physiologically-sensed variable \( p_{CO_2} \). The size of this shift is approximately equal to the lung-to-carotid delay multiplied by the rate at which \( p_{ET,CO_2} \) increases with time during rebreathing. Either this shift must be deemed negligible or it must be accounted for. [DMV+00] does not explicitly mention either.

7 Again, these are the slopes with respect to \( p_{CO_2} \) and the thresholds in terms of \( p_{CO_2} \). Both depend upon \( p_{a,O_2} \). The slopes and thresholds discussed earlier were in terms of the chemical drive; these are independent of \( p_{a,O_2} \). Only through the chemical drive does oxygen play a direct role in the model. The high-oxygen regime just described in the text, where the slopes and thresholds with respect to \( p_{CO_2} \) become insensitive to changes in \( p_{a,O_2} \), corresponds to the flattening (and, effectively, vanishing) of the \( p_{a,O_2} - p_{A,CO_2,\text{asymptote}} \) multiplier in the chemical drive expression.

8 Again, only for the determination of \( f_R \). Recall that the tidal volume and ventilation depend upon \( f_R \), but they are not determined by anything as simple as the Duffin trichotomy.

9 [DMV+00] actually notes that the patterning threshold was not even reached in many of their experimental runs, so if the trichotomy is real, the published patterning threshold values seem to be underestimates.
Adopted Model

**Ventilatory Drive** In both PNEUMA and [DMV+00], an unobservable variable - the ventilatory drive – is used to represent the need to ventilate, as determined by the ventilatory controller from current measured gas levels. From the drive, the tidal volume, respiratory rate, and hence ventilation are determined. In the real system, neural signals from the ventilatory control center in the brainstem direct the activity of the respiratory muscles. The drive may then be interpreted as providing some rough representation of the behaviour of these signals on a multibreath timescale. (The drive does not code for individual inspirations.) We too will use a drive variable, \( d \), for this purpose. Perfectly consistent with PNEUMA and [DMV+00], we let \( d \) take the form

\[
d = G_a (p_{a,O_2}, s_{a,O_2}) \left[ p_{a,CO_2} - P_{a,CO_2,TH} \right]^+ + G_b [p_{b,CO_2} - P_{b,CO_2,TH}]^+, \tag{3.54}
\]

where, assuming a roughly constant general physiological state, \( G_b \) is a constant and \( G_a \) is a function only of the oxygen level seen by the peripheral chemosensor.

Since we are considering ventilation to be a function of drive, and drive to be a function of measured gas levels, we recast the Khoo model described in (3.50) as:

\[
d_{Khoo} = G_{Khoo,a} [s_{a,O_2}, TH - s_{a,O_2}]^+ \left[ p_{a,CO_2} - P_{a,CO_2,TH} \right]^+ + G_{Khoo,b} [p_{b,CO_2} - P_{b,CO_2,TH}]^+ \tag{3.55}
\]

\[
\phi_{Khoo} = d_{Khoo} \tag{3.56}
\]

making the forms of the Khoo and PNEUMA drive models identical.

**Peripheral Chemoreflex Component Response to Oxygen** Consider the peripheral drive component in (3.51):

\[
d_{PNEUMA,p} = G_{PNEUMA,a} [s_{a,O_2}, TH - s_{a,O_2}]^+ \left[ p_{a,CO_2} - P_{a,CO_2,TH} \right]^+
\]

\[
= \begin{cases} 
0 & \text{if } p_{a,CO_2} \leq P_{a,CO_2,TH} \\
G_{PNEUMA,a} [s_{a,O_2}, TH - s_{a,O_2}]^+ (p_{a,CO_2} - P_{a,CO_2,TH}) & \text{if } p_{a,CO_2} > P_{a,CO_2,TH}
\end{cases}
\]
3.3. MODEL DETAILS

Since our model does not yet include any representation of oxygen levels, we would prefer to use a peripheral drive model of the form

\[ d_p = G_a \left[p_{a,CO_2} - P_{a,CO_2,TH}\right]^+ \]

\[ = \begin{cases} 
0 & \text{if } p_{a,CO_2} \leq P_{a,CO_2,TH} \\
G_a \left(p_{a,CO_2} - P_{a,CO_2,TH}\right) & \text{if } p_{a,CO_2} > P_{a,CO_2,TH}
\end{cases} \]  

(3.57)

where \(G_a\) is a constant. The results of our PNEUMA CSA simulation suggest that this may not be unreasonable. Figure 3.8 shows three cycles of filtered, simulated \(p_{a,CO_2}\) and \(s_{a,O_2}\) oscillations (each cycle corresponds to one cycle of unstable breathing).

![Waveforms](image)

Figure 3.8: Filtered \(p_{a,CO_2}\) (blue) and \(s_{a,O_2}\) (red) waveforms from our PNEUMA simulation of CSA, showing oscillations over three cycles of unstable breathing. The dotted line marks the mean values of the waveforms.

Notice that the two waveforms are roughly in antiphase, as would be expected. Thus, roughly: \(p_{a,CO_2}\) rises (falls) as \(s_{a,O_2}\) falls (rises), so \((p_{a,CO_2} - P_{a,CO_2,TH})\) and \((S_{a,O_2,TH} - s_{a,O_2})\) rise and fall together. Therefore, when \(d_{PNEUMA,p}\) is nonzero (that is, when \(s_{a,O_2} < S_{a,O_2,TH}\) and \(p_{a,CO_2} > P_{a,CO_2,TH}\)), it rises and falls with \([p_{a,CO_2} - P_{a,CO_2,TH}]^+\). Now, PNEUMA's default value for \(S_{a,O_2,TH}\) is over 100%, while \(s_{a,O_2}\) by definition cannot exceed 100%. This means that the peripheral chemoreflex response cannot be silenced by hyperoxia alone\(^{10}\); the peripheral contribution will be zero if and only if \(p_{a,CO_2}\) drops safely below the corresponding apneic threshold. With this, we see that \(d_{PNEUMA,p}\) and \([p_{a,CO_2} - P_{a,CO_2,TH}]^+\) rise, fall, and vanish together. (Figure 3.8

---

\(^{10}\)In [KKSS82], Khoo et al. model the sensitivity of the peripheral contribution to ventilation as being proportional to \(\exp(-0.05p_{a,O_2})\); this halves with every 14-mmHg increase in \(p_{a,O_2}\), so hyperoxia silences the peripheral chemoreflex component in that model.
CHAPTER 3. A NEW, SIMPLE MODEL

illustrates this.) So there is certainly hope for approximating \( \Delta P_{NEMA,p} \) by \( \Delta p \) as defined in (3.57).

![Figure 3.9: Plots of \([p_a,CO_2 - P_{a,CO_2,TH}]^+\) (blue), \([S_{a,O_2,TH} - s_{a,O_2}]^+\) (red), and \([p_a,CO_2 - P_{a,CO_2,TH}]^+ [S_{a,O_2,TH} - s_{a,O_2}]^+\) (black) corresponding to the filtered simulated \( p_a,CO_2 \) and \( s_a,O_2 \) waveforms shown in figure 3.8.](image)

Notice from Figure 3.8 that \([S_{a,O_2,TH} - s_{a,O_2}]^+\) varies much less than does \([p_a,CO_2 - P_{a,CO_2,TH}]^+\) (each compared, say, to its mean value). This suggests that the drive waveform would indeed change little if \([S_{a,O_2,TH} - s_{a,O_2}]^+\) were replaced by a constant (as we intend to do). For the particular case of the simulation result we have been discussing, simply multiplying \( G_{PNEUMA,a} \) by the ratio of the height of the \([p_a,CO_2 - P_{a,CO_2,TH}]^+ [S_{a,O_2,TH} - s_{a,O_2}]^+\) waveform to the height of the \([p_a,CO_2 - P_{a,CO_2,TH}]^+\) waveform gives an acceptable value to use for \( G_a \) in (3.57), as the excellent agreement between the plots in Figure 3.10 demonstrates.

![Figure 3.10: Plots of \( G_{PNEUMA,a} [p_a,CO_2 - P_{a,CO_2,TH}]^+ [S_{a,O_2,TH} - s_{a,O_2}]^+\) (black) and \( G_a [p_a,CO_2 - P_{a,CO_2,TH}]^+\) (green) corresponding to the filtered simulated \( p_a,CO_2 \) and \( s_a,O_2 \) waveforms shown in figure 3.8 and with \( G_a \) chosen as described in the text. The unfiltered simulated \( \Delta P_{NEMA,p} \) waveform is shown in magenta.](image)

We therefore comfortably adopt (3.57) as a model of the peripheral component of the chemical
3.3. MODEL DETAILS

ventilatory drive. For the total chemical drive, we now have

\[ d = G_a [p_{a, CO_2} - p_{a, CO_2, TH}]^+ + G_b [p_{b, CO_2} - p_{b, CO_2, TH}]^+, \]  

(3.58)

where \( G_a \) and \( G_b \) are both constant (assuming constant general physiological state).

Drive to Tidal Volume, Respiratory Rate, and Ventilation  In PNEUMA, the pathway from chemical drive to ventilation is detailed and complex, and it has no place in our simple model. Some of this complexity is needed to produce pressure and volume waveforms for individual breaths; luckily, our model will not be describing behaviour on such short timescales. To explore the relationship that PNEUMA produces between the chemical drive and quantities that are relevant to our model – namely, \( \phi \), \( v_T \), and \( f_R \) – we break the chemoreflex loop in PNEUMA and supply a constant chemical drive to the model. We then observe the mean ventilation, tidal volume, and respiratory rate that result from each chemical drive value we set. Since in our CSA simulation, the chemical drive oscillates between 0.18 and 2.11, we explore the range \([0, 2.2]\). The results are shown in Figure 3.11.
Figure 3.11: The steady-state mappings in PNEUMA from chemical drive ($d_{PNEUMA}$) to ventilation ($\dot{\phi}$), tidal volume ($v_T$), and respiratory rate ($f_R$).

Witness the effect of PNEUMA’s use of the Duffin model: when $d_{PNEUMA} < 0.80$, PNEUMA assigns to $f_R$ its basal value, but once the chemical drive exceeds the basal threshold, the respiratory rate grows linearly with $d_{PNEUMA}$. (Again, the higher, patterning threshold is never reached.) The steady-state $\dot{\phi}$-versus-$d_{PNEUMA}$ and $v_T$-versus-$d_{PNEUMA}$ plots are, as we expected, nonlinear. PNEUMA includes a drive threshold (dependent upon sleep state) below which there is no ventilation. Through PNEUMA’s sleep state-dependent drive scaling and thresholding, any particular chemical drive level will produce less ventilation in sleep than it would in wakefulness.\textsuperscript{11} Very low

\textsuperscript{11}It is not clear how PNEUMA’s developers selected their scaling-and-thresholding model and parameter values.
3.3. MODEL DETAILS

drive values produce apneas in sleep but not in wakefulness. This is consistent with the principle of
"wakefulness drive" that is associated with basal ventilation in [DMV+00]. However, while Duffin
et al. show a significant level of basal ventilation in wakefulness, there is no corresponding positive
floor for \( v_T \) and \( \phi \) in PNEUMA. For apneas to be possible, it must indeed be possible to have tidal
volume and ventilation fall to zero when the drive to ventilate is sufficiently low, so the minimum
possible \( v_T \) and \( \phi \) in sleep really should be zero. (That PNEUMA also allows this in wakefulness
conflicts with Duffin et al. However, since we are developing a model for central sleep apnea, we
can ignore the peculiarities of wakefulness drive.)

