Inspired Oxygen Control for Preterm Infants

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Summary

Inspired oxygen control for preterm infants is performed to maintain oxygen saturation (SpO_2) in the blood in a target range. Exposure to insufficient or excess levels of fraction of inspired oxygen (FiO_2) may increase the risk of mortality and morbidity in these patients. Despite this sensitivity, manual control is still the common practice largely due to immaturity of the existing control algorithms in dealing with the challenging task. Accordingly, this thesis aimed to initially identify the shortcomings of the existing automated controllers and then to provide indications for addressing these shortcomings.

Through comprehensive analysis of the literature, the main design challenges of automated controllers were identified as oxygenation variability, technologic insufficiencies of infant monitoring and safety considerations. The thesis then largely focused on addressing the variability issue. Oxygenation variability means that a given FiO_2 adjustment may lead to a different SpO_2 response on different occasions. A first order transfer function characterised by a delay, a time-constant and a gain was used to model the FiO_2-SpO_2 relationship following FiO_2 adjustments in a large dataset from preterm infants receiving supplemental oxygen. The model was found representative for 37% of the adjustments from which an image of the parameter variations was obtained. The model was more representative for FiO_2 increments than decrements and predictability was low in the collective set of model parameters.

The study was followed by a thorough characterisation of the oxygenation response which most notably indicated intra and inter-patient variability as well as influence

of severity of lung dysfunction on the gain of the oxygenation system. These findings support the superiority of adaptive control algorithms over robust and rule-based approaches. Moreover, these results provide a quantitative basis for developing adaptive algorithms and point to the severity of lung dysfunction reflected in baseline FiO_2 as a viable basis for the adaptation.

Frequent fluctuations of SpO_2 being another challenging aspect of variability was then investigated. Apnoea, loss of circuit pressure and motion artefact concomitant with falls in SpO_2 (e.g. hypoxia) were of interest. The high frequency of these factors as well as relevance of respiratory pauses with the characteristics of the following hypoxic events indicated potential benefits of incorporating respiratory rate in automated control methods. Finally, the issue of oximetry signal dropouts was studied and the results indicated that pre-emptive increments to FiO_2 when SpO_2 is missing during automated control may not be necessary. Parts of the outcomes of this thesis were used in development of a neonatal oxygen control algorithm for which a patent application is in progress.

In a nutshell, the main contributions of this thesis to the research area include 1) Identification of the main challenges in automated control of FiO_2 for preterm infants, indications for overcoming the challenges, 2) Providing a quantitative image of the characteristics of oxygenation system in preterm infants with a representation suitable for developing automated control algorithms, 3) Identifying the severity of lung dysfunction as a predictor of oxygenation response variability, 4) Revealing the frequency and relevance of factors such as apnoea and motion artefact concomitant to hypoxic events which can complicate automated FiO_2 control, 5) Obtaining information concerning the SpO_2 changes before and after episodes of signal dropout which assists in decision-making of a controller during these periods and 6) Providing information which acted as a basis for developing a control algorithm with commercialisation prospects.

Declaration of Originality

"This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright."

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Omid Sadeghi Fathabadi

09/02/2016

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Statements of Ethical Conduct and Authority of Access

"The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University. Approval was obtained from the Human Research Ethics Committee (HREC) prior to using data (H10837,H12388)."

Omid Sadeghi Fathabadi

09/02/2016

Statement of Co-Authorship

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- **Paper 1** Omid Sadeghi Fathabadi, Timothy J Gale, JC Olivier and Peter A Dargaville, (2016). "Automated control of inspired oxygen for preterm infants: what we have and what we need". Biomedical Signal Processing and Control 28: 9-18.

  Located in Chapter 2.

  Candidate was the primary author (proportion of work undertaken: 90%) who evaluated the literature, wrote the first draft and finalised the manuscript. Authors 1-3 enhanced the contents and assisted with manuscript editing.

- **Paper 2** Omid Sadeghi Fathabadi, Timothy J Gale, Kathleen Lim, Brian P Salmon, Kevin I Wheeler, JC Olivier and Peter A Dargaville. (2014). "Assessment of validity and predictability of the FiO_2-SpO_2 transfer-function in preterm infants." Physiological Measurement 35(7): 1425-1437.

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- **Paper 4** Omid Sadeghi Fathabadi, Timothy J Gale, Kevin I Wheeler, Gemma Plottier, Louise S Owen, JC Olivier, Peter A Dargaville (2016). "Hypoxic events and concomitant factors in preterm infants on non-invasive ventilation." Journal of Clinical Monitoring and Computing 1-7.

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Candidate was a co-author (proportion of work undertaken: 10%) who assisted with data interpretation and manuscript editing together with authors 1, 3, 4, 10. Author 6 collected and analysed data and wrote the first draft and finalised the manuscript. Authors 1, 3 were also involved in data collection.

- **Paper 6** Omid Sadeghi Fathabadi, Timothy J Gale, JC Olivier, Peter A Dargaville, Kevin I Wheeler, and Kathleen Lim (2013). "Binary search for time-constant estimation in first order systems, FiO_2-SpO_2 case study." The 2013 Biomedical Engineering International Conference (BMEiCON-2013)

  Located in Appendix A.

  Candidate was the primary author (proportion of work undertaken: 90%) who conceived the idea, implemented the methods, wrote the first draft, updated and finalised the manuscript, presented the paper in the conference. Authors 1, 3, 6 were involved in data collection. Authors 1-4, 6 assisted with manuscript refinement.

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Nomenclature

Latin Symbols

AIC	Akaike Information Criterion
ANN	Artificial Neural Network
$ANOVA$	Analysis of Variance
AUC	Area Under Receiver Operating Characteristic Curve
$CPAP$	Continuous Positive Airway Pressure
EM	Expectation Maximization
FiO_2	Fraction of Inspired Oxygen
G	Gain
$IPPV$	Intermittent Positive Pressure Ventilation
IQR	Inter Quartile Range
$NCPAP$	Nasal Continuous Positive Pressure Ventilation
$NIPPV$	Nasal Intermittent Positive Pressure Ventilation
PaO_2	Partial Pressure of Arterial Oxygen
PiO_2	Oxygen Pressure Inside Incubator
PID	Proportional-Integral-Derivative
QCV	Quartile Coefficient of Variation
R^2	Coefficient of Determination $= 1 - \frac{Residual\ Sum\ of\ squares}{Total\ Sum\ of\ Squares}$
$RMSE$	Root Mean-Square Error

SpO_2 Peripheral Capillary Oxygen Saturation

T_d Time Delay

TPR True Positive Rate

Greek Symbols

δSpO_2 Difference in Oxygen Saturation (before and after a sensor drop-out)

ΔFiO_2 Baseline-Removed Fraction of Inspired Oxygen

ΔSpO_2 Baseline-Removed Oxygen Saturation

τ Time Constant

χ^2 Statistical Test, H_0: There is no significant difference between the observed and the expected value.

Chapter 1

Introduction

Neonates, particularly premature infants often need respiratory support in a period following their birth. Respiratory support includes delivery of humidified air-oxygen mixture which can be performed through mechanical ventilation or a non-invasive setting such as continuous positive airway pressure (CPAP). Maintaining oxygen level in the blood in an optimal range by making adjustments to fraction of inspired oxygen (FiO_2) is required in order to minimise four associated risks especially for the premature infants. The risks are mortality, retinopathy of prematurity, damage to the brain and chronic lung disease (Silverman, 2004; Stenson, 2013; Saugstad and Aune, 2014).

The adjustments in FiO_2 are currently predominantly performed manually based on oxygen saturation (SpO_2) readings (figure 1.1), however clinical evidence suggests that manual targeting of a SpO_2 range is not very effective (Hagadorn *et al.*, 2006; Laptook *et al.*, 2006; Schmidt *et al.*, 2014, 2013). Even a recent report indicated to an average of only 35 and 38% of the time spent within the target range for routine and algorithm-based manual control, respectively, in a group of preterm infants (Clarke *et al.*, 2015).

Due to the logical benefits of automation of oxygen control (Claure and Bancalari, 2013b) such as providing on-time adjustments, it has long been investigated as a potential solution with the early efforts dating back to 1970s (Beddis *et al.*, 1979; Collins *et al.*, 1979). Notwithstanding significant progress over-time and relatively improved outcomes, clinical trials on automated controllers suggest that they too are far from optimal (Claure *et al.*, 2009, 2011; Zapata *et al.*, 2014; Hallenberger *et al.*, 2014).

The obvious sub-optimality of the existing controllers motivated this research project. The project aimed to 1) Identify high level issues complicating the design of automated oxygen controllers for preterm infants and 2) Provide suggestions for addressing the identified issues through analysis of datasets obtained from preterm
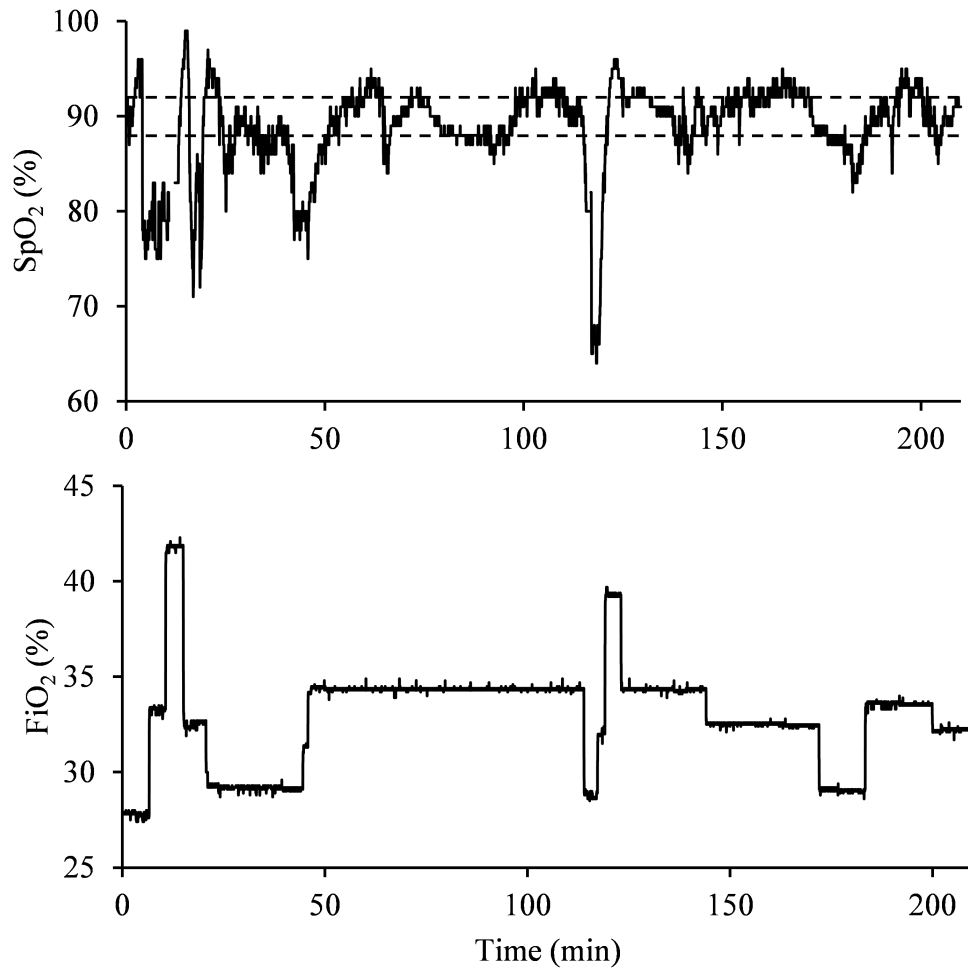
Figure 1.1: A sample of several hours of FiO_2 and SpO_2 recordings during manual control showing the SpO_2 trace, FiO_2 targeting adjustments and the SpO_2 target range (dashed lines).

infants. Thus, the project started with a comprehensive evaluation of the existing algorithms and their performance. Three main categories of identified challenges were namely variability of the oxygenation system, technologic shortcomings of infant monitoring and safety considerations. The outcomes of this part of the project are presented in Chapter 2.

Based on these results, two chapters of the thesis were dedicated to investigation of the variability of the SpO_2 response to FiO_2 adjustments because of the huge gap in that area and significance of a potential outcome. Chapter 3 was concerned with modelling of the oxygenation response as well as assessing the validity of the

model. This chapter also investigated the possibility of cluster-based prediction of the oxygenation system response.

Chapter 4 was a continuation of Chapter 3, where the parameters of the estimated model were investigated to characterise the oxygenation response. Through these studies, variables which could predict any of the model parameters and potentially be used during automated control for adaptation purpose were sought. In addition, intra and inter-infant variability in the response were analysed.

The thesis, then focused on another aspect of variability in oxygenation, being the frequent declines in SpO_2 (episodes of hypoxia) observed in preterm infants. An underlying mechanism causing a real or perceived hypoxia may interfere with the performance of an automated controller by disrupting the anticipated oxygenation response to an FiO_2 adjustment. Therefore, identifying the cause of hypoxia may assist a controller in making prospective decisions. Chapter 5 was then dedicated to investigation of the factors concomitant with hypoxia. The factors were namely apnoea (respiratory pauses), loss of gas pressure and motion artefact. Moreover, relevance between characteristics of hypoxic and apnoeic events was investigated.

Chapter 6 is concerned with the issue of oximetry signal dropouts which is a shortcoming of infant monitoring that imposes a security challenge to an automated controller. This is because in the absence of a SpO_2 measurement, blindly adjusting FiO_2 could unpredictably change the actual level of oxygen saturation. On the other hand, inaction in such an occasion if an adjustment is required may also lead to undesired levels of oxygen saturation. Hence, in Chapter 6 the oximetry readings were analysed before and after signal dropouts in a large dataset in order to obtain an evidence-supported indication for appropriate actions during signal dropouts.

It is worthwhile to mention that Chapters 3-6 are self contained in having their own introduction, methodology, results and discussions for two reasons. Firstly, the nature of the study makes the presentation of the outcomes more appropriate in a

modular fashion without interruption of the flow of the thesis. Secondly, different datasets with various available channels became available during the course of the project at different stages. Given the necessities of each chapter, appropriate parts of the dataset were used. Self-contained chapters allowed for providing information on the dataset which was used for each chapter.

The chapters of the thesis overall reflect its main contributions to automated control of inspired oxygen in preterm infants being increased understanding of the existing challenges and their potential solutions, quantitative characterisation of the neonatal oxygenation response, identifying predictors of the oxygenation response variability and finally obtaining indications which help to deal with real-time interrupting factors such as apnoea, motion artefact and SpO_2 signal drop-outs during automated control.

1.1 Background

The respiratory system is responsible for exchange of oxygen and carbon dioxide between the body and environment. It starts at the airway openings, proceeds to the internal airways and ends in alveoli as shown in figure 1.2. The deoxygenated blood perfusing the lungs comes from the right ventricle of the heart through the pulmonary artery and once oxygenated, it is carried to the left atrium of the heart via pulmonary vein. The oxygenated blood is then pumped to the systemic circuit from the left ventricle through the Aorta. A view of the heart is available in figure 1.3.

A central point in the gas exchange process in the body is the alveolus. Alveoli are millions of gas chambers surrounded by pulmonary capillaries where the gas exchange between the lungs and the blood takes place. The gas is exchanged through diffusion in alveolus membrane because of the gradient concentration of the O_2 and
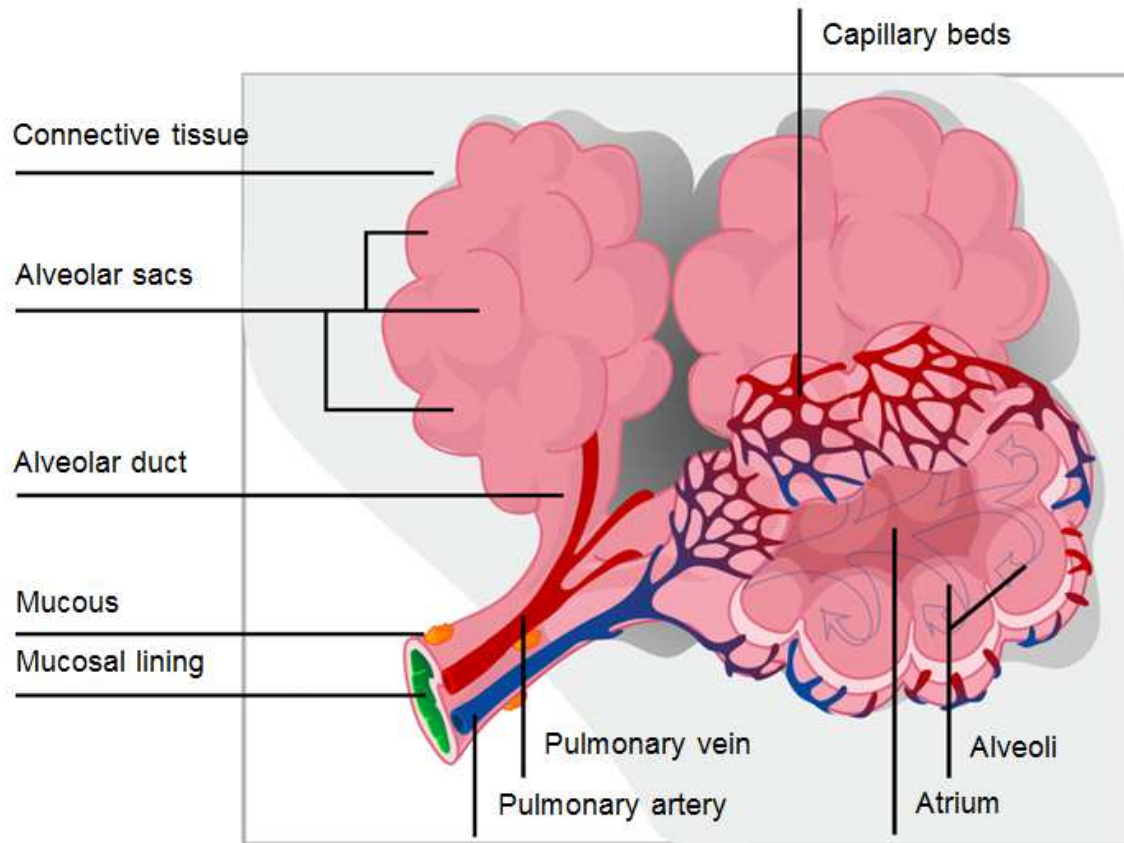
Figure 1.2: A schematic view of the alveoli. Public Domain image from Wikipedia: $https://en.wikipedia.org/wiki/Pulmonary_alveolus$.

CO_2 in alveolus and capillary. The fraction of inspired oxygen defines the alveolar partial pressure of oxygen which in turn determines the arterial partial pressure of oxygen (PaO_2).