It may be that we need not include a nonzero drive threshold in our model at all; it may be
that the chemoreflex thresholds \( (P_{a,CO_2,TH}, S_{a,\text{O}_2,TH}, \text{ and } P_{b,\text{CO}_2,TH}, \text{ for instance}) \) model all the
necessary effects. If so, apneas would only appear when both the central and peripheral chemoreflex
components were silent. (This never occurs in our PNEUMA simulation, since \( p_{b,\text{CO}_2} \) there always
happens to be above \( P_{b,\text{CO}_2,TH} \).) Still, since both PNEUMA and the Duffin model do describe a
drive threshold below which the ventilatory response is flat, we include one, namely \( D_{TH} \geq 0 \), in
our model. However, we cannot really justify using distinct thresholds for respiratory rate versus
drive and tidal volume or ventilation versus drive.

Now, note in Figure 3.11 that the \( \phi \)-versus-\( d_{PNEUMA} \) characteristic above the drive threshold
may be approximated quite well by a straight line. Our form of the Khoo model simply has
\( \phi = d_{Khoo} \). Duffin et al. approximate the relationship between \( \phi \) and \( d_{Duffin} \) in the intermediate
drive regime by a line segment (as they do \( v_T \)-versus-\( d_{Duffin} \) and \( f_R \)-versus-\( d_{Duffin} \)). The real
point is that under isoxia, in the intermediate drive regime, ventilation is modelled in each case
as varying linearly with \( [p_{a,\text{CO}_2} - P_{a,\text{CO}_2,TH}]^+ \) for fixed \( p_{b,\text{CO}_2} \) and with \( [p_{b,\text{CO}_2} - P_{b,\text{CO}_2,TH}]^+ \) for
fixed \( p_{a,\text{CO}_2} \).

We will do this in our model as well, letting

\[
\phi = K_{d\phi} (d - D_{TH})^+ = \begin{cases} 
0 & \text{if } d \leq D_{TH} \\
K_{d\phi} (d - D_{TH}) & \text{if } d > D_{TH} 
\end{cases}
\tag{3.59}
\]

Also, note that the scaling and thresholding do impact all three plots in Figure 3.11, but only the breakpoint visible in
the respiratory rate plot depends upon both the Duffin-like basal threshold value used in PNEUMA and PNEUMA's
own drive scaling and thresholding.
where $K_{d\phi} > 0$ is the slope of the $\phi$-versus-$d$ characteristic above the drive threshold. (Note that the characteristic is continuous. Also, since apneas must be possible in our model, our "basal" ventilation is zero.)

Like the Duffin model (and PNEUMA's implementation of it), we also take $f_R$ to vary linearly with $d$, for $d > D_{TH}$:

$$f_R = \begin{cases} 
0 & \text{if } d \leq D_{TH} \\
K_{df} (d - D_{TH}) + F_{R, \text{basal}} & \text{if } d > D_{TH}
\end{cases}$$

where $K_{df} \geq 0$ is the slope of the $f_R$-versus-$d$ characteristic above the drive threshold, and $F_{R, \text{basal}} \geq 0$ is the respiratory rate "just above" the drive threshold. Obviously, we also have:

$$\nu_T = \begin{cases} 
0 & \text{if } d \leq D_{TH} \\
\frac{\phi}{f_R} & \text{if } d > D_{TH}
\end{cases}$$

**Alveolar Ventilation**

Alveolar ventilation is given by

$$\phi_A = [\phi - f_R V_D]^+$$

$$= \begin{cases} 
0 & \text{if } d \leq D_{TH} \\
[K_d \phi (d - D_{TH}) - [K_{df} (d - D_{TH}) + F_{R, \text{basal}}] V_D]^+ & \text{if } d > D_{TH}
\end{cases}$$

$$= \begin{cases} 
0 & \text{if } d \leq D_{TH} \\
[(K_d \phi - K_{df} V_D) (d - D_{TH}) - F_{R, \text{basal}} V_D]^+ & \text{if } d > D_{TH}
\end{cases}$$

$$= \begin{cases} 
0 & \text{if } d \leq D_{TH} + \frac{F_{R, \text{basal}} V_D}{K_{d\phi} - K_{df} V_D} \\
(K_d \phi - K_{df} V_D) (d - D_{TH}) - F_{R, \text{basal}} V_D & \text{if } d > D_{TH} + \frac{F_{R, \text{basal}} V_D}{K_{d\phi} - K_{df} V_D}
\end{cases}$$

$$= \begin{cases} 
0 & \text{if } d \leq D_{TH,A} \\
K_{d\phi,A} (d - D_{TH,A}) & \text{if } d > D_{TH,A}
\end{cases}$$

$$= K_{d\phi,A} [d - D_{TH,A}]^+$$
where $K_{d\phi,A} = K_{d\phi} - K_{df} V_D$ and $D_{TH,A} = D_{TH} + \frac{F_{R,basal} V_D}{K_{d\phi,A}}$, provided $K_{d\phi,A} > 0$. If $K_{d\phi,A} \leq 0$, then $\phi_A = 0$ for all $d$.$^{12}$

### 3.4 Model Parameters

Table 3.1: Parameter values for our pulmonary gas exchange plant ($P_A$) model.

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Normal Value</th>
<th>CSA Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{BS}$ (mmHg)</td>
<td>863</td>
<td></td>
<td>As explained in Section 3.3.1.</td>
</tr>
<tr>
<td>$P_I$ (mmHg)</td>
<td>0</td>
<td></td>
<td>Reflects the corresponding PNEUMA settings; inspired air contains very little carbon dioxide.</td>
</tr>
<tr>
<td>$C_v$ (mL CO$_2$/mL blood)</td>
<td>0.551</td>
<td>0.533</td>
<td>The mean value of the PNEUMA-simulated venous CO$_2$ concentration.</td>
</tr>
<tr>
<td>$Q$ (L/min)</td>
<td>5.08</td>
<td>4.38</td>
<td>The mean value of the PNEUMA-simulated volumetric systemic blood flow rate.</td>
</tr>
<tr>
<td>$V_A$ (L)</td>
<td>3.11</td>
<td>3.11</td>
<td>The mean value of the PNEUMA-simulated carbon dioxide storage volume of the lungs.</td>
</tr>
<tr>
<td>$F_{c,A}$ (mL CO$_2$/mL blood mmHg)</td>
<td>0.00506</td>
<td>0.00535</td>
<td>The slope of the least-squares line through the uniformly-sampled filtered PNEUMA-simulated ($p_A,c_A$) points.</td>
</tr>
<tr>
<td>$C_{A0}$ (mL CO$_2$/mL blood)</td>
<td>0.287</td>
<td>0.274</td>
<td>The $c_A$-axis intercept of the least-squares line through the uniformly-sampled filtered PNEUMA-simulated ($p_A,c_A$) points.</td>
</tr>
</tbody>
</table>

$^{12}$In this latter case (say, if $V_D$ is very large), even when the drive is large enough ($d > D_{TH}$) to produce ventilation, the tidal volume never exceeds the dead space volume. Hence (assuming as always no mixing in the dead space) the modelled subject only ever rebreathes dead space air. No fresh air ever reaches the alveoli, so $\phi_A = 0$. 

Table 3.2: Parameter values for our lung-to-carotid transport plant (\( P_a \)) model.

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Normal Value</th>
<th>CSA Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_a (s) )</td>
<td>9.96</td>
<td>16.2</td>
<td>Following the discussion in the “Overall Effect” subsection in Section 3.3.3...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In each case, we assign to ( \tau_{PNEUMA,a} ) and ( \tau_{PNEUMA,b} ) the values of the lung-to-carotid mixing time constants in PNEUMA (following the Lange model), and to ( D_{PNEUMA} ) the mean value of the PNEUMA-simulated lung-to-carotid (pure) transport delay.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the normal case, we assign to ( D_a ) the value for which the step response of a system governed by ( H_a(s) = e^{-sD_a} ) (our ( P_a ) model) best approximates the step response of a system governed by ( H_{a,PNEUMA}(s) = \frac{e^{-sD_{PNEUMA}}}{(\tau_{PNEUMA,a}s+1)(\tau_{PNEUMA,b}s+1)} ) (the corresponding PNEUMA model).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the CSA case, we assign to ( D_a ) the value for which, at the fundamental frequency of the filtered PNEUMA-simulated ( p_A ) waveform, the phase delay produced by ( H_a(s) ) matches that produced by ( H_{a,PNEUMA}(s) ).</td>
</tr>
<tr>
<td>( D_{a,1/1} (s) )</td>
<td>9.96</td>
<td>16.2 or 31.5</td>
<td>Following the discussion in the “Padé Approximation” subsection in Section 3.3.3...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the normal case, we set ( D_{a,1/1} = D_a ).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the CSA case, we may use ( D_{a,1/1} = D_a ). Alternatively, we could set the value of ( D_{a,1/1} ) so that, at the fundamental frequency of the filtered PNEUMA-simulated ( p_A ) waveform, the phase delay produced by ( H_{a,1/1}(s) ) matches that produced by ( H_a(s) ).</td>
</tr>
<tr>
<td>( D_{a,2/2} (s) )</td>
<td>9.96</td>
<td>16.2 or 16.7</td>
<td>Following the discussion in the “Padé Approximation” subsection in Section 3.3.3...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the normal case, we set ( D_{a,2/2} = D_a ).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the CSA case, we may use ( D_{a,2/2} = D_a ). Alternatively, we could set the value of ( D_{a,2/2} ) so that, at the fundamental frequency of the filtered PNEUMA-simulated ( p_A ) waveform, the phase delay produced by ( H_{a,2/2}(s) ) matches that produced by ( H_a(s) ).</td>
</tr>
</tbody>
</table>
3.4. MODEL PARAMETERS

Table 3.3: Parameter values for our cerebral gas exchange plant ($P_b$) model.