Except for a small proportion dissolved in the blood plasma, the oxygen is almost completely carried by the haemoglobin in the red blood cells. Oxygen-carrying haemoglobin (oxyhaemoglobin) and desaturated haemoglobin (deoxyhaemoglobin) account for most of the haemoglobin protein in the blood. The oxygen saturation obtained from pulse oximetry (SpO_2) is a measure of the ratio of the amount of oxyhemoglobin to the summation of the amounts of oxyhaemoglobin and deoxy-haemoglobin (Nitzan *et al.*, 2014). This ratio defines the amount of oxygen delivered to the tissues and must be kept in a target range (about 90%) in order to ensure adequate body development while avoiding toxicity.
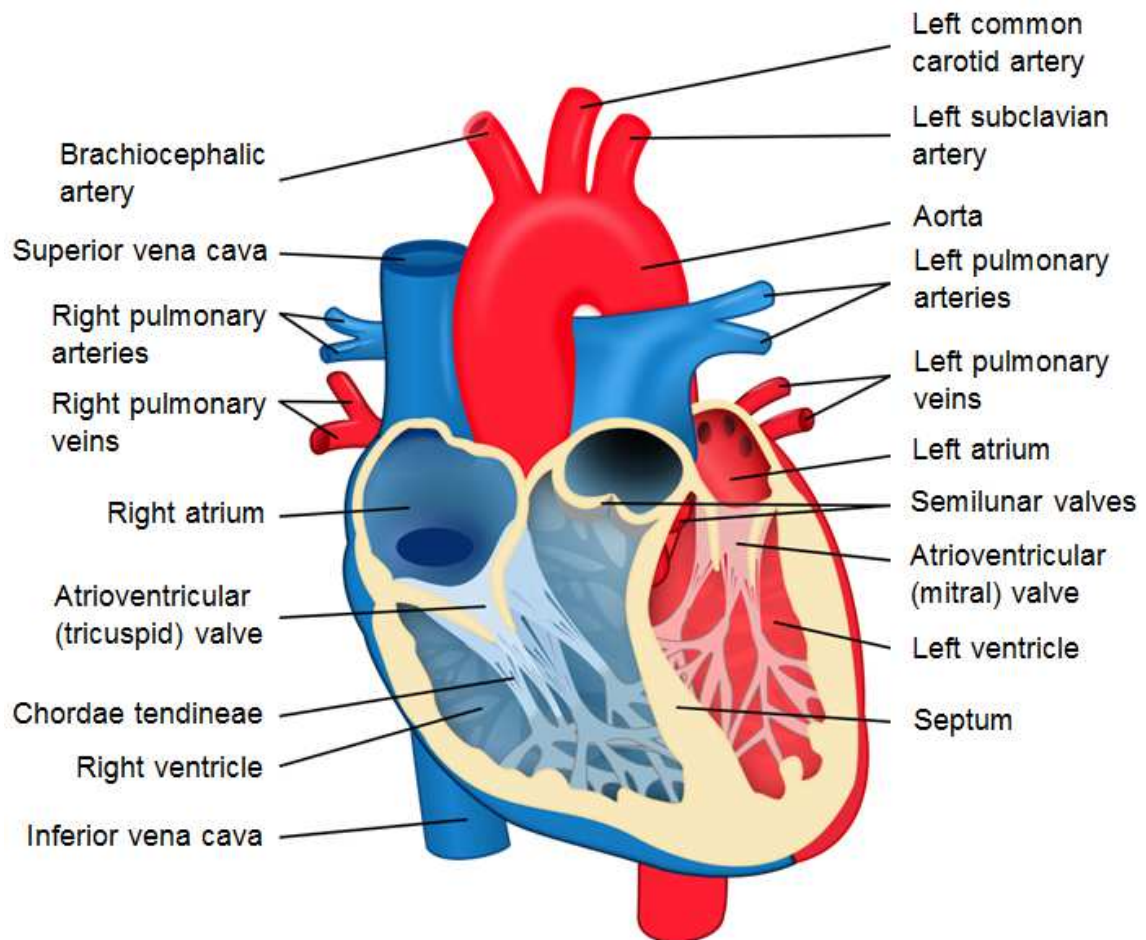
Figure 1.3: A schematic view of the heart. Obtained from https:commons.wikimedia.org/wiki/File:Heart_diagram-en.svg under the Creative Commons Attribution-Share Alike 3.0 Unported license.

In a preterm infant several factors relevant to prematurity interrupt the natural capability of the body in stably maintaining required oxygen levels. One issue is the underdeveloped lungs e.g. fewer alveoli and stiff tissue which together with compliant chest wall and weak muscles make it difficult for the neonate to maintain a minimum required volume at the end of expiration. Also underdeveloped nervous system inadequately driving respiration may play a role. Occasions of cessation of respiratory effort or airflow called apnoea are also common in preterm infants (Donn and Sinha, 2012).

To make things worse, various respiratory diseases such as infant respiratory distress syndrome may affect ability of the neonates in oxygenating their blood. This

particular disease is associated with lack of a substance called surfactant. This natural material helps to prevent alveoli from collapsing at the end of expiration and facilitates its inflation during inspiration. In order to tackle these issues respiratory support devices are utilised (Reininger *et al.*, 2005) which assist the infants by first improving the ventilation of the lungs and then providing supplement oxygen to the infants if needed. The supplemental oxygen is administered to provide adequate blood oxygenation using the available respiratory functionality of the immature body despite the existing deficiencies.

For inspiration to occur the pressure inside the lung should be less than the atmospheric pressure. During spontaneous breathing this pressure difference is created by reduced alveolar pressure while in so called "mechanical breathing" it is created by positive atmospheric pressure (Donn and Sinha, 2012). This positive atmospheric pressure and even in some cases a negative pressure in the lungs comes from respiratory support devices. Respiratory support devices can be broadly divided into two categories namely invasive and non-invasive.

In invasive respiratory support the air-oxygen mixture is usually delivered via an endotracheal tube inserted through the mouth. The infant is then enforced to/assisted in breathing by the pressure changes in lungs caused by the ventilator. These devices can be further divided into sub-categories based on the parameter that they try to control e.g. pressure, volume or flow (Wheeler *et al.*, 2011). Using invasive support in preterm infants is associated with the risk of bronchopulmonary dysplasia; a disease caused by abnormal development of the lungs as a result of ventilator-induced injuries (Jobe and Ikegami, 1998). Moreover, weaning from mechanical ventilators may be complicated by failure of the infant to breathe spontaneously.

Increasingly-popular non-invasive respiratory support devices on the other hand deliver the gas using a non-invasive instrument such nasal prongs, nasal cannula, face-mask, hood or and incubator. Infants breathing spontaneously can then inhale

the air-oxygen mixture. A schematic diagram and photos of a typical CPAP device are presented in figure 1.4, and 1.5. There are various types of non-invasive respiratory support which differ mainly in terms of the type of pressure delivery at the airway. For instance while a continuous positive airway pressure (CPAP) apparatus delivers a constant pressure, a nasal intermittent positive pressure ventilator (NIPPV) delivers a baseline pressure with frequent spikes (Davis *et al.*, 2009). NIPPVs may in turn be synchronous or asynchronous with the spontaneous breathing in triggering the pressure spikes. Bi-level CPAP as another example, delivers two frequently alternating constant pressures.

The choice of the invasive or non-invasive support depends on the needs of an infant at a particular time and these two modes may be used as complements. The non-invasive respiratory devices are the main area of focus in this thesis for which the control of FiO_2 is a key aspect.

Figure 1.4: Top: A schematic diagram of a typical non-invasive ventilator, Middle right: air-oxygen blender, left: humidifier, Bottom: an infant receiving CPAP

Figure 1.5: Photo of a Neotech Medical Systems bubble CPAP device

Chapter 2

Automated Control of Inspired Oxygen, What We Have and What We Need

2.1 Summary

This review provides the first comprehensive technically-focused image of algorithms developed for automation of inspired oxygen control in preterm infants. The chapter has two main parts; the first provides an overview of the existing algorithms and the second presents the major design challenges of automated controllers. In the first section, the algorithms are classified in four categories, namely rule-based, proportional-integral-derivative, adaptive, and robust. The second section discusses variability in oxygenation, technologic shortcomings of infant monitoring and safety considerations as the three major challenges for designing automated controllers. These challenges, particularly the variations in oxygenation both in the form of response vagaries following FiO_2 adjustments and hypoxia, are selected as the main areas of focus for the thesis in the upcoming chapters.

2.2 Introduction

Newborn infants, particularly those born prematurely, often need respiratory support in a period following their birth. This frequently includes supply of a warmed and humidified mixture of air and oxygen, delivered either via a stand-alone gas blender as part of non-invasive respiratory support, or by a blender incorporated into a mechanical ventilator. Regardless of the mode of respiratory support, adjustment of the fraction of inspired oxygen (FiO_2) is critical, with the aim of keeping partial pressure of oxygen in the arterial blood (PaO_2) in an optimal range. In the neonate, PaO_2 levels that are too low (hypoxia) or too high (hyperoxia) are dangerous, being associated with an increased risk of mortality, retinopathy, brain injury and chronic lung disease (Silverman, 2004).

A compelling argument thus exists for avoiding extremes of oxygenation in the newborn infant, especially for prolonged periods. Putting this into practice is challenging enough, but the difficulty is compounded by the lack of a direct, continuous and precise measure of PaO_2 in the neonate. For this reason a proxy measure of oxygenation is used, that of oxygen saturation (SpO_2) measured via a skin probe by a pulse oximeter, rather than PaO_2 itself. Given that the SpO_2-PaO_2 relationship is far from linear, reliance on measurement of SpO_2 to guide titration of oxygen therapy imposes an additional layer of complexity to the problem of optimising oxygenation in the newborn.

The current approach to titration of oxygen therapy in the preterm newborn is that of manual adjustment of FiO_2 by bedside caregivers in an effort to maintain oxygen saturation (SpO_2) in the target range. It is well-established, however, that this method is not very effective (Hagadorn *et al.*, 2006; Laptook *et al.*, 2006). Recent reports indicate that the average proportion of time spent within the target range during manual control, can be as low as 30-40% (Lim *et al.*, 2014; Clarke *et al.*, 2015). Accordingly, there have been efforts to automate this process (Claure and Bancalari,

2013b). While early efforts towards automation of FiO_2 control for preterm infants date back to 1970s (Beddis *et al.*, 1979; Collins *et al.*, 1979), manual control is still the common practice.

Previous reviews of automated control of FiO_2 have discussed the rationale and potential benefits and risks of automated control for preterm infants (Claure, 2007; Bancalari and Claure, 2012; Claure and Bancalari, 2013b,a, 2015a,b) as well as reviewing the available evidence from clinical trials (Claure and Bancalari, 2015a,b), (Hummler *et al.*, 2014). These papers point to the potential for automated control to more effectively maintain oxygenation in a target range and reduce the workload of bedside caregivers. The need to perform large-scale clinical trials of automated control has also been highlighted, including a study of longer term outcomes in preterm infants receiving this form of support.

The published reviews appear not to reflect the importance of the technical characteristics of automated oxygen control systems. The existing algorithms have not been comprehensively described, critically appraised and compared. Accordingly, the first aim of the current chapter is to summarise and classify algorithms for automated control, and identify directions for future improvement. The second objective is to identify the main obstacles in developing automated FiO_2 control devices, and suggest some potential solutions.

2.3 Existing Algorithms for Automated Control of FiO_2

During automated or closed loop FiO_2 control, regular adjustments to the fraction of inspired oxygen are made based on a feedback of oxygenation. The control loop includes the control algorithm programmed in a computer or an embedded processing unit. This algorithm receives the oxygenation feedback and provides the suggested FiO_2. The other part of the loop is composed of the infant to whom

the air-oxygen mixture with the desired FiO_2 is delivered and from whom the oxygenation measurement is obtained. The control loop is closed by the electrical and mechanical actuators which receive the proposed FiO_2 from the algorithm and deliver the blended air-oxygen mixture.