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Normal Value</th>
<th>CSA Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_b \left( \frac{\text{mL CO}_2}{100 \text{ g brain tissue-mmHg}} \right)$</td>
<td>0.36</td>
<td>Assigned the same value as the corresponding PNEUMA parameter.</td>
<td></td>
</tr>
<tr>
<td>$S \left( \frac{\text{mL CO}_2}{\text{mL blood-mmHg}} \right)$</td>
<td>0.0043</td>
<td>Assigned the same value as the corresponding PNEUMA parameter.</td>
<td></td>
</tr>
<tr>
<td>$M_b \left( \frac{\text{mL CO}_2}{100 \text{ g brain tissue-s}} \right)$</td>
<td>0.0439</td>
<td>Reflects the corresponding PNEUMA settings.</td>
<td></td>
</tr>
<tr>
<td>$H \left( \frac{\text{mL CO}_2}{100 \text{ g brain tissue-s}} \right)$</td>
<td>0.0183</td>
<td>Assigned the same value as the corresponding PNEUMA parameter.</td>
<td></td>
</tr>
<tr>
<td>$F_{q,b} \left( \frac{\text{mL CO}_2}{100 \text{ g brain tissue-s-mmHg}} \right)$</td>
<td>0.0354</td>
<td>The slope of the least-squares line fitted to PNEUMA's $q_b$-versus-$p_b$ curve – as defined by (3.15) – for $46 \text{ mmHg} \leq p_b \leq 52 \text{ mmHg}$.</td>
<td></td>
</tr>
<tr>
<td>$Q_{b0} \left( \frac{\text{mL CO}_2}{100 \text{ g brain tissue-s}} \right)$</td>
<td>-0.912</td>
<td>The $q_b$-intercept of the least-squares line fitted to PNEUMA's $q_b$-versus-$p_b$ curve – as defined by (3.15) – for $46 \text{ mmHg} \leq p_b \leq 52 \text{ mmHg}$.</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.4: Parameter values for our chemoreflex controller model. We choose our parameters so that, given filtered PNEUMA-simulated $p_a$, $p_b$, and $s_{a,O_2}$ waveforms as input, our drive function, $d(p_a,p_b)$ generates approximately the same waveform as PNEUMA's chemical drive function, $d_{PNEUMA}(p_a,p_b,s_{a,O_2})$.

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Normal Value</th>
<th>CSA Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{a,TH}$ (mmHg)</td>
<td>38</td>
<td></td>
<td>Assigned the same value as the corresponding PNEUMA parameter.</td>
</tr>
<tr>
<td>$P_{b,TH}$ (mmHg)</td>
<td>45</td>
<td></td>
<td>Assigned the same value as the corresponding PNEUMA parameter.</td>
</tr>
<tr>
<td>$G_b$ (mmHg$^{-1}$)</td>
<td>0.075</td>
<td></td>
<td>Assigned the same value as the corresponding PNEUMA parameter.</td>
</tr>
<tr>
<td>$G_a$ (mmHg$^{-1}$)</td>
<td>0.0290 0.218</td>
<td></td>
<td>Using the filtered PNEUMA-simulated $p_a$, $p_b$, and $s_{a,O_2}$ waveforms...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the CSA case – following the discussion in the “Peripheral Chemoreflex Component Response to Oxygen” subsection in Section 3.3.4 – we divide the amplitude of the $d_{PNEUMA,a}(p_a,p_b,s_{a,O_2})$ waveform by that of $\max(0,p_a - P_{a,TH})$.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• In the normal case, we divide the mean value of $d_{PNEUMA,a}(p_a,p_b,s_{a,O_2})$ by that of $\max(0,p_a - P_{a,TH})$.</td>
</tr>
</tbody>
</table>
### 3.4. MODEL PARAMETERS

Table 3.5: Parameter values for our ventilation plant model.

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{TH}$</td>
<td>0.0930</td>
<td>From the $(K_{d\phi}, D_{TH})$ value assignment that was found to minimize the sum of squared differences between $K_{d\phi}$ max $(0, d - D_{TH})$ and $\phi$ over all the points in the steady-state, open-loop $\phi$-versus-$d$ characteristic in Figure 3.11.</td>
</tr>
<tr>
<td>$K_{d\phi}$ ($\frac{1}{\text{min}}$)</td>
<td>9.69</td>
<td>From the $(K_{d\phi}, D_{TH})$ value assignment that was found to minimize the sum of squared differences between $K_{d\phi}$ max $(0, d - D_{TH})$ and $\phi$ over all the points in the steady-state, open-loop $\phi$-versus-$d$ characteristic in Figure 3.11.</td>
</tr>
<tr>
<td>$K_{df}$ ($\frac{\text{breaths}}{\text{min}}$)</td>
<td>2.91</td>
<td>The slope of the increasing linear part of the $f_R$-versus-$d$ characteristic shown in Figure 3.11.</td>
</tr>
<tr>
<td>$F_{R,\text{basal}}$ ($\frac{\text{breaths}}{\text{min}}$)</td>
<td>10.5</td>
<td>The $f_R$ value at $d = D_{TH}$ along the extended line through the increasing linear part of the $f_R$-versus-$d$ characteristic shown in Figure 3.11. (Our $f_R$-versus-$d$ characteristic differs from the PNEUMA (or Duffin) version. Our model allows for only one drive threshold, and we have chosen to use the threshold associated with $\phi$ rather than that associated with $f_R$. We then set the values of $K_{df}$ and $F_{R,\text{basal}}$ to agree with certain aspects of the PNEUMA $f_R$-versus-$d$ characteristic. The roughness of this approximation should not cause any significant problems, considering in particular the shallowness of the PNEUMA $f_R$-versus-$d$ characteristic: over the range of $d$ values of interest, $f_R$ varies much less relative to its central value than does $\phi$.)</td>
</tr>
<tr>
<td>$V_D$ (mL)</td>
<td>150</td>
<td>Reflects the corresponding PNEUMA settings.</td>
</tr>
</tbody>
</table>

#### 3.4.1 The System Operating Point

Recall that we must select a suitable equilibrium point of our nonlinear model of $P_A$ as the operating point $(\phi_A, p_A) = (\Phi_{A,\text{OP}}, P_{A,\text{OP}})$ about which we construct our linearized model. The resulting
A NEW, SIMPLE MODEL

model provides a reasonable approximation of the nonlinear model in the vicinity of this operating point. The same goes for \( P_b \) and the corresponding operating point, \( (p_a, p_b) = (P_{a,OP}, P_{b,OP}) \).

Considering now the full closed-loop system, we should select \( (\Phi_{A,OP}, P_{A,OP}, P_{a,OP}, P_{b,OP}) \) corresponding not only to equilibrium states of \( P_A \) and \( P_b \) in isolation, but to an equilibrium state of the whole system.

Locating the Operating Point by Solving a System of Equations

Recall from (3.4) the equilibrium condition for our nonlinear model of \( P_A \):

\[
\Phi_{A,OP} = \frac{P_{BS}Q (C_v - F_{c,A} P_{A,OP} - C_{A0})}{P_{A,OP} - P_l}.
\]  

(3.62)

The corresponding condition for \( P_b \), from (3.16), is

\[
P_{a,OP} = P_{b,OP} + \frac{H - M_b}{S (F_{q,b} P_{b,OP} + Q_{b0})}.
\]  

(3.63)

Now, consider our \( P_a \) model, which represents a pure delay. If its input were \( P_{A,OP} \) for all time, then its output would be \( P_{A,OP} \) also, for all time.

Clearly, then, \( (\Phi_{A,OP}, P_{A,OP}, P_{a,OP}, P_{b,OP}) \) represents an equilibrium state of the system shown in Figure 3.12 if and only if (3.62), (3.63), and

\[
P_{A,OP} = P_{a,OP}
\]  

(3.64)

all hold. These conditions together provide the equilibrium condition for \( (\Phi_{A,OP}, P_{b,OP}) \) determined by the model plants\(^{13}\):

\[
\Phi_{A,OP} = \frac{P_{BS}Q (C_v - F_{c,A} \left[ P_{b,OP} + \frac{H - M_b}{S (F_{q,b} P_{b,OP} + Q_{b0})} \right] - C_{A0})}{P_{b,OP} + \frac{H - M_b}{S (F_{q,b} P_{b,OP} + Q_{b0})} - P_l}
\]  

(3.65)

\(^{13}\)Excluding the ventilation plant.
3.4. MODEL PARAMETERS

Figure 3.12: The subsystem made up of the gas exchange and transport model systems.

Now, since \( d_a = G_a[p_a - P_{a,TH}]^+ \), \( d_b = G_b[p_b - P_{b,TH}]^+ \), \( d = d_a + d_b \), and \( \phi_A = K_{d\phi,A}[d - D_{TH,A}]^+ \), therefore \((\Phi_{A,OP}, P_{A,OP}, P_{a,OP}, P_{b,OP})\) represents an equilibrium state of the complete closed-loop model system if and only if in addition to (3.62), (3.63), and (3.64), we also have

\[
\Phi_{A,OP} = K_{d\phi,A}[D_{OP} - D_{TH,A}]^+, \quad (3.66)
\]

where

\[
D_{OP} = D_{a,OP} + D_{b,OP} \quad (3.67)
\]
\[
D_{a,OP} = G_a[p_{a,OP} - P_{a,TH}]^+ \quad (3.68)
\]
\[
D_{b,OP} = G_b[p_{b,OP} - P_{b,TH}]^+ \quad (3.69)
\]

(These are the values of \( d, d_a, \) and \( d_b \), respectively, when \( p_a = P_{a,OP} \) and \( p_b = P_{b,OP} \)).

Now, (3.66) – (3.69) and (3.63) together provide the equilibrium condition for \((\Phi_{A,OP}, P_{b,OP})\) determined by the chemoreflex controller\(^\text{14}\):

\[
\Phi_{A,OP} = K_{d\phi,A}\left[G_a\left[P_{b,OP} + \frac{H - M_b}{S(P_{q,b}P_{b,OP} + Q_{b,0})} - P_{a,TH}\right]^+ + G_b\langle P_{b,OP} - P_{b,TH} - D_{TH,A}\rangle^+\right] \quad (3.70)
\]

The common solutions of (3.65) and (3.70) form the set of all the system's equilibrium points in the \((\phi_A, p_b)\) plane. Each such point corresponds to exactly one equilibrium state; the values of all other signals in the system may be uniquely determined from \(\Phi_{A,OP}\) and \(P_{b,OP}\) using (3.63), (3.64), (3.69), (3.68), and (3.67).

Using either the "normal" or "CSA" parameter values presented in Section 3.4, we find only one valid common solution of (3.65) and (3.70), and therefore only one valid equilibrium state.\(^\text{15}\)

\(^{14}\)Along with the ventilation and cerebral gas exchange plants.

\(^{15}\)We solved the system graphically.
(An additional solution to the equations does exist, but it lies well outside the range of validity of our model of cerebral blood flow autoregulation. At this inadmissible solution, \( p_b \) is so low that \( F_{q,b}p_b + Q_{bo} \) is negative.)

**Locating the Operating Point by Simulation**

In the "normal" case, the appropriate equilibrium operating point for the model system is just the constant steady state toward which the nonlinear model system tends. Therefore, to determine the equilibrium operating state, we may simply simulate the nonlinear model system (under "normal" parameter values) over a period of time long enough for each simulated model variable to level off (i.e., converge in value to within an acceptably narrow band). For this simulation, we may choose initial conditions \( p_A(0), p_a(0), \) and \( p_b(0) \) approximately equal to the mean values at steady state of the corresponding system variables in our PNEUMA simulation.