Published reports reveal four major approaches to algorithm design for inspired oxygen control in the neonate: a) rule-based, b) proportional-integral-derivative (PID), c) adaptive and d) robust approaches. These are defined and examined in detail below.

2.3.1 Rule-Based Controllers

Rule-based controllers make adjustments to FiO_2 based on a set of rules which stem from expert knowledge. A rule-based controller may be in the form of a simple if-then loop or can engage fuzzy logic (Oviedo *et al.*, 2006).

Non-Fuzzy Algorithms

Automation of oxygen control for preterm infants began with a simple rule-based controller proposed by Beddis *et al.* (1979) and technically described in more detail by Collins *et al.* (1979). This servo-controller adjusted FiO_2 in 5% single step increments or decrements at 1-min intervals if the measured partial pressure of arterial oxygen (PaO_2) was out of the desired range, or took no action if the PaO_2 was acceptable. Later rule-based algorithms (Morozoff *et al.*, 1993; Urschitz *et al.*, 2004) were similar in terms of making step adjustments in FiO_2 with a period of inaction thereafter, but were significantly more elaborate in their decision-making. The algorithm of Morozoff *et al.* (1993) used three error-based indices as inputs to a state machine controller.

The controller inputs were the signs of the magnitude, velocity and acceleration of the error based on which the state machine determined a qualitative parameter called trend of the error. The value of the trend defined the next state of the machine, an FiO_2 adjustment and a delay to give time for reaction to the adjustment. Although the authors defined the states and trends in a table, they did not present detailed information about transitions between the states, how the delay and adjustments were determined and what were the actual values of these outputs (Morozoff *et al.*, 1993). The state machine was updated every second.

Along similar lines, the more recent controller of Urschitz *et al.* (2004) utilised the concept of trend in its decision-making but defined it a totally different way. The algorithm made a decision based on so called "state analysis" (180 seconds) and "trend analysis" (60 seconds) followed by "no action" episodes (180 seconds). There were five possible adjustments (-2%, -1%, 0, +2%, +5%) according to the state, which could be postponed according to the extracted trend.

Qualitative descriptions (state and trend) were extracted from moving windows of the recorded oxygen saturation (SpO_2). There were five possible states (substantially above, above, normal range, below, substantially below), and three possible trends (increasing, stable, decreasing). The abstraction method was presented by Miksch *et al.* (1999) and included linear regression steps; the basis of control algorithm was introduced by Seyfang *et al.* (2001). The authors stated that this controller was not designed to respond to acute severe hypoxic episodes (Urschitz *et al.*, 2004).

Fuzzy Algorithms

The application of a fuzzy logic controller to neonatal inspired oxygen control was first reported by Sun *et al.* (1994), paralleling the efforts of Morozoff (1996). Fuzzy logic controllers are similar to simple rule-based controllers in using if-then pairs but they make it possible for a given set of inputs to correspond to more than one
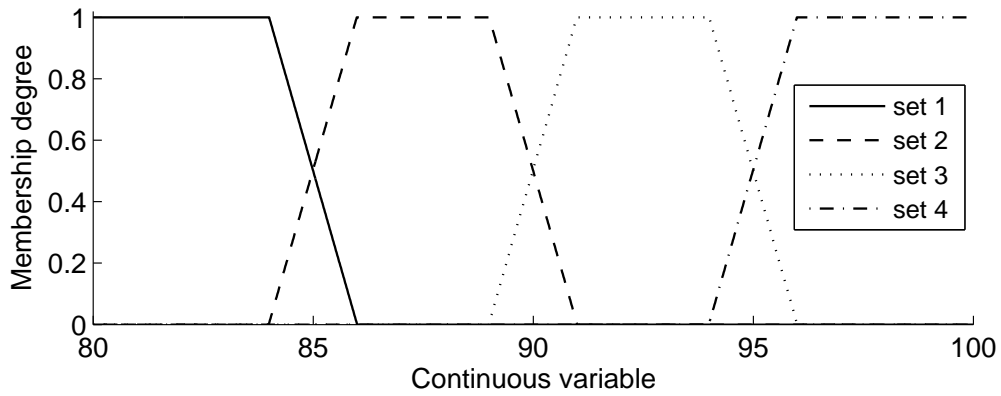
Figure 2.1: Sample membership functions for a four-subset fuzzy set, a value of 1 denotes full membership to a subset while a value between 0 and 1 indicates to the extent of partial membership.

rule with variable extents. This work is performed using membership functions (figure 2.1) which define the extent of membership of a variable to subsets of a fuzzy set. The final control decision is then made in a procedure using the outputs of the relevant rules as well as the obtained memberships.

Putative advantages of fuzzy control over classical control theory are a) the applicability to systems which are hard to model mathematically and are nonlinear, b) the capacity to incorporate expert knowledge in the algorithm, c) the possibility to facilitate linguistic description of continuous variables associated with fuzzy subsets, d) less noise sensitivity and more robustness, and finally e) less complexity of the design and faster computations in real-time (Sun *et al.*, 1994).

In the first use of fuzzy logic for this purpose, Sun *et al.* (1994) used the values of error and SpO_2 slope as inputs which were then fuzzified into 7 and 5 regions, respectively, using triangular membership functions. The error was defined as the difference between the average and the target SpO_2 while SpO_2 slope was obtained from a regression line; both were updated every 10 seconds. The fuzzification process created 35 combined regions which corresponded to 35 if-then fuzzy inference rules. The logic of the fuzzy inference rules was defined based on neonatologists' knowledge.

Along similar lines, a more recent fuzzy logic controller incorporated within a medical device (Auto-mixer) (Lopez *et al.*, 2014) created a fuzzy inference system including 35 rules with the error and derivative of the SpO_2 as its inputs. Unlike Sun *et al.* (1994) however, the error was divided into five and the derivative into seven regions.

In the following defuzzification stage, where Sun *et al.* (1994) used a weighted-mean method to combine the outputs of the rules and to create a control action, by contrast Lopez *et al.* (2014) prescribed 11 possible values for an adjustment ranging from -5% to +5% based on the pre-defined rules. Implementation of both controllers was performed using a look-up table to expedite the computation process in real time.

The test conditions of rule-based controllers have been widely disparate, which must be taken into account in assessing their performance. Beddis *et al.* (1979) tested their controller on 12 infants receiving supplemental oxygen via headbox, continuous positive airway pressure (CPAP) or intermittent positive pressure ventilation (IPPV). Morozoff *et al.* (1993) on the other hand studied only neonates that were intubated and requiring assisted ventilation.

In many cases the tests were performed in two stages. As an example, Urschitz *et al.* (2004) initially tested their algorithm on preterm infants under nasal continuous positive airway pressure but later (Hallenberger *et al.*, 2014) on patients receiving mechanical ventilation and CPAP. Similarly, Sun *et al.* (1994) reported some preliminary clinical results, before testing the algorithm in open loop on 16 mechanically ventilated infants (Sun *et al.*, 1997).

Lopez *et al.* (2014) used a first-order model of FiO_2-SpO_2 relationship for their preliminary tests on their controller and later reported the results of a randomized controlled trial (Zapata *et al.*, 2014). The patients in this trial received supplemental oxygen using nasal cannula without mechanical ventilation.

One major issue with the performance of rule-based controllers is that step adjustments are followed by a lockout period with no action. It is thus possible that the response to a sudden change in oxygenation will be inappropriately postponed. Additionally, the different sets of rules based on clinical knowledge appear to be incompletely validated. A clinical comparison of the effectiveness of these algorithms would be the only way to assess their overall performances.

2.3.2 PID Controllers

PID control, the most popular form of control algorithm in industry, defines an error (e) which is the deviation of the process signal from the set-point. The value of the manipulated signal output (u) at each moment is proportional to the value of error, its integral and derivative (equation 2.1), with a different multiplying coefficient (K_p, K_i, K_d) in each case. The integral term considers accumulated past error and can eliminate steady state error, whereas the derivative term is in essence a prediction of the future error (Visioli, 2006).

$$u(t) = K_p e(t) + K_i \int e(\tau) d\tau + K_d \frac{de(t)}{dt} \tag{2.1}$$

A conventional PID algorithm was first applied to automated oxygen control by Tehrani and Bazar (1994), and updated in 2001 (Tehrani, 2001). These controllers were designed for infants given oxygen via an oxyhood or incubator, and were tested in simulation studies using a mathematical model of the neonatal respiratory system. For both algorithms, although oxygen saturation was measured, the PID algorithm used partial pressure of arterial oxygen derived from SpO_2 as the input.

One of the features of the earlier algorithm (Tehrani and Bazar, 1994) was frequent adjustment of the setpoint of PaO_2 within the range of 80-90 mmHg while in the later

version (Tehrani, 2001) a stepwise algorithm was incorporated to respond to abrupt desaturations, followed by a switch back to the PID algorithm for fine regulation.

Beyond those mentioned above, Morozoff and Evans (1992) described a "differential" feedback-control algorithm, which was studied in ventilated infants. The algorithm used the sign of the error as well as the velocity and acceleration of the filtered SpO_2 to make FiO_2 adjustments, followed by a delay in which no further adjustment was made. Based on the described inputs and function of the controller, and with a lack of further detail about the manner of reaching control decisions, this algorithm can hardly be considered a subset of PID family.

The controller was too slow to properly respond to rapid desaturations and manual interventions were regularly necessary. The authors suggested that incorporation of an algorithm to identify and respond to rapid desaturations would improve performance. In the most-recently published and the only experimentally-tested example of a PID algorithm for automated FiO_2 control (Morozoff and Smyth, 2009) the performance of three different controllers was compared. The results indicated that besides its need for manual tuning, the tuned PID algorithm performed comparably to a state-machine controller in terms of SpO_2 targetting and manual interventions but not as good as an adaptive one.

2.3.3   Adaptive Controllers

Adaptive control is an approach to control in which the behaviour of the algorithm is adjusted based on varying characteristics of the process and its signals (Isermann, 1989). This approach has been used in a number of the automated oxygen control devices for newborn infants described in the past 3 decades. One of the earliest and most significant contributions was made by Sano and Kikucki (1985). Their adaptive feedback controller was intended for newborn infants receiving supplemental oxygen in an incubator.

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In their study, the relationship between FiO_2 and oxygen pressure inside the incubator (PiO_2) was described by a first order differential equation, and the association between PiO_2 and PaO_2 was estimated by another first order equation. The second equation was then estimated as a linear equation (equation 2.2) neglecting the time constant of the body compared to the incubator.

The slope and intercept of the line described in equation 2.2 namely K_1 and K_2 were considered the changing variables during adaptive control. The two equations were then combined to create a discrete mathematical model of the PaO_2 in response to FiO_2. This combined model with average K_1 and K_2 for infants with lung disease was called the nominal model.

$$PaO_2 = K_1 \times PiO_2 + K_2 \tag{2.2}$$

A model reference adaptive control approach was then used, consisting of two parts, an adaptive compensator and an optimum digital controller (figure 2.2). The optimum controller was designed to make FiO_2 adjustments to control the nominal model. The adaptive compensator on the other hand, was in charge of compensating the dynamics of the subject's respiratory system so that the combination of the compensator and the subject remained equal to the nominal model from the controller's point of view. In other words, the optimum controller assumed a constant nominal model of the system while the adaptive compensator adaptively updated itself so that the overall input-output model assumed by the optimum controller was realised.

The controller was tested using an analytical model of the respiratory system and in experimental animals. Despite sophistication of the approach and an apparent depth of physiological understanding on the part of the authors, this work is lacking for supporting clinical data and has shortcomings such as the restricted focus on delivery of ambient oxygen, and the reliance on transcutaneous PO_2 measurement.
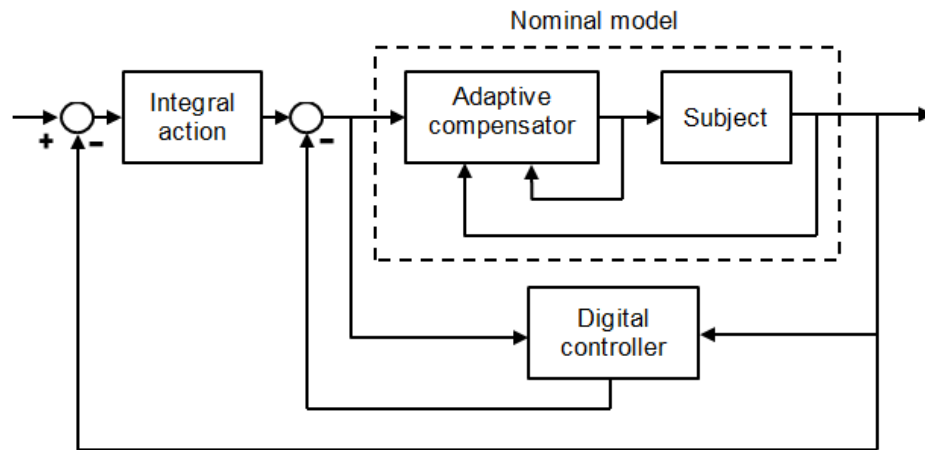
Figure 2.2: Adaptive controller of Sano and Kikucki (1985). Reproduced by permission of the Institution of Engineering & Technology.

In work inspired by Sano and Kikucki (1985), Bhutani *et al.* (1992) examined the performance of a PID algorithm developed within their group (Taube *et al.*, 1988; Taube and Bhutani, 1991). The sole adaptively-tuned parameter was the slope of the PaO_2-FiO_2 relationship. This slope was iteratively calculated using SpO_2 measurement, with the new value of slope being a weighted summation of the previous value and the current ratio of PaO_2 (derived from SpO_2) to FiO_2.

Again the focus was on infants receiving supplemental oxygen by hood. Studies on fourteen infants showed superior performance of the adaptive algorithm compared to both standard protocol-based and bedside manual control in terms of the time spent in the target range, SpO_2 stability and reduced overshoots introducing adaptive approach as an efficient solution.

A further adaptive oxygen controller for neonates was proposed by Morozoff *et al.* (1994), operating on the basis of changes to the FiO_2-SpO_2 relationship. This method described the relationship by a curve (figure 2.3) which consisted of three lines with various slopes and covering various ranges of FiO_2 and SpO_2. The algorithm adjusted the lines periodically by evaluating the proportion of time that was spent within, over or under the target range. The controller made its periodic adjustments
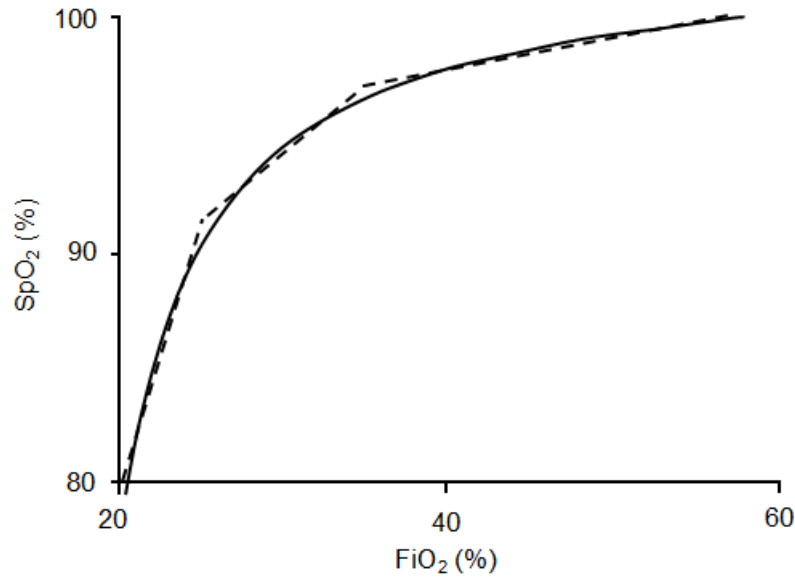
Figure 2.3: A typical FiO_2-SpO_2 relationship and a piecewise linear model for illustration of the method used by Morozoff *et al.* (1994). The solid line depicts the FiO_2-SpO_2 curve and the dashed lines represent the model.

to FiO_2 on the basis of the updated model (curve) at each time.

Shortcomings of this work were the limited justification for the method of updating the lines, and for the determination of the magnitude of FiO_2 adjustments based on the model. The algorithm was compared with manual control, a state machine controller and a PID controller in several infants and appeared overall to achieve the highest proportion of time in the target SpO_2 range, with little need for manual intervention. However the study conditions including the target range were variable and the results were not presented in detail. Morozoff and Smyth (2009) later included these algorithms in clinical experiments with similar findings.

The most clinically-tested algorithm thus far developed for automated oxygen control is also adaptive. Claure *et al.* (2001), devised a hybrid algorithm which is a combination of differential feedback and rule-based control to maintain SpO_2 in a target range. Both timing and magnitude of the FiO_2 adjustments are calculated based on parameters such as current SpO_2, direction and rate of variations in SpO_2, severity and duration of hypxoic/hyperoxic episodes, current FiO_2 and basal FiO_2

during normoxia. Adjustments during hyperoxia are of lesser magnitude and speed than during acute hypoxia episodes.

The algorithm is adaptive in the sense that FiO_2 adjustments are directly proportional to the severity of lung dysfunction, as measured by the current baseline oxygen requirement. After the initial clinical study in mechanically ventilated preterm infants (Claure *et al.*, 2001), several clinical trials have compared the performance of this algorithm with manual control in preterm infants (Claure *et al.*, 2009, 2011; Van Kaam *et al.*, 2015; Waitz *et al.*, 2015). Automated control was associated with a greater proportion of time in the target SpO_2 range compared with manual control in all studies.

Time spent in the hyperoxic range was reduced. In the early studies this appeared to be at the cost of more time spent in mild hypoxia (Claure *et al.*, 2009, 2011), although in the two most recent studies time in mild hypoxia has been on par with or less than during manual control (Van Kaam *et al.*, 2015; Waitz *et al.*, 2015). This algorithm is incorporated as an option ($CliO_2^{TM}$) in a mechanical ventilator (Avea, Carefusion, Seven Hills, Australia), and is approved for use in numerous countries. The ($CliO_2^{TM}$) option has not been approved by the US Food and Drug Administration and is thus not currently available in the United States.

Review of existing adaptive control algorithms reveals that their design is based on numerous underlying assumptions. The first assumption is possibility of modelling the oxygenation system a certain way for instance by a single or three lines. The next assumption is that the variables which are used for the purpose of adaptation are predictive of the variations of the system e.g. proportion of time that was spent within the target range or severity and duration of hypxoic/hyperoxic episodes.

Finally, it is assumed that the association of these input variables and the oxygenation dynamics is well known and accommodated by the algorithm. In absence of independent studies on the extent of reliability of these assumptions, results of
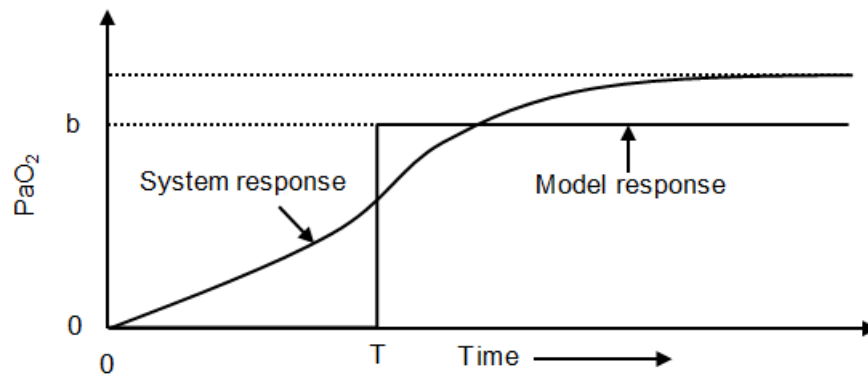
Figure 2.4: An assumed monotonic PaO_2 response to a step change in FiO_2 and its step function model used by Dugdale *et al.* (1988). Reproduced by permission from IOP Publishing.

clinical trials are the only indirect references for assessing their appropriateness.