We cannot apply a similar approach to the "CSA" case, since (as we hoped) the nonlinear CSA model system (i.e., the nonlinear model system with "CSA" parameter values applied) typically tends toward a nonconstant periodic steady state. However, suppose we modify our nonlinear CSA model by letting \( p_a = P_a \) describe our model of \( P_a. \)\(^{16}\) Recall that at equilibrium, the output of \( P_a \) is equal to its input. Therefore the equilibria of the modified nonlinear CSA model system must be identical to those of the original nonlinear CSA model system. However, being delay-free, the modified system is far less prone to instability in the form of sustained oscillations. We therefore have a good chance of being able to locate the operating point for the "CSA" case by simply simulating the modified nonlinear CSA model system.

**Operating Point Estimates**

We located the equilibrium operating points of our model system under normal and CSA conditions. In each case, the system-of-equations method and the simulation method just described produced identical results. These results are presented in Table 3.6.

\(^{16}\)Equivalently, we could simply set \( D_a = 0 \) or replace our \( P_a \) block with a "wire".
3.5 Simulation Results

We implemented our model in Simulink, set its parameters according to the values listed in Section 3.4 for CSA, assigned initial conditions slightly offset from the equilibrium state, then ran the simulation. Figure 3.13 shows the resulting waveforms, along with the corresponding waveforms from the PNEUMA CSA simulation. Our $\phi_A$, $p_A$, and $d$ waveforms agree nicely with those generated by PNEUMA. The periods of oscillation of our waveforms appear to very nearly match those of the PNEUMA waveforms. The $p_a$ and $p_b$ waveforms generated by our model have lower mean values and greater amplitudes than the corresponding PNEUMA waveforms. (On our multibreath timescale, the same is to some degree true of the two $p_A$ waveforms as well.)

These results are very encouraging, but we would expect to see much better agreement between the two sets of waveforms if the parameters of our model were estimated by systematically fitting the model to the (filtered) PNEUMA waveforms.

### Table 3.6: Equilibrium operating points for our model.

<table>
<thead>
<tr>
<th>System Variable (Units)</th>
<th>Normal Operating Point</th>
<th>CSA Operating Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi_A$ (\text{mmHg})</td>
<td>44.7</td>
<td>40.3</td>
</tr>
<tr>
<td>$p_A$ (mmHg)</td>
<td>51.3</td>
<td>47.9</td>
</tr>
<tr>
<td>$p_a$ (mmHg)</td>
<td>0.194</td>
<td>0.491</td>
</tr>
<tr>
<td>$d_a$</td>
<td>0.471</td>
<td>0.215</td>
</tr>
<tr>
<td>$d$</td>
<td>0.665</td>
<td>0.706</td>
</tr>
</tbody>
</table>
3.5.1 Incorporating Padé Approximants

We now consider four variants of our model, in which the pure-delay lung-to-carotid transport model is replaced by (1) the order 1/1 Padé-based model with $D_{a,1/1} = D_a$, (2) the order 1/1 model with $D_{a,1/1}$ adjusted as described in Section 3.4, (3) the order 2/2 Padé-based model with $D_{a,2/2} = D_a$, and (4) the order 2/2 model with $D_{a,2/2}$ adjusted as described in Section 3.4. These results, along with those already shown in Figure 3.13, are presented in Figure 3.14.
3.5. SIMULATION RESULTS

Figure 3.14: Simulation results from our model when Padé-approximated transport models are used.

The model variant in which the order 2/2 lung-to-carotid transport model is used produces waveforms that quite closely resemble the waveforms generated by PNEUMA and our original model. Our adjustment to $D_{a,2/2}$ has proven unhelpful: the fundamental period of the corresponding waveforms is a little too long. The fundamental period of the waveforms produced using the unadjusted order 1/1 model is too short, and the apnea duration-to-period ratio too great. Our $D_{a,1/1}$ adjustment renders the fundamental period too long and does not improve the apnea-to-period ratio. Furthermore, the amplitudes of the waveforms in this case are far too large.

We conclude that the order 2/2 Padé-based lung-to-carotid transport model may serve as a
reasonable substitute for the pure-delay model. The order $1/1$ model, on the other hand, performs very badly. Finally, our suggested adjustments to $D_{a,1/1}$ and $D_{a,2/2}$ do not bring our model variants into closer agreement with the original model or PNEUMA. Therefore, for the rest of this thesis, we use $d_a$, unadjusted, in all Padé approximants.

### 3.5.2 Using Linearized Plant Models

In Figure 3.15, we show the waveforms produced when we simulate our model with one or both of the pulmonary and cerebral gas exchange plant models replaced by their linearized analogues. We also show the waveforms produced by PNEUMA and our original model.

Figure 3.15: Simulation results from our model when linearized gas exchange models are used.
We observe that using the linearized cerebral gas exchange plant in place of the full nonlinear model has virtually no effect on the model variables. Linearizing the pulmonary gas exchange plant model has a noticeable but small effect. Finally, we observe that the $p_h$ waveforms generated by our model do not oscillate around the equilibrium operating point, but below it.
3.5. SIMULATION RESULTS
Chapter 4

Stability Analysis

4.1 Linear Stability Analysis

4.1.1 The Linearized Model

For any signal $x(t)$ in our model system:

- Define $\bar{x} = x - X_{OP}$: the signal’s excursion from the associated operating point, $X_{OP}$.

- Define $X(s) = \int_{-\infty}^{+\infty} e^{-st} x(t) dt$: the (bilateral) Laplace transform of $x(t)$.

For any system whose dynamics are described by a rational transfer function $H(s)$, let $\alpha(s)$ and $\beta(s)$ denote coprime polynomials $\sum_{k=0}^{m} \alpha_k s^k$ and $\sum_{k=0}^{n} \beta_k s^k$, respectively, that satisfy $H(s) = \frac{\alpha(s)}{\beta(s)}$.

We will first examine the small-signal stability of the closed-loop system through a linear analysis. This will involve investigating the behaviour of a linearized model of the system about an equilibrium operating point. Specifically, we will use the Routh-Hurwitz stability criterion, which is applied to the characteristic polynomial associated with the linear model. We must therefore describe each dynamical element of our model as a system governed by a rational transfer function whose input and output signals represent excursions from an equilibrium operating point of the nonlinear closed-loop model system.

We begin by defining suitable dynamical plant models:

- Let $\tilde{P}_A$, with input $\tilde{A}$ and output $\tilde{p}_A$, represent our linearized pulmonary gas exchange plant model. From (3.10), we have $\alpha_A(s) = -K_A$ and $\beta_A(s) = \tau_A s + 1$, where $K_A$ and $\tau_A$ are
positive and finite.

- Let $\tilde{P}_b$, with input $\tilde{p}_a$ and output $\tilde{p}_b$, represent our linearized cerebral gas exchange plant model. From (3.24), we have $\alpha_b(s) = K_b$ and $\beta_b(s) = \tau_b s + 1$, where $K_b$ and $\tau_b$ are positive and finite.

- Let $P_{a,m/n}$, with input $p_A$ and output $p_a$, represent a lung-to-carotid transport plant model whose dynamics are described by $\alpha_{a,m/n}(s)$ and $\beta_{a,m/n}(s)$ — the numerator and denominator polynomials, respectively, in the order $m/n$ Padé approximant of $e^{-D_{a,m/n}s}$, where $D_{a,m/n}$ is positive and finite. Have $m \leq n^1$. For example:

  - For $P_{a,1/1}$, $\alpha_{a,1/1}(s) = -\frac{1}{2}D_{a,1/1}s + 1$ and $\beta_{a,1/1}(s) = \frac{1}{2}D_{a,1/1}s + 1$, corresponding to the transfer function $H_{a,1/1}(s)$ defined in (3.48).

  - For $P_{a,2/2}$, $\alpha_{a,2/2}(s) = \frac{1}{12}D_{a,2/2}s^2 - \frac{1}{2}D_{a,2/2}s + 1$ and $\beta_{a,2/2}(s) = \frac{1}{12}D_{a,2/2}s^2 + \frac{1}{2}D_{a,2/2}s + 1$, corresponding to the transfer function $H_{a,2/2}(s)$ defined in (3.49).

Let $\tilde{P}_{a,m/n}$ represent the equivalent model with input $\tilde{p}_A$ and output $\tilde{p}_a$. The polynomials $\alpha_{a,m/n}(s)$ and $\beta_{a,m/n}(s)$ still describe the dynamics of this linearized model block, since the original system was already linear and time-invariant.

The hard nonlinearities corresponding to apneic and drive thresholds cannot appear in our linear model, so suppose that $P_{a,OP} > P_{a,TH}$, $P_{b,OP} > P_{b,TH}$, and $G_a(P_{a,OP} - P_{a,TH}) + G_b(P_{b,OP} - P_{b,TH}) > D_{TH,A}$. Our operating point, and the set of states sufficiently close to the operating point, then reside in the regime where $d_a = G_a(p_a - P_{a,TH})$, $d_b = G_b(p_b - P_{b,TH})$, and $\phi_A = K_{d\phi,A}(d - D_{TH,A})$.

The controller gains, $G_a$ and $G_b$, and the ventilation plant gain, $K_{d\phi,A}$, are positive and finite.

Finally, we introduce a disturbance signal, $w_{d\phi,A}$, which contributes additively to the alveolar ventilation.

We may now assemble the model shown in Figure 4.1.