2.3.4 Robust Controllers

A robust controller is a constant controller which is designed to remain stable and perform within a particular range of control performance despite inexact process model and large parameter changes (Isermann, 1989). Two algorithms designed for automated oxygen control can be classified in this category. The first, by Dugdale *et al.* (1988) was designed to respond to PaO_2 measured using an in-dwelling oxygen sensor in neonates with respiratory distress syndrome (RDS). The algorithm was developed to account for dynamic characteristics of the system under study, and the potential differences between infants.

A monotonic response in PaO_2 was assumed (figure 2.4), and preliminary studies in 5 infants became a basis for calculation of system characteristics. The PaO_2 response was represented by a delayed (T) and scaled (b) step function (figure 2.4). Variables 'b' and 'T' became the design parameters chosen to achieve stability criteria. The stability criteria were defined based on b and T.

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The control rule was very simple; the sampling interval was chosen equal to 'T' and the value of input to the system was equal to the summation of the previous input and ratio of the current error to 'b'. Once the algorithm had been established, function of the controller was evaluated in seven premature infants receiving supplemental oxygen via a headbox and improved targeting compared to manual control was observed. The authors suggested that enhancing the safety aspects of their controller could make it appropriate for routine use.

A further robust controller was described by Keim *et al.* (2011). Clinical data from premature infants was collected during recovery from hypoxia. A first-order transfer function was fitted to the observed FiO_2-SpO_2 relationships, and the parameters of the first-order model were estimated. An error model based on the estimated parameter ranges was created, and consequently developed into a μ-synthesis robust controller (Skogestad and Postlethwaite, 2005).

A detailed description of this method is beyond the scope of this review but as a general statement, this design approach results in the controller in a mathematical optimisation process considering the stability and performance requirements. Keim *et al.* (2011) did not take the time delay of the response into account and the controller was not tested in clinical studies. Moreover, both the assumption of a first order model and the way the parameter estimation was performed had limitations which will be mentioned when discussing the oxygenation variability inherent in the premature infant.

2.3.5   Target Range Achievement and Automated Control

Performance of automated control algorithms can be measured in several ways, including proportion of time in the target range, time spent in varying degrees of hypoxia and hyperoxia when receiving oxygen, number of episodes of prolonged hypoxia and hyperoxia, as well as the number of manual FiO_2 adjustments required.

The analysis should examine the performance in the group of infants overall, but also focus on the most challenging cases (outliers) within the group. Results of clinical trials since 2000 are presented in brief in table 2.1 and 2.2. The manual control outcomes are consistent with the results of independent investigations on target range achievement during manual control (Hagadorn *et al.*, 2006; Laptook *et al.*, 2006; Lim *et al.*, 2014), and in part reflect the span of the target range.

The recent clinical trials have all found automated control to improve time in the target SpO$_2$ range compared with standard manual control, although in some cases the benefit has been modest. The variable extent of improvement in different trials may stem from factors such as the chosen target range and the approach to manual control, but also reflect the effectiveness of the algorithm itself. Further information about these trials can be found in a systematic review by Hummler *et al.* (2014) and elsewhere (Claure and Bancalari, 2015a,b).

Table 2.1: Settings and outcomes of clinical trials on automated oxygen control for preterm infants.

Author, year	Control algorithm	Target Range	Time proportion within target range (manual)	Time proportion within target range (automated)
Claure et al. (2001)	Claure et al. (2001)	88-96%	66% (dedicated)	75%
Urschitz et al. (2004)	Urschitz et al. (2004)	87-96%	82% (routine) 91% (dedicated)	91%
Morozoff and Smyth (2009)	Morozoff et al. (1993) Morozoff et al. (1994)	Manual (90-96%) Automated (target±3%)	57%	73% (adaptive) 71% (others)
Claure et al. (2009)	Claure et al. (2001)	88-95%	42%	58%
Claure et al. (2011)	Claure et al. (2001)	87-93%	32%	40%
Hallenberger et al. (2014)	Urschitz et al. (2004)	Centre-specific	61%	72%*
Zapata et al. (2014)	Lopez et al. (2014)	85-93%	34%	58%
Waitz et al. (2015)	Claure et al. (2001)	88-96%	69%	76%
Van Kaam et al. (2015)	Claure et al. (2001)	89-93% 91-95%	54% 58%	62% 62%

*In this case the automated mode of trial is called routine manual control supported with closed-loop control.

Table 2.2: Other findings of trials on automated oxygen control for preterm infants.

Author, year	Other findings†
Claure *et al.* (2001)	-
Urschitz *et al.* (2004)	Fewer hyperoxic episodes with automated control.
Morozoff and Smyth (2009)	-
Claure *et al.* (2009)	More time in hypoxic range (SpO$_2$ <88%) with automated control, less time in severe hyperoxia.
Claure *et al.* (2011)	More time in moderate hypoxic range (SpO$_2$ 80-86%) with automated control, severe hypoxia not different between groups,less time and fewer episodes of severe hyperoxia.
Hallenberger *et al.* (2014)	Less time below target range with automated control.
Zapata *et al.* (2014)	More time in moderate hypoxic range (SpO$_2$ <85%) with automated control, less time with SpO$_2$ >94%.
Waitz *et al.* (2015)	Severe hypoxia reduced during automated control, and fewer episodes with SpO$_2$ <80% for >60 sec.
Van Kaam *et al.* (2015)	Severe hypoxia reduced with automated control for both target ranges and severe hyperoxia reduced for lower target range, in both cases with fewer 60 sec episodes.

†Definitions: severe hypoxia - SpO$_2$ <80%; hyperoxia - SpO$_2$ >96% when in supplemental oxygen; severe hyperoxia - SpO$_2$ >98% when in oxygen.

2.4 Design Challenges for Automated Controllers

Analysis of the existing approaches reveals challenges which need to be overcome in order to significantly improve the performance of automated oxygen control in preterm infants. Three fundamental issues stand out, these being the variability in the biological system controlling oxygenation, technological shortcomings of both physiological monitoring and oxygen delivery and finally safety considerations including the need to choose an appropriate SpO_2 target range. These challenges are discussed further below.

2.4.1 Variability in Oxygenation

Unpredictable Variability of the Oxygenation Response

The oxygenation response refers to the way in which SpO_2 changes as a result of a change in FiO_2. A variable oxygenation response means that a given FiO_2 adjustment may lead to a different SpO_2 response on different occasions. An automated control algorithm must remain stable and perform reasonably in spite of such variability. Although many existing rule-based controllers attempt to deal with this variability based on expert clinical knowledge, in the field of control engineering, design techniques are heavily dependent on characterising the system under control in the form of an input-output model, and quantifying the possible variations in it as a basis for controller design (as exemplified earlier).

A first-order relationship between FiO_2 and oxygen level in the blood (SpO_2 or PaO_2) has been assumed in algorithms used for automated control in various studies in the past (Sano and Kikucki, 1985; Keim *et al.*, 2011; Lopez *et al.*, 2014), but the applicability and characteristics of a first order model have been insufficiently understood. One factor which is known to cause variability is the non-linearity of the PaO_2-SpO_2
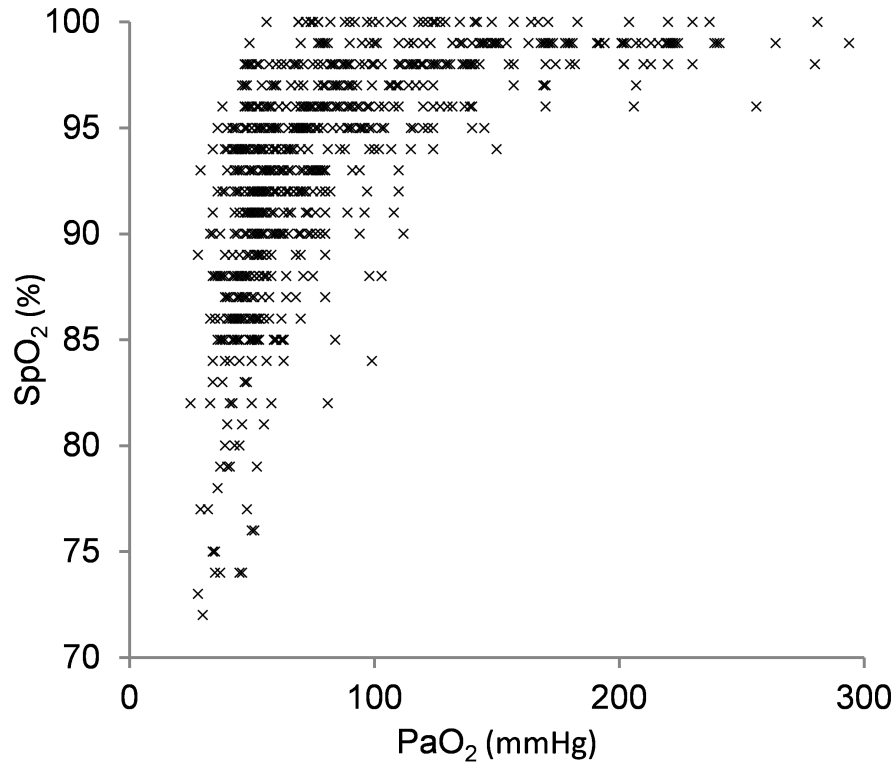
Figure 2.5: The relationship between SpO_2 and PaO_2. Data from 122 preterm infants (Castillo *et al.*, 2008). Reproduced with permission from the American Academy of Pediatrics.

relationship (Castillo *et al.*, 2008) (figure 2.5).

The shape of the PaO_2-SpO_2 relationship results in poor resolution of SpO_2 for estimation of PaO_2 at high levels of saturation; with wide variation in PaO_2 for a single SpO_2 reading (figure 2.5). Use of SpO_2 may thus fail to detect a wide departure in PaO_2 from an acceptable range and distort the first order behaviour. Additionally, parameters that influence the SpO_2-PaO_2 relationship such as temperature and acidity of the blood (Severinghaus, 1979) can also influence the response. Identifying factors which affect the oxygenation response could have important implications and potential applications for adaptation of an automated controller. It is particularly important to find predictors which are available in real time.

Fluctuating Oxygenation in Preterm Infants on Respiratory Support

A major issue with control of FiO_2 in preterm infants is fluctuating SpO_2, limiting the proportion of time a given target range can be achieved. Hyperoxia in preterm infants is related to unnecessarily high levels of FiO_2 (Bancalari and Claure, 2012) and automated controllers developed so far are relatively successful in managing this condition. Note that SpO_2 values above target range ($\geqslant 96\%$) when in room air are not considered hyperoxia, and simply reflect intact oxygen transfer. Hypoxia on the other hand has a legion of causes, including worsening lung dysfunction, transient airway blockage, diaphragmatic splinting and apnoea (Poets *et al.*, 1992; Bolivar *et al.*, 1995; Poets, 2010).

Decrease in lung volume and development of an intrapulmonary shunt as result of diaphragmatic splinting in expiration has been identified as one cause of hypoxia in mechanically ventilated preterm infants (Bolivar *et al.*, 1995), with agitation and hypoventilation more generally being additional factors (Bancalari and Claure, 2012). Agitation and hypoventilation are also important in the genesis of hypoxia in non-ventilated infants on non-invasive support, with apnoea being an important additional cause (Pantalitschka *et al.*, 2009).

Hypoxia imposes two challenges on the design of a controller. The first is that characteristics of hypoxic events, including their frequency and severity, should be considered in algorithm design. For instance rule-based controllers making periodic FiO_2 adjustments may not be optimally effective in treatment of infants with fast and frequent declines in SpO_2. The severity of a hypoxic event on the other hand defines the position on the oxygen dissociation curve, which as discussed earlier affects the oxygenation response and ultimately the magnitude of adjustment in FiO_2 that is required.

The second challenge is that the appropriate response to a hypoxic event should vary according to its cause. Apnoea-induced hypoxia is an example, with an FiO_2

increment before apnoea cessation being unlikely to immediately increase alveolar PO_2, given that the infant is not breathing. Repeated FiO_2 increments during apnoea would likely increase the risk of post-apnoeic hyperoxic overshoot. Identifying the cause of hypoxic events using additional inputs to the control algorithm may thus be useful in scheduling FiO_2 adjustments. Identification of the causative mechanism of hypoxia may also be useful in prediction of the likely oxygenation response, and allow adaptation of the control algorithm accordingly.

2.4.2   Technologic Shortcomings of Automated Control

Oxygenation Monitoring

Apart from early automation efforts using PaO_2 measured via indwelling umbilical artery electrodes or transcutaneous sensors as the feedback signal (Beddis *et al.*, 1979; Sano and Kikucki, 1985; Dugdale *et al.*, 1988), more recent control devices have relied on SpO_2 derived from pulse oximetry as the primary, indeed the sole input. This is due to the ease of measurement of SpO_2 in comparison with partial pressure of oxygen in the blood. However, pulse oximetry has well-known shortcomings (Poets and Southall, 1994). The non-linear SpO_2-PaO_2 relationship discussed earlier is the major inherent issue. If with technological advances the possibility emerges to measure PaO_2 non-invasively and accurately for extended periods, this might be the preferred oxygenation input to guide automated oxygen control.

Other practical shortcomings of monitoring SpO_2, especially poor accuracy in low perfusion and most notably motion artefact, deserve consideration. Among other issues with pulse oximetry, low accuracy even of newer generation devices at low saturation levels (Dawson *et al.*, 2014) and the problem of signal dropout are most prominent. These problems are particularly relevant during automated control when FiO_2 adjustments are being made solely based on SpO_2.

Respiratory Monitoring

Apart from oxygenation, monitoring of respiratory motion (i.e. spontaneous breathing movements) is another area where technological advances can offer a benefit in automated FiO_2 control for preterm infants. As stated above, alterations in respiratory pattern can trigger hypoxic events and require increments in FiO_2. Furthermore, other informative parameters such as estimations of the lung volume during non-invasive ventilation and phase shift between the thoracic and abdominal movements are potential outputs from respiratory monitoring. Continuous measurement of respiratory motion might thus provide future automated controllers with an unprecedented level of knowledge about the infant when making control decisions.

The existing respiratory monitoring methods can be divided into contact and noncontact approaches. Contact devices including respiratory inductance plethysmography (Mazeika, 2007) and pressure sensor plethysmography (Banovcin *et al.*, 1995) are capable of relatively reliably monitoring respiratory patterns but they are difficult to use continuously and may intervene the routine nursing care of the infant. Noncontact devices on the other hand are preferable in terms of minimal disturbance to the patient but they have not reached an adequate level of maturity for becoming a part of routine clinical care (AL Khalidi *et al.*, 2011).

Examples of noncontact approaches include radar (Lee *et al.*, 2014), vision-based (Tan *et al.*, 2010) and thermal (Abbas *et al.*, 2011) methods. Despite the potential benefits, measurement of respiratory patterns beyond respiration rate is currently not a part of routine clinical care for preterm infants.

Lack of specialised hardware for automated control of oxygen delivery

Beyond the important technological issues mentioned above, a further problem that can be addressed more easily is the lack of specialised equipment capable of

receiving control commands from a digital signal and producing a desired FiO_2. Whilst there are several purpose-built devices for automated control, these are not widely available in NICUs worldwide. Mechanical ventilators into which a control algorithm has been incorporated have the disadvantage of high capital cost, with the end result being lack of access to the automated control technology.

A stand-alone automated oxygen control device with a state-of-the-art adaptive algorithm, specifically designed for non-invasive ventilation, would thus be an advantage. Such a device would find a place in NICUs in the developed world, but also in low-resource settings in which the standard of care for preterm infants is gradually improving, but risk of mortality and retinopathy of prematurity remain high (Maida *et al.*, 2008; Howson *et al.*, 2012).

2.4.3 Safety Considerations and Target Range

Safety Considerations in the Existing Controllers and Role of Caregivers

A high priority should be given to safety in the design of any medical equipment to be used in preterm infants, and it appears that attention has been paid to this concern in current automated oxygen control devices. In-built safety precautions currently include various alarms to alert bedside caregivers, along with rudimentary SpO_2 validation procedures and suspension of algorithm function and default to a preset FiO_2 if the signal is invalid.

These actions were triggered by repeated FiO_2 adjustments in a single direction (Beddis *et al.*, 1979; Dugdale *et al.*, 1988), sudden/rapid SpO_2 falls (Tehrani and Bazar, 1994; Urschitz *et al.*, 2004), low quality SpO_2 signal (Urschitz *et al.*, 2004; Claure *et al.*, 2009; Hallenberger *et al.*, 2014; Zapata *et al.*, 2014), low SpO_2 values (Tehrani *et al.*, 2002; Urschitz *et al.*, 2004), SpO_2 remaining outside the target range for a minimum

duration (Lopez *et al.*, 2014), and missing signal or device disconnection (Morozoff and Evans, 1992; Claure *et al.*, 2001, 2009).

The process of automated oxygen control is complicated by the fact that a change in FiO_2 alone may not always be the best action, and intervention of clinical staff may be necessary particularly in cases where a hypoxic event stems from impaired ventilation including apnoea (Bancalari and Claure, 2012; Claure and Bancalari, 2013a). Thus, rather than entirely replacing manual care, automated controllers should be thought of as providing "on-time care" for preterm infants, decreasing the workload of the nursing staff (Claure, 2007). The potential for reduced attentiveness of the bedside staff, and failure to recognize deterioration of an infant's condition, are concerns which have been expressed (Bancalari and Claure, 2012; Claure and Bancalari, 2013a). Design of alarms to alert staff to persistent increase in oxygen requirement is thus important (Claure and Bancalari, 2015b).

Target Range Limits

Regardless of the type of control algorithm, another difficulty of oxygen targeting both in manual and automated control is the selection of the target range boundaries. Three recent large scale clinical trials involving thousands of preterm infants (SUPPORT, 2010; BOOSTII *et al.*, 2013; Schmidt *et al.*, 2013) have compared a lower oxygen saturation range (85-89%) with a higher range (91-95%). Two of these studies (SUPPORT, 2010; BOOSTII *et al.*, 2013), as well as a systematic review and meta-analysis of all the three (Saugstad and Aune, 2014), suggested that the lower range resulted in a reduction in retinopathy of prematurity but an increase in mortality.

Recommendations to avoid saturations below 90% have followed (Askie, 2013), (Triven Bashambu *et al.*, 2012; Bancalari and Claure, 2013; Saugstad and Aune, 2014), but some uncertainty about the most appropriate target range remains (Sola *et al.*, 2014). Saugstad and Aune (2014) also highlighted other unanswered questions, such

as whether the target range should be altered for different gestational ages, or over time, or based on patient conditions.

Apart from the safety considerations, selection of the SpO_2 target range may have consequences for FiO_2 control, including on the incidence of hypoxia. Di Fiore *et al.* (2012) found an association between lower target range and higher rate of intermittent hypoxia at certain postnatal ages. In another study of the effect of target range on outcome of automated control in 21 infants, a narrower and higher target range (90-93% vs. 87-93%) did not increase the time spent in the range of 87-93% but it made the SpO_2 distribution tighter (Wilinska *et al.*, 2014).

The optimal span of the SpO_2 target range for automated control remains to be determined, and should be a topic for further research. A further related question for study in this context is where within the target range to locate the "set point", and whether to attenuate error where SpO_2 readings fall within the desired range.

2.5 The Road Map

The identified challenges direct us towards investigation of the oxygenation system variability both in the form of response vagaries following FiO_2 adjustments and also hypoxia. Modelling the the oxygenation response in large datasets obtained from preterm infants and assessing the validity of these models can be of great value. Such models can quantify the variations of the oxygenation response and be utilised as a basis for developing automated controllers. Performing prediction studies on the model and seeking predictors of the variability are also necessary in order to develop adaptive algorithms.

Another area where further research is required is assessment of hypoxic events and the concomitant factors of apnoea, loss of CPAP pressure and motion artefact. These factors can complicate the process of automated control by increasing the risk

of overshoot; thus, having an account of the frequency of such incidences would clarify the necessity of any potential design consideration to address the issue. The relationship between various types of apnoea and the associated hypoxia is also important because existence of this association could help to differentiate different types of apnoea-induced hypoxia and react to them correspondingly.

Finally, SpO_2 signal dropouts may impose a safety risk during automated control by leaving the controller with no reference to make the decisions. Therefore, investigation of these incidences and the signal values before and after their occurence helps to identify the appropriate actions while the signal is missing. The rest of this thesis is dedicated to following these directions.