\footnote{Otherwise the transfer function will be improper and the model plant unstable.}
4.1. LINEAR STABILITY ANALYSIS

In Figure 4.2, we show the corresponding small-signal model, in which all signals represent (sufficiently small) excursions from the equilibrium operating point of the system.\(^2\)

\[^2\text{It is easy to see that the two block diagrams are equivalent. In particular, note that}\]

- \(\tilde{d}_a = G_a\tilde{p}_a\) because \(D_{a,OP} = G_a(P_{a,OP} - P_{a,TH})\),
- \(\tilde{d}_b = G_b\tilde{p}_b\) because \(D_{b,OP} = G_b(P_{b,OP} - P_{b,TH})\),
- \(\tilde{d} = \tilde{d}_a + \tilde{d}_b\) because \(D_{OP} = D_{a,OP} + D_{b,OP}\), and
- \(\tilde{\phi}_A = K_{d\phi,A}\tilde{d} + w_{\phi,A}\) because \(\Phi_{A,OP} = K_{d\phi,A}(D_{OP} - D_{TH,A})\).
CHAPTER 4. STABILITY ANALYSIS

Let \( \mathcal{S} \) denote this system. Suppose it is initially at rest. That is, suppose that \( \mathcal{S} \) is at equilibrium (i.e., all signals are zero) until it is disturbed (i.e., until \( w_{\phi,A} \) becomes nonzero). Then:

\[
\begin{align*}
\tilde{P}_A &= \frac{\alpha_A}{\beta_A} \tilde{\Phi}_A \\
\tilde{P}_a &= \frac{\alpha_a}{\beta_a} \tilde{P}_A = \frac{\alpha_a \alpha_A}{\beta_a \beta_A} \tilde{\Phi}_A \\
\tilde{P}_b &= \frac{\alpha_b}{\beta_b} \tilde{P}_a = \frac{\alpha_b \alpha_a \alpha_A}{\beta_b \beta_a \beta_A} \tilde{\Phi}_A \\
\tilde{D}_a &= G_a \tilde{P}_a = \frac{G_a \alpha_a \alpha_A}{\beta_a} \tilde{\Phi}_A \\
\tilde{D}_b &= G_b \tilde{P}_b = \frac{G_b \alpha_b \alpha_a \alpha_A}{\beta_b \beta_a \beta_A} \tilde{\Phi}_A \\
\tilde{D} &= \tilde{D}_a + \tilde{D}_b = \frac{G_a \beta_b + G_b \alpha_b}{\beta_b \beta_a \beta_A} \alpha_a \alpha_A \tilde{\Phi}_A
\end{align*}
\]

Now at last we determine \( \tilde{\Phi}_{A,w_{\phi,A}} \), the transfer function from \( w_{\phi,A} \) to \( \tilde{\phi}_A \):

\[
\tilde{\Phi}_A = K_{d\phi,A} \tilde{D} + W_{\phi,A} = K_{d\phi,A} (G_a \beta_b + G_b \alpha_b) \alpha_a \alpha_A \tilde{\Phi}_A + W_{\phi,A}
\]

\[
W_{\phi,A} = \tilde{\Phi}_A \left( 1 - \frac{K_{d\phi,A} (G_a \beta_b + G_b \alpha_b) \alpha_a \alpha_A}{\beta_b \beta_a \beta_A} \right)
\]

\[
\tilde{\Phi}_A = \frac{\beta_b \beta_a \beta_A - K_{d\phi,A} (G_a \beta_b + G_b \alpha_b) \alpha_a \alpha_A}{\beta_b \beta_a \beta_A - K_{d\phi,A} (G_a \beta_b + G_b \alpha_b) \alpha_a \alpha_A}
\]

4.1.2 Stability of the Linear Model System

The Characteristic Polynomial

Note that there are no pole-zero cancellations among the dynamical elements in the system, \( \tilde{P}_A \), \( \tilde{P}_{a,m/n} \), and \( \tilde{P}_b \). That is, \( \alpha_A \alpha_a \alpha_b \) and \( \beta_A \beta_a \beta_b \) have no common zeros.\(^3\) The right-hand side of (4.1) is therefore a rational function in “lowest terms”. Let \( \chi(s) \) denote the denominator polynomial:

\[
\chi = \beta_b \beta_a \beta_A - K_{d\phi,A} (G_a \beta_b + G_b \alpha_b) \alpha_a \alpha_A
\]

\(^3\)Unless by some coincidence \( \alpha_{a,m/n} \) shared a zero with either \( \beta_A = r_A s + 1 \) or \( \beta_b = r_b s + 1 \). This is actually impossible if \( m = n = 1 \), since \( \alpha_{a,1/1} \) has only a positive zero while the only zero of each of \( \beta_A \) and \( \beta_b \) is negative. It is also impossible when \( m = n = 2 \), since \( \alpha_{a,2/2} \) has no real zeros.
4.1. LINEAR STABILITY ANALYSIS

Since all the system’s dynamic elements are included in the feedback loop(s) and there are no pole-zero cancellations, none of the characteristic modes of the system are hidden from the “input” \( w_{\phi,A} \) or the “output” \( \phi_A \).\(^4\) In other words, the system with input \( w_{\phi,A} \) and output \( \phi_A \) is completely controllable and observable. As a result, the poles of the transfer function \( \frac{\phi_A}{w_{\phi,A}} \), namely the zeros of \( \chi \), describe all the characteristic modes of the system. Hence, the system is internally asymptotically stable if and only if the real part of each of the zeros of \( \chi \) is negative.

Before we begin examining the locations of the zeros of \( \chi \) in the complex plane, we define the open left half plane (OLHP) and open right half plane (ORHP) as follows: the OLHP (ORHP) is the region of the complex plane that represents the set of complex numbers with negative (positive) real parts. The imaginary axis bisects the complex plane into the OLHP and ORHP. We will sometimes refer to zeros residing in the OLHP (ORHP) as OLHP (ORHP) zeros.

We now examine \( \chi \), the characteristic polynomial of \( \tilde{S} \). In the case \( m = n = 1 \) with \( D_{a,1/1} = D_a \), we have:

\[
\chi(s) = (\tau_b s + 1) \left( \frac{1}{2} D_a s + 1 \right) (\tau_A s + 1) - K_{d\phi,A} [G_a (\tau_b s + 1) + G_b K_b] \left( -\frac{1}{2} D_a s + 1 \right) (-K_A)
\]

\[
= \chi_3 s^3 + \chi_2 s^2 + \chi_1 s + \chi_0
\]

where

\[
\chi_3 = \frac{1}{2} D_a \tau_A \tau_b 
\]

\[
\chi_2 = \tau_A \tau_b + \frac{1}{2} D_a \tau_A + \frac{1}{2} D_a \tau_b - \frac{1}{2} G'_a D_a \tau_b 
\]

\[
\chi_1 = \frac{1}{2} D_a + \tau_A + \tau_b - \frac{1}{2} G'_a D_a + G'_b \tau_b - \frac{1}{2} G'_b D_a
\]

\[
\chi_0 = G'_a + G'_b + 1
\]

with \( G'_a = G_a K_{d\phi,A} K_A \) and \( G'_b = G_b K_{d\phi,A} K_A K_b \). (Recall that \( K_{d\phi,A} \) denotes the gain of the ventilation plant, while \( K_A \) and \( K_b \) denote the DC gains of the linearized pulmonary and cerebral gas exchange plant models, respectively.) Note that \( D_a, \tau_A, \) and \( \tau_b \) are all positive, so \( \chi_3 \) is positive. Also, since \( G_a, G_b, K_{d\phi,A}, K_A, \) and \( K_b \) are all positive, it follows that \( G'_a \) and \( G'_b \) are positive, so

\(^4\)Witness that \( \tilde{P}_A \) and \( \tilde{P}_b \) are first-order linear systems, while \( \tilde{P}_a \) is an \( n \)th-order linear system. The degree of the denominator of the irreducible transfer function in (4.1) is \( n + 2 \).
The parameter values listed in Section 3.4 yield

- in the normal case, \( \tau_b = 74.1 \) s, \( \tau_A = 7.25 \) s \( \approx \frac{1}{15} \tau_b \), and \( \frac{1}{2}D_a = 4.98 \) s \( \approx \frac{1}{15} \tau_b \);

- in the CSA case, \( \tau_b = 79.8 \) s, \( \tau_A = 7.55 \) s \( \approx \frac{1}{15} \tau_b \), and \( \frac{1}{2}D_a = 8.1 \) s \( \approx \frac{1}{15} \tau_b \).

If we assume that \( \tau_b \gg \tau_A \) and \( \tau_b \gg \frac{1}{2}D_a \) generally in cases of interest to us, we obtain simplified expressions for \( \chi_2 \) and \( \chi_1 \):

\[
\chi_2 = \tau_A \tau_b + \frac{1}{2} D_a \tau_A + \frac{1}{2} D_a \tau_b - \frac{1}{2} G'_a D_a \tau_b = \tau_A \left( \tau_b + \frac{1}{2} D_a \right) + \frac{1}{2} D_a \tau_b - \frac{1}{2} G'_a D_a \tau_b \\
\approx \tau_A \tau_b + \frac{1}{2} D_a \tau_b - \frac{1}{2} G'_a D_a \tau_b \\
= \left[ \tau_A + \frac{1}{2} D_a \left( 1 - G'_a \right) \right] \tau_b
\]

(4.6)

\[
\chi_1 = \frac{1}{2} D_a + \tau_A + \tau_b - \frac{1}{2} G'_a D_a + G'_a \tau_b - \frac{1}{2} G'_b D_a \\
= \left( \frac{1}{2} D_a + \tau_A + \tau_b \right) + G'_a \left( -\frac{1}{2} D_a + \tau_b \right) - \frac{1}{2} G'_b D_a \\
\approx \tau_b + G'_a \tau_b - \frac{1}{2} G'_b D_a \\
= (1 + G'_a) \tau_b - \frac{1}{2} G'_b D_a
\]

(4.7)

**Determining Stability from the Characteristic Polynomial**

We now apply the Routh-Hurwitz criterion, which states that the number of zeros of \( \chi \) that have positive real part is equal to the number of sign changes in the second (middle) column of the Routh array for \( \chi(s) \) shown in Table 4.1.

**Table 4.1: The Routh array.**

| \( s^3 \) | \( \gamma_{0,1} = \chi_3 \) | \( \gamma_{0,2} = \chi_1 \) |
| \( s^2 \) | \( \gamma_{1,1} = \chi_2 \) | \( \gamma_{1,2} = \chi_0 \) |
| \( s^1 \) | \( \gamma_{2,1} = \chi_1 - \frac{\lambda_2 \lambda_0}{\lambda_1} \) |
| \( s^0 \) | \( \gamma_{3,1} = \chi_0 \) |

If we assume that \( \gamma_{1,1} \) and \( \gamma_{2,1} \) are nonzero, then there are four possible cases, shown in Table
4.1. LINEAR STABILITY ANALYSIS

4.2.

Table 4.2: Four possible sign sequences for the second column of the Routh array.

<table>
<thead>
<tr>
<th>Case</th>
<th>( \gamma_{0,1} )</th>
<th>( \gamma_{1,1} )</th>
<th>( \gamma_{2,1} )</th>
<th>( \gamma_{3,1} )</th>
<th>Number of ORHP Zeros of ( \chi ) = Number of Sign Changes in the Sequence ((\gamma_{0,1}, \gamma_{1,1}, \gamma_{2,1}, \gamma_{3,1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>2</td>
</tr>
</tbody>
</table>

Now to address some boundary cases:

- If \( \gamma_{1,1} = \chi_2 = 0 \), then obviously \( \gamma_{2,1} = \chi_1 - \frac{\chi_2 \chi_0}{\chi_2} \neq 0 \). In this case, we may replace \( \chi_2 \) by \( \epsilon \) in the Routh array. We then observe that as \( \epsilon \) approaches zero from above, \( \gamma_{1,1} = \epsilon \) approaches zero from above, while \( -\gamma_{2,1} = -\chi_1 + \frac{\chi_2 \chi_0}{\epsilon} \) increases without bound. This approach gives the sign sequence \((+, +, -, +)\) for \((\gamma_{0,1}, \gamma_{1,1}, \gamma_{2,1}, \gamma_{3,1})\). There are two sign changes in this sequence, so \( \chi \) has two zeros with positive real parts when \( \gamma_{1,1} = 0 \).

- If \( \gamma_{2,1} = \chi_1 - \frac{\chi_2 \chi_0}{\chi_2} = 0 \), then \( \chi_1 \neq 0 \) and \( \gamma_{1,1} = \chi_2 \neq 0 \).

- \( \chi \) cannot have a zero at the origin since \( \chi_0 \neq 0 \).

- Note that \( \chi \) has a purely imaginary zero at \( j\omega \) iff \( \chi_3 (j\omega)^3 + \chi_2 (j\omega)^2 + \chi_1 (j\omega) + \chi_0 = 0 \) and \( \omega^2 \in \mathbb{R}^+ \).

\[
\chi_3 (j\omega)^3 + \chi_2 (j\omega)^2 + \chi_1 (j\omega) + \chi_0 = 0 \text{ and } \omega^2 \in \mathbb{R}^+ \\
\Leftrightarrow -j\chi_3 \omega^3 - \chi_2 \omega^2 + j\chi_1 \omega + \chi_0 = 0 \text{ and } \omega^2 \in \mathbb{R}^+ \\
\Leftrightarrow \chi_0 = \chi_2 \omega^2 \text{ and } \chi_1 \omega = \chi_3 \omega^3 \text{ and } \omega^2 \in \mathbb{R}^+ \\
\Leftrightarrow \chi_0 = \chi_2 \omega^2 \text{ and } \chi_1 = \chi_3 \omega^2 \text{ and } \omega^2 \in \mathbb{R}^+ \\
\Leftrightarrow \omega = \pm \sqrt[3]{\frac{\chi_1}{\chi_3}} = \pm \sqrt[3]{\frac{\chi_0}{\chi_2}} \text{ and } \chi_0 \chi_3 = \chi_1 \chi_2 \text{ and } \chi_1 \chi_2 > 0 \\
\Leftrightarrow \omega = \pm \sqrt[3]{\frac{\chi_1}{\chi_3}} = \pm \sqrt[3]{\frac{\chi_0}{\chi_2}} \text{ and } \gamma_{2,1} = 0 \text{ and } \chi_1 \chi_2 > 0
\]

So \( \chi \) has a purely imaginary zero iff \( \gamma_{2,1} = 0 \) and \( \chi_1 > 0 \) (or equivalently, iff \( \gamma_{2,1} = 0 \) and \( \chi_2 > 0 \)). If this condition is met, then \( \chi \) has exactly two purely imaginary zeros, and they form
CHAPTER 4. STABILITY ANALYSIS

a nonzero complex conjugate pair: \( \pm j \sqrt{\frac{x_1}{x_3}} \left( = \pm j \sqrt{\frac{x_0}{x_2}} \right) \). (Note that there is no possibility of zeros with multiplicity greater than one on the imaginary axis.) We can then easily find that the remaining zero, which is real and negative, is \(-\frac{x_2}{x_3} \left( = -\frac{x_0}{x_1} \right)\).

- Note that if \( \gamma_{2,1} = 0 \), then \( \chi_1 = \frac{x_3 x_0}{x_2} \), and hence:

\[
\chi(s) = x_3 s^3 + x_2 s^2 + \frac{x_3 x_0}{x_2} s + x_0 \\
= s^2 \left( x_3 s + x_2 \right) + \frac{x_0}{x_2} \left( x_3 s + x_2 \right) \\
= \left( s^2 + \frac{x_0}{x_2} \right) \left( x_3 s + x_2 \right)
\]

So:

- As already mentioned, if \( \gamma_{2,1} = 0 \) and \( \frac{x_0}{x_2} > 0 \) (or equivalently, if \( \gamma_{2,1} = 0 \) and \( x_2 > 0 \), or again equivalently, if \( \gamma_{2,1} = 0 \) and \( x_1 > 0 \)), then the zeros are \( \pm j \sqrt{\frac{x_0}{x_2}} \left( = \pm j \sqrt{\frac{x_1}{x_3}} \right) \) and \( -\frac{x_2}{x_3} \left( = -\frac{x_0}{x_1} \right) \).

- However, if \( \gamma_{2,1} = 0 \) and \( \frac{x_0}{x_2} < 0 \) (or equivalently, if \( \gamma_{2,1} = 0 \) and \( x_2 < 0 \), or again equivalently, if \( \gamma_{2,1} = 0 \) and \( x_1 < 0 \)), then \( \chi \) has three real zeros, one negative and two positive: \(-\sqrt{-\frac{x_1}{x_3}} \left( = -\sqrt{-\frac{x_0}{x_2}} \right), \sqrt{-\frac{x_1}{x_3}} \left( = \sqrt{-\frac{x_0}{x_2}} \right), \) and \( -\frac{x_2}{x_3} \left( = -\frac{x_0}{x_1} \right) \).

(These are the only two possible cases for \( \gamma_{2,1} = 0 \).)

Also, note that:

- Since \( x_3, x_2, x_1, \) and \( x_0 \) are all real, it follows that if \( \chi \) has a zero, \( s_0 \), whose imaginary part is nonzero, then the three zeros of \( \chi \) are distinct: one is \( s_0 \), another is the complex conjugate of \( s_0 \), and the third is real.

- If \( \chi \) has exactly two zeros with positive real parts, then the third zero must be real and negative.

- If \( \gamma_{1,1} > 0 \) and \( \gamma_{2,1} > 0 \), then according to Table 4.2, \( \chi \) has no zeros with positive real parts. This implies that \( \chi \) has three zeros with negative real parts, since there cannot be any purely imaginary zeros when \( \gamma_{2,1} \neq 0 \).
Table 4.3 summarizes the results of our discussion so far. Note that the cases in the table are mutually exclusive and exhaustive.

Table 4.3: Characteristics of zeros implied by signs of Routh array elements.

<table>
<thead>
<tr>
<th>If...</th>
<th>...then...</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_{1,1} &gt; 0$ and $\gamma_{2,1} &gt; 0$</td>
<td>All three zeros of $\chi$ have negative real parts.</td>
</tr>
<tr>
<td>$\gamma_{1,1} &gt; 0$ and $\gamma_{2,1} &lt; 0$</td>
<td>Two zeros of $\chi$ have positive real parts. The remaining zero is real and negative.</td>
</tr>
<tr>
<td>$\gamma_{1,1} &lt; 0$ and $\gamma_{2,1} &gt; 0$</td>
<td>Two zeros of $\chi$ have positive real parts. The remaining zero is real and negative.</td>
</tr>
<tr>
<td>$\gamma_{1,1} &lt; 0$ and $\gamma_{2,1} &lt; 0$</td>
<td>Two zeros of $\chi$ have positive real parts. The remaining zero is real and negative.</td>
</tr>
<tr>
<td>$\gamma_{1,1} = 0$</td>
<td>Two zeros of $\chi$ have positive real parts. The remaining zero is real and negative.</td>
</tr>
<tr>
<td>$\gamma_{2,1} = 0$ and $\chi_2 &gt; 0$</td>
<td>Two zeros of $\chi$ form a purely imaginary nonzero complex conjugate pair. The remaining zero is real and negative.</td>
</tr>
<tr>
<td>$\gamma_{2,1} = 0$ and $\chi_2 &lt; 0$</td>
<td>All three zeros of $\chi$ are real. Two are positive and one is negative.</td>
</tr>
</tbody>
</table>

Now, define $\chi_{\Delta} = \chi_1\chi_2 - \chi_0\chi_3$ and witness that

- $\gamma_{1,1} = \chi_2 > 0$ and $\gamma_{2,1} = \chi_1 - \frac{\chi_0\chi_2}{\chi_2} > 0$ iff $\chi_2 > 0$ and $\chi_{\Delta} > 0$.
- $\gamma_{2,1} = \chi_1 - \frac{\chi_0\chi_2}{\chi_2} = 0$ and $\chi_2 > 0$ iff $\chi_2 > 0$ and $\chi_{\Delta} = 0$.

Using Table 4.3, we can now identify three mutually exclusive and exhaustive regimes:

- **Regime I: $\chi_2 > 0$ and $\chi_{\Delta} > 0$**

  All three zeros of $\chi$ have negative real parts. Therefore, the linear system is stable. Following any bounded disturbance of finite duration, the system will eventually return to rest.

- **Regime II: $\chi_2 > 0$ and $\chi_{\Delta} = 0$**

  Two zeros of $\chi$ form a purely imaginary nonzero complex conjugate pair: $\pm j \sqrt{\frac{\chi_0}{\chi_2}} = \pm j \sqrt{\frac{\chi_1}{\chi_3}}$. The remaining zero, $\frac{-\chi_2}{\chi_3} = \frac{-\chi_0}{\chi_1}$, is real and negative. Therefore, the linear system is marginally stable. Following any bounded disturbance of finite duration, the system will eventually either return to rest or fall into a sustained constant-amplitude periodic oscillation about zero. (There exist disturbances that produce each of these outcomes.) In the latter case, the angular frequency of the oscillation will be $\sqrt{\frac{\chi_0}{\chi_3}} = \sqrt{\frac{\chi_1}{\chi_3}}$. 
CHAPTER 4. STABILITY ANALYSIS

- **Regime III:** All remaining possibilities: either $\chi_2 > 0$ and $\chi_\Delta < 0$, or $\chi_2 \leq 0$

Two zeros of $\chi$ have positive real parts. The remaining zero is real and negative. Therefore, the linear system is unstable. We partition regime III into two subregimes:

- **Subregime IIIa:** $\chi$ has three real zeros

  Following any bounded disturbance of finite duration, the system will eventually either return to rest or grow (monotonically) without bound. (There exist disturbances that produce each of these outcomes.)

- **Subregime IIIb:** $\chi$ has only one real zero

  The two zeros with positive real parts are distinct and form a complex conjugate pair. Following any bounded disturbance of finite duration, the system will eventually either return to rest or exhibit an exponentially-growing oscillation about zero. (There exist disturbances that produce each of these outcomes.)

**Crossing into the Unstable Regime in Parameter Space**

Suppose we begin with some assignment of values to model parameters for which our linear system is stable. (Our linear analysis would then predict “normal” breathing.) We must then be operating in regime I, with all three zeros of $\chi$ residing in the OLHP. Now, suppose we continuously vary the values of the model parameters so that the coefficients of $\chi$ change continuously, and hence the zeros of $\chi$ move continuously in the complex plane. The system remains stable exactly as long as all the zeros remain in the OLHP. Now assume the system does leave the stable regime (I) and enters the unstable regime (III), where $\chi$ has exactly one real negative zero and exactly two ORHP zeros. Since the zeros move continuously, they must cross the imaginary axis to move from the OLHP to the ORHP. Thus, the two zeros now in the ORHP must first have crossed the imaginary axis. They must have entered and left the imaginary axis together, and they must only have existed on the axis as a nonzero complex conjugate pair, with the system then residing in the (boundary) marginally stable regime (II). In other words, the system can only leave the stable regime (I) through the marginally stable regime (II). Since in regime II, the two zeros with nonnegative real parts form a purely imaginary nonzero complex conjugate pair, and since the zeros move continuously, the system cannot enter the unstable regime (III) with all its zeros real. So if the system does enter the
unstable regime (III), it will enter it in subregime IIIb.

### 4.2 Influence of Central and Peripheral Gains on Stability

One key feature of our model is that it distinguishes between the central and peripheral components of chemoreflex control. We now apply our linear stability analysis to exploring the influence of the central and peripheral chemoreflex gains on system stability. More precisely, given \( \tau_A, D_a, \) and \( \tau_b, \) we will map the stability boundary for the linear system onto the the first quadrant of the \((G'_a, G'_b)\) plane, partitioning the quadrant into stable and unstable regions.

Using the expressions for the coefficients of \( \chi \) given by (4.2) - (4.5), we obtain

\[
\chi_A = \chi_1 \chi_2 - \chi_0 \chi_3
\]

\[
= -\chi_{\Delta, 2, 0} G'^2_a + \chi_{\Delta, 1, 1} G'_a G'_b + \chi_{\Delta, 1, 0} G'_a - \chi_{\Delta, 0, 1} G'_b + \chi_{\Delta, 0, 0}
\]

(4.8)

where

\[
\chi_{\Delta, 2, 0} = \frac{1}{2} D_a \tau_b^2 - \frac{1}{4} D_a^2 \tau_b
\]

(4.9)

\[
\chi_{\Delta, 1, 1} = \frac{1}{4} D_a^2 \tau_b > 0
\]

(4.10)

\[
\chi_{\Delta, 1, 0} = -\frac{1}{2} D_a^2 \tau_b - \frac{1}{4} \tau_A D_a^2 - \tau_A D_a \tau_b + \tau_A \tau_b^2
\]

(4.11)

\[
\chi_{\Delta, 0, 1} = \frac{1}{4} D_a^2 \tau_A + \frac{1}{4} D_a \tau_b + D_a \tau_A \tau_b > 0
\]

(4.12)

\[
\chi_{\Delta, 0, 0} = \frac{1}{4} D_a^2 \tau_A + \frac{1}{4} D_a \tau_b^2 + \frac{1}{2} D_a \tau_A^2 + D_a \tau_A \tau_b + \frac{1}{2} D_a \tau_b^2 + \tau_A \tau_b^2 + \tau_A \tau_b^2 > 0
\]

(4.13)

If we assume that \( \tau_b \gg \tau_A \) and \( \tau_b > \frac{1}{2} D_a, \) then – using instead of (4.3) and (4.4) the approximate
expressions for $\chi_2$ and $\chi_1$ given by (4.6) and (4.7) – we obtain:

\[
\chi_{\Delta,2,0} \approx \frac{1}{2} D_a \tau_b^2 > 0 \tag{4.14}
\]

\[
\chi_{\Delta,1,1} = \frac{1}{4} D_a^2 \tau_b > 0 \tag{4.15}
\]

\[
\chi_{\Delta,1,0} \approx \tau_A \tau_b^2 - \frac{1}{2} D_a \tau_A \tau_b
= \tau_A \tau_b \left( \tau_b - \frac{1}{2} D_a \right)
\approx \tau_A \tau_b^2 > 0 \tag{4.16}
\]

\[
\chi_{\Delta,0,1} \approx \frac{1}{4} D_a \tau_b^2 + D_a \tau_A \tau_b
= D_a \tau_b \left( \frac{1}{4} D_a + \tau_A \right) > 0 \tag{4.17}
\]

\[
\chi_{\Delta,0,0} \approx \frac{1}{2} D_a \tau_b^2 + \tau_A \tau_b^2 - \frac{1}{2} D_a \tau_A \tau_b
= \tau_b \left[ \frac{1}{2} D_a (\tau_b - \tau_A) + \tau_A \tau_b \right]
\approx \tau_b^2 \left( \frac{1}{2} D_a + \tau_A \right) > 0 \tag{4.18}
\]

Now, the stability boundary is defined by $\chi_2 > 0$ and $\chi_\Delta = 0$. We have

\[
\chi_2 \geq 0 \iff \tau_A \tau_b + \frac{1}{2} D_a \tau_A + \frac{1}{2} D_a \tau_b - \frac{1}{2} G'_a D_a \tau_b \geq 0
\]

\[
\iff G'_a \leq \frac{\tau_A \tau_b + \frac{1}{2} D_a \tau_A + \frac{1}{2} D_a \tau_b}{\frac{1}{2} D_a \tau_b}
\]

\[
\iff G'_a \leq \Psi_2 \tag{4.19}
\]

where

\[
\Psi_2 = \frac{2 \tau_A}{D_a} + \frac{\tau_A}{\tau_b} + 1 \approx \frac{2 \tau_A}{D_a} + 1 \tag{4.20}
\]
4.2. INFLUENCE OF CENTRAL AND PERIPHERAL GAINS ON STABILITY

The approximation follows from assuming \( \tau_b \gg \tau_A \). As for the condition on \( \chi_\Delta \):\(^5\)

\[
\chi_\Delta = 0 \iff -\chi_{\Delta,2,0} G_{a}^2 - \chi_{\Delta,1,1} G_{a}^2 G_{b}^2 + \chi_{\Delta,1,0} G_{a}^2 G_{b}^2 - \chi_{\Delta,0,1} G_{b}^2 + \chi_{\Delta,0,0} = 0
\]

\[
\iff \left( \chi_{\Delta,1,1} G_{a} - \chi_{\Delta,0,1} \right) G_{b}^2 = \chi_{\Delta,2,0} G_{a}^2 - \chi_{\Delta,1,0} G_{a}^2 - \chi_{\Delta,0,0}
\]

\[
\iff G_{b}^2 = \frac{\chi_{\Delta,2,0} G_{a}^2 - \chi_{\Delta,1,0} G_{a}^2 - \chi_{\Delta,0,0}}{\chi_{\Delta,1,1} G_{a}^2 - \chi_{\Delta,0,1}} \quad \text{and} \quad \chi_{\Delta,1,1} G_{a} - \chi_{\Delta,0,1} \neq 0
\]

\[
\iff G_{b}^2 = \psi_\Delta \left( G_{a}^2 \right) \quad \text{and} \quad G_{a}^2 \neq \kappa_4
\]

where

\[
\psi_\Delta \left( G_{a}^2 \right) = \frac{\chi_{\Delta,2,0} G_{a}^2 - \chi_{\Delta,1,0} G_{a}^2 - \chi_{\Delta,0,0}}{\chi_{\Delta,1,1} G_{a}^2 - \chi_{\Delta,0,1}} = \kappa_1 G_{a}^2 + \kappa_2 + \frac{\kappa_3}{G_{a}^2 - \kappa_4}
\]

\[
\kappa_1 = \frac{\chi_{\Delta,2,0}}{\chi_{\Delta,1,1}} = \frac{2 \tau_b}{D_a} - 1 \\
\approx \frac{2 \tau_b}{D_a}
\]

\[
\kappa_2 = \frac{1}{\chi_{\Delta,1,1}} \left( \frac{\chi_{\Delta,2,0} \chi_{\Delta,0,1}}{\chi_{\Delta,1,1}} - \chi_{\Delta,1,0} \right) = \frac{2 \tau_A}{D_a} + \frac{2 \tau_b}{D_a} + \frac{4 \tau_A \tau_b}{D_a^2} + 1 \\
\approx \frac{2 \tau_b}{D_a} \left( 1 + \frac{2 \tau_A}{D_a} \right)
\]

\[
\kappa_3 = \frac{1}{\chi_{\Delta,1,1}} \left[ \frac{\chi_{\Delta,0,1}}{\chi_{\Delta,1,1}} \left( \frac{\chi_{\Delta,2,0} \chi_{\Delta,0,1}}{\chi_{\Delta,1,1}} - \chi_{\Delta,1,0} \right) - \chi_{\Delta,0,0} \right]
\]

\[
= \frac{4 \tau_A}{D_a} + \frac{8 \tau_A^2 \tau_b}{D_a^2} + \frac{16 \tau_A \tau_b}{D_a^2} + \frac{8 \tau_A \tau_b}{D_a^2}
\]

\[
\approx \frac{8 \tau_b \tau_A}{D_a^2} \left( 1 + \frac{2 \tau_A}{D_a} \right)
\]

\[
\kappa_4 = \frac{\chi_{\Delta,0,1}}{\chi_{\Delta,1,1}} = \frac{4 \tau_A}{D_a} + \frac{\tau_A}{\tau_b} + 1 \\
\approx 1 + \frac{4 \tau_A}{D_a}
\]

\(^5\)We ignore the pathological possibility of \( G_{a}^2 = \frac{\chi_{\Delta,0,1}}{\chi_{\Delta,1,1}} \) being a zero of \( \chi_{\Delta,2,0} G_{a}^2 - \chi_{\Delta,1,0} G_{a}^2 - \chi_{\Delta,0,0} \).
Again, the approximations are obtained by assuming $\tau_b \gg \tau_A$ and $\tau_b \gg \frac{1}{2} D_a$. Note that $\kappa_1 > 0$ as long as $\tau_b > \frac{1}{2} D_a$. Also, $\kappa_2, \kappa_3, \kappa_4 > 0$.

For the remainder of this section, we assume that the values of $\tau_A$, $D_a$, and $\tau_b$ are fixed. We also assume that these values satisfy $\tau_b > \frac{1}{2} D_a$. Thus, $\kappa_1, \kappa_2, \kappa_3,$ and $\kappa_4$ are all fixed and positive.

Our domain of discourse for the remainder of this section is the first quadrant of the $(G'_a, G'_b)$ plane. There, the locus of points for which $\chi_\Delta = 0$ is just the graph of the hyperbola described by $G'_b = \psi_\Delta (G'_a)$, $G'_a \neq \kappa_4$. With $\tau_b > \frac{1}{2} D_a$, $\psi_\Delta = 0$ has only one nonnegative solution. Let $G'_{a_0}$ denote this lone first-quadrant $G'_a$-intercept of the hyperbola:

$$G'_{a_0} = 1 + \frac{2 \tau_A}{D_a} \quad (4.24)$$

Also, let $G'_{b_0}$ denote the curve’s $G'_b$-intercept, which is positive:

$$G'_{b_0} = \psi_\Delta (0) = \kappa_2 - \frac{\kappa_3}{\kappa_4} = \frac{\kappa_2}{\kappa_4} \left( \frac{\tau_A}{\tau_b} + 1 \right) \approx \frac{\kappa_2}{\kappa_4} \quad (4.25)$$

We now have enough information to produce a sketch, shown in Figure 4.3, of the $\chi_\Delta = 0$ hyperbola in the first quadrant of the $(G'_a, G'_b)$ plane. It has a vertical asymptote given by $G'_a = \kappa_4 > 0$ and an oblique asymptote, $G'_b = \kappa_1 G'_a + \kappa_2$, whose slope and $G'_b$-intercept are positive. The branch to the left (right) of the vertical asymptote opens down (up). In the first quadrant, the left branch intersects the $G'_a$ axis at $G'_{a_0}$ and the $G'_b$ axis at $G'_{b_0}$.

---

We include the nonnegative parts of the $G'_a$ and $G'_b$ axes to help us describe curves and regions of interest. However, since $G'_a$ and $G'_b$ are positive, our results are only valid in the interior of the quadrant.
4.2. **INFLUENCE OF CENTRAL AND PERIPHERAL GAINS ON STABILITY**

Now, recall from (4.20) that $\Psi_2 = 1 + \frac{2\gamma a}{D_0} + \frac{2a}{\tau_b}$. Since $G'_a = 1 + \frac{2\gamma a}{D_0}$ and $\kappa_4 = 1 + \frac{4\gamma a}{D_0} + \frac{7a}{\tau_b}$, therefore $G'_a < \Psi_2 < \kappa_4$. The vertical line $G'_a = \Psi_2$ therefore lies strictly between the left branch of the $\chi_\Delta = 0$ hyperbola and the hyperbola's vertical asymptote. Hence, the line must lie strictly between the two branches of the hyperbola. Recall from (4.19) that $X_2 > 0$ along this line, $\chi_2 > 0$ to the left of this line, and $\chi_2 < 0$ to the right of this line. Therefore the stability boundary, which is described by $\chi_2 > 0$ and $\chi_\Delta = 0$, maps onto the left branch of the hyperbola.

Recall also that the linear system is stable if and only if $\chi_2 > 0$ and $\chi_\Delta > 0$. Now, note once again that $\chi_2 > 0 \iff G'_a < \Psi_2$. Also, since $\Psi_2 < \kappa_4 = \frac{\chi_{\Delta,0,1}}{\chi_{\Delta,1,1}}$ and $\chi_{\Delta,1,1} > 0$, therefore $G'_a < \Psi_2 \implies G'_a < \frac{\chi_{\Delta,0,1}}{\chi_{\Delta,1,1}} \implies \chi_{\Delta,1,1}G'_a - \chi_{\Delta,0,1} < 0$. Ergo:

$\chi_\Delta > 0$ and $\chi_2 > 0 \iff -\chi_{\Delta,2,0}G'_a + \chi_{\Delta,1,1}G'_b + \chi_{\Delta,1,0}G'_a - \chi_{\Delta,0,1}G'_b + \chi_{\Delta,0,0} > 0$ and $G'_a < \Psi_2$

$\iff (\chi_{\Delta,1,1}G'_a - \chi_{\Delta,0,1})G'_b > \chi_{\Delta,2,0}G'_a - \chi_{\Delta,1,0}G'_a - \chi_{\Delta,0,0}$ and $G'_a < \Psi_2$

$\iff G'_b < \frac{\chi_{\Delta,2,0}G'_a - \chi_{\Delta,1,0}G'_a - \chi_{\Delta,0,0}}{\chi_{\Delta,1,1}G'_a - \chi_{\Delta,0,1}}$ and $G'_a < \Psi_2$

$\iff G'_a < \psi_\Delta (G'_a)$ and $G'_a < \Psi_2$
The stable regime therefore corresponds to the region under the left branch of the hyperbola.

Finally, the region in the quadrant that corresponds to the unstable regime is made up of all the points that belong to neither the stable region nor the marginally stable curve (the stability boundary). Figure 4.4 shows the stable and unstable regions, along with the marginally stable curve separating them.

4.3 Stability of our Nonlinear Model System

In this section, we compare the stability regions associated with the linear small-signal model system to those associated with our original nonlinear model system. Throughout this section, we will always use the CSA values from Section 3.4 for all parameters apart from the chemoreflex controller gains.

We have analytically determined the stability regions only for the case $m = n = 1$ (i.e., using an order 1/1 Padé approximant for the lung-to-carotid transfer function). We may also use a numerical approach: For each point in a set of discrete points of interest in parameter space, we can evaluate
the coefficients of the characteristic polynomial, \( \chi \), compute its zeros numerically\(^7\), then place the point in the stable regime if all the zeros of \( \chi \) have negative real parts. Otherwise, we place it in the unstable regime. The results of this method agree with our analytical result, as Figure 4.5 illustrates.

\[ \text{Figure 4.5: Stability boundary, along with numerically-determined stability of points in the } \left( G'_a, G'_b \right) \text{ plane, using } m = n = 1. \]

We can of course apply the same numerical approach when the Padé order is not 1/1. We need only use the appropriate expressions for \( \alpha_a (s) \) and \( \beta_a (s) \) when determining the characteristic polynomial. We are thus able to explore two cases for which the analysis is too daunting, \( m = n = 2 \) and \( m = n = 3 \).

- For \( m = n = 2 \), \( \alpha_a (s) = \frac{1}{12} D_a s^2 - \frac{1}{2} D_a s + 1 \) and \( \beta_a (s) = \frac{1}{12} D_a s^2 + \frac{1}{2} D_a s + 1 \).
- For \( m = n = 3 \), \( \alpha_a (s) = -\frac{1}{120} D_a s^3 + \frac{1}{10} D_a s^2 - \frac{1}{2} D_a s + 1 \) and \( \beta_a (s) = \frac{1}{120} D_a s^3 + \frac{1}{10} D_a s^2 + \)

\(^7\)We use the MATLAB \texttt{roots} function for this.
We compare our numerical results for $m = n = 1$, $m = n = 2$, and $m = n = 3$ in Figure 4.6. The shapes of the three stability regions are quite similar, but the stability region for $m = n = 1$ is significantly larger than the region for $m = n = 2$, which in turn is only slightly larger than the stability region for $m = n = 3$. Considering that the order $m/m$ Padé approximant improves in accuracy as $m$ increases, the figure suggests that the stability boundary obtained when $m = n = 2$ or $m = n = 3$ provides a very good approximation of the stability boundary that would be associated with the linear model if $\tilde{P}_{a,m/n}$ were to be replaced by a block representing a true time delay of duration $D_a$.

![Figure 4.6: Stability boundary using $m = n = 1$, along with numerically-determined stability of points in the $(G'_a, G'_b)$ plane, using $m = n = 2$ and $m = n = 3$.](image)

We now return to our original nonlinear model system as developed in Chapter 3. We explore a
4.3. **STABILITY OF OUR NONLINEAR MODEL SYSTEM**

lattice of points in the $(G_a, G_b)$ plane, including both the linear stable region and part of the linear unstable region. For each point, we simulate the model system and observe whether the ventilation waveform appears to exhibit sustained oscillations. If it does, we take that $(G_a, G_b)$ point to lie in the unstable regime for the system; otherwise, we place the point in the stable regime. In Figure 4.7, we show that the results agree very nicely with the stability results for the linear model at the same points in the $(G_a, G_b)$ plane.

![Figure 4.7: Stability of the nonlinear and linearized models.](image-url)
Chapter 5

Conclusion

In this thesis, we have developed and analyzed a simple grey-box model that describes the pathophysiology of central sleep apnea. We began by considering the complex physiological model PNEUMA, using it to simulate CSA. In the vicinity of the associated parameter configuration, we found that relevant model outputs are insensitive to changes in all but approximately twenty model parameters. This motivated us to develop a model, with few state variables and parameters, that is able to produce physiologically-accurate output waveforms and capture fundamental phenomena of interest in CSA. Such a model could be helpful in the development and evaluation of treatments for CSA. If its parameters can be reliably estimated from a patient’s data records, the model could be used to provide customized treatments.

Drawing from physical and physiological principles and models described in the literature, we constructed a model that describes the dynamics of alveolar gas exchange, lung-to-carotid blood gas transport, and cerebral gas exchange, along with a ventilation controller that responds to arterial and cerebral carbon dioxide tensions. Using PNEUMA to estimate appropriate parameter values for our model, we showed that in simulation our model outputs agree well with the corresponding PNEUMA waveforms. We observed that replacing our nonlinear gas exchange models with linearized models did not significantly change the simulated output waveforms. We also used Padé approximants to obtain finite-dimensional alternatives to our pure delay lung-to-carotid transport model, and found that the order 2/2 Padé-based transport model approximated the behaviour of our original pure delay model fairly well in simulation.

Using our linearized gas exchange plant models and Padé-based lung-to-carotid transport mod-
We constructed a linearized small-signal version of our model. We developed small-signal stability criteria using the Routh-Hurwitz criterion, then determined how the peripheral and central chemoreflex gains influence small-signal stability. We concluded by comparing our analytically-determined stability boundary in the \((G_a, G_b)\) plane both to stability boundaries obtained numerically using higher-order (improved) Padé approximants, and to the stability boundaries associated with our original nonlinear model system (which we deduced by simulation). We found that using our order 2/2 lung-to-carotid transport model, the linear analysis provides a very good approximation of the stability boundary for the full nonlinear system.

### 5.1 Future Work

The work and results described in this thesis suggest many possible directions for future research, some of which we outline below. We have already begun to explore some of these avenues.

- Using parameter values estimated from PNEUMA parameter values and simulation results, our model produced waveforms in simulation that agreed reasonably well with the corresponding PNEUMA waveforms.
  - Can we systematically assign values to our model's parameters such that its outputs agree optimally (in some reasonable sense) with PNEUMA's outputs?
  - Is our model (fully) identifiable from a standard collection of physiological data recorded from a single individual during an episode of CSA?

- We modelled the chemoreflex controller as a static system.
  - Is there any experimental evidence that the chemoreflex controller includes integral or derivative components? What effect would such elements have on model behaviour?

- Using the order 2/2 Padé-based lung-to-carotid transport transfer function, we predict stability regions in the \((G_a, G_b)\) plane that agree very well with the behaviour of our original, full, nonlinear model.
  - Can acceptable predictions be obtained using an appropriately-adjusted order 1/1 lung-to-carotid transport model?
5.1. FUTURE WORK

- Can any simple stability criteria be formulated using the order 2/2 transfer function?

- The stability regions predicted using the order 2/2 and 3/3 models do differ somewhat from the stability regions associated with the original model. How can these differences be explained?

- If a different valid operating point were used to predict the stability regions, would the results be equally good?

- How do the stability regions associated with our model compare to the stability regions associated with PNEUMA?

- What predictions can be made about how parameters other than $G_a$ and $G_b$ influence system stability?

- How well do the predictions of our linear stability analysis compare with real physiological system behaviour, and with the predictions of previously-published analyses?

- Does our linear stability analysis make any counterintuitive, testable predictions?

- How do the frequencies of oscillations generated by our linearized model system compare with the frequencies of sustained oscillations in our nonlinear model?
References