Chapter 3

FiO$_2$-SpO$_2$ Modelling, Assessment of Validity and Predictability

3.1 Summary

This chapter presents an investigation of the gain, delay, and time-constant parameters of the transfer function describing the relation between fraction of inspired oxygen (FiO_2) and oxygen saturation in the blood (SpO_2) in preterm infants. The parameters were estimated following FiO_2 adjustments and goodness of fit was used to assess the validity of the model when using an assumed first-order transfer function. For responses identified to be first-order, the estimated parameters were then clustered to identify areas where they tended to be concentrated. Each group described an operating region of the transfer function; thus, predicting the right operating region could potentially assist a range-based robust inspired oxygen controller to provide more optimal control by adapting to different clusters. Accordingly, the samples were assigned labels based on their cluster associations and 14 features available at the time of each adjustment were used as inputs to an artificial neural network to classify the clustered samples. The validity study suggested that 37% of the adjustments were followed by first-order responses. Prediction studies on the first-order responses indicated that the clusters could be predicted with an average accuracy of 64% when the parameters were divided into two groups.

3.2 Introduction

One of the main challenges in automatic control of FiO_2 in newborn infants is the varying behaviour of their individual respiratory system (Sano and Kikucki, 1985). These variations are caused by the different respiration patterns as well as problems that are associated with keeping the alveoli open (Donn and Sinha, 2012). In order to design a controller, the system's behaviour needs to be characterised first.

First-order transfer-functions describing the relation between a change in FiO_2 and the consequent change in the oxygen level in the blood are usually used to design controllers (Yu *et al.*, 1987; Sano *et al.*, 1988; Keim *et al.*, 2009, 2011; Krone, 2011). The transfer function consists of three parameters namely gain, time-constant and delay. One of the important issues in using the model and estimating its parameters is the feedback signal, as the oxygen saturation and partial pressure of oxygen (PaO_2) in the blood have a nonlinear relationship described by the oxyhemoglobin dissociation curve (Severinghaus, 1979; Castillo *et al.*, 2008; Donn and Sinha, 2012) and the first order relation between oxygen saturation and FiO_2 is only true by making a linear approximation of PaO_2 and SpO_2 around an operating point (Yu *et al.*, 1987).

When SpO_2 is measured using pulse oximetry an error is introduced (Trivedi *et al.*, 1997) due to limitations of the technology used in identifying different forms of hemoglobin (Donn and Sinha, 2012). This is important because the SpO_2 signal is the preferred feedback in more recent works (Tehrani *et al.*, 2002; Urschitz *et al.*, 2004; Iobbi *et al.*, 2007; Morozoff and Smyth, 2009; Claure *et al.*, 2011; Tehrani, 2012) due to its non-invasive method of acquiring measurements and existing use in clinical practice.

In the preterm infant, the nature of the feedback signal is not the only concern, as other factors including the presence of respiratory distress syndrome and tendency to have apnoea (temporary cessation of breathing) may interfere with oxygenation

(Belal *et al.*, 2011; Lee *et al.*, 2012) in a chaotic and un-predictable manner. In the case of apnoea, increasing FiO_2 may not affect the oxygen saturation, especially when infants are being supported with a device delivering continuous positive airway pressure (CPAP), which unlike mechanical ventilation relies on spontaneous breathing for delivery of air-oxygen mixture to the airspaces.

Despite these factors that make it difficult to characterise the oxygenation behaviour in neonates, a number of previous studies (Versmold *et al.*, 1978; Sano and Kikucki, 1985; Dugdale *et al.*, 1988; Bhutani *et al.*, 1992) have investigated the oxygenation response to FiO_2 adjustments in this group of patients. Particular attention was given to the estimation of the first order transfer function parameters with SpO_2 feedback (Keim *et al.*, 2011; Krone, 2011) in an attempt to design robust FiO_2 controllers for preterm infants. However, in both these studies only a subset of SpO_2 increases was used for parameter estimation and in neither case was the time-delay estimated.

Although variations of the parameters are accounted for in (Keim *et al.*, 2011; Krone, 2011), using a subset of events for parameter estimation is inappropriate as it does not encapsulate the nature of the excluded events when estimating the parameters. It should be noted that these estimated parameters are used to design robust controllers that must cater for both positive and negative adjustments.

The question that arises is to what extent does the first order transfer function, which incorporates a time delay between SpO_2 and FiO_2, represent the oxygenation response of preterm infants? Another question is whether it is possible to divide the set of parameters into groups with less variability and predict at each time the group that the transfer function parameters belong to. As the parameter range in each cluster is narrower than the entire set, the operating region of the transfer function is more exactly specified and the controller can thus provide more optimal control by adapting itself to the parameter range in each group.

The objective of this chapter is to clarify these issues for newborn infants who are

receiving supplemental oxygen from a CPAP device. An introduction to the dataset as well as the detailed methodology is presented in Section 3.3 and the results are presented in Section 3.4 followed by the discussion and conclusions in Section 3.5 and Section 3.6, respectively.

3.3 Material and Methods

3.3.1 Dataset

The data set was obtained from 34 preterm infants recorded over 3475 hours at a sampling frequency of 1 Hz at the Neonatal and Paediatric Intensive Care Unit (NPICU) of the Royal Hobart Hospital (Lim *et al.*, 2014). The study was approved by the institutional ethics committees and performed after obtaining parental consents. The enrolled infants were all receiving CPAP, and were in supplemental oxygen (i.e. $FiO_2 > 0.21$) at the start of each 24 hour recording. Median (interquartile range) gestational age was 31 weeks (28-32 weeks) and birth weight 1.4 (1.0-2.0) kg. Inspired oxygen concentration was being regulated by manually applying step adjustments using an air-oxygen blender.

For this analysis, FiO_2 adjustments of at least ± 0.01 were identified, and the consequent changes in SpO_2 were logged to examine the input-output relation of the system. These adjustments were not instant step changes as the transitions took a few seconds. The step position was defined as the first point where the change in FiO_2 was detected. Isolated FiO_2 adjustments, with no other FiO_2 change within 2 minutes before and after, were extracted for analysis.

This isolation was checked tolerantly to be more inclusive. Suppose that a time-window of 2 minutes ending at the step position is called $episode_1$ and another window starting at the end-point of the adjustment and ending 2 minutes after the

step position is called $episode_2$. To check the isolation, the difference between the FiO_2 values at the first sample of $episode_2$ and last sample of $episode_1$ was first calculated as an estimation of the magnitude and checked to be at least ± 0.01.

An adjustment was considered isolated if the FiO_2 values during $episode_1/episode_2$ did not deviate from the FiO_2 at the end/beginning point of the episode more than 25% of the step magnitude for longer than 10 seconds. This means that small deviations in comparison with the large step as well as large deviations for a short time were tolerated. Because of this tolerant selection, the difference in mean FiO_2 in $episode_2$ and $episode_1$ was considered as the adjustment magnitude and rechecked to see if it was still at least ± 0.01.

The time-window in SpO_2 that was considered for parameter estimation started at the step position and covered the next 2 minutes. Adjustments for which the SpO_2 signal was missing at the step position, or for more than 30 seconds during the next 2 minutes, were excluded. The previous sample was used to fill the missing points for short SpO_2 dropouts. A total number of 2369 adjustments met the requirements and were used in the analysis. As the transfer function described the relation of the changes of SpO_2 and FiO_2, the measurements were reported relative to their value at the step position. This was accomplished by subtracting the magnitude recorded at the step position from all of the sequential measurements. Additionally, the percentage of inspired oxygen, ($FiO_2 \times 100$) was used for estimation of the transfer function parameters (Keim *et al.*, 2011).

3.3.2 Methods

The gain, time-constant and delay of the transfer function were first estimated following FiO_2 adjustments using the dataset. For this purpose, inspired by (Krone, 2011) it was initially attempted to estimate the gain and the delay directly from the data while obtaining the time-constant in an optimisation process. The inovative

Binary optimisation method used for this purpose led to a conference publication (Fathabadi *et al.*, 2013) which can be found in the Appendix A. However, since the direct estimations of gain and delay were not accurate, it was decided to estimate all the three parameters in an optimisation process. This was done by fitting the corresponding difference equation of the transfer-function describing the FiO_2-SpO_2 relation to the experimental data.

Minimisation of the error between the simulated and experimental data was performed using a genetic algorithm. R^2 metric was then used as a measure of validity of the assumed first-order transfer-function.

Responses for different levels of fitness were observed and a threshold was selected so that the adjustments with a better fit were recognised as first order. The percentage of the recognised adjustments was considered as an indicator of the validity of the model. This step was followed by applying an expectation-maximisation (EM) clustering algorithm (Witten and Frank, 2005) to the transfer-function parameters for the identified first-order responses. The adjustments were then labelled by their cluster assignments and for each of them 14 features were extracted. These features which include available signals and patient information, were used as inputs to an artificial neural network to predict the labels.

Parameter Estimation

The S-domain transfer function describing changes in SpO_2 after FiO_2 adjustments using pulse oximetry for measurement of SaO_2 (Yu *et al.*, 1987) is given as

$$\frac{\Delta SpO_2}{\Delta FiO_2} = \frac{G}{\tau s + 1} e^{-T_d s}.$$ (3.1)

In this equation, the parameter G denotes the gain, τ the time-constant and T_d the

delay. This transfer-function represents a time-shifted decaying exponential impulse response. This system can alternatively be represented by a discrete transfer-function in the Z domain (Widrow and Stearns, 1985) as

$$\frac{\Delta SpO_2}{\Delta FiO_2} = \frac{cZ^{-k_0}}{1 - dZ^{-1}}, \tag{3.2}$$

where $k_0 \in \mathbb{N}$ is the time-delay, $c/(1-d)$ is the gain (Z=1), with $c, d \in \mathbb{R}$ and $-1/\ln d$ is the time-constant. Since the step changes of FiO$_2$ in the experimental data were used and the initial levels of the two signals were negated, equation 3.2 for the remaining signals could be written in the form of a first order difference equation given as

$$SpO_2(k) = dSpO_2(k-1) + cFiO_2(k-k_0). \tag{3.3}$$

The variables d, c, and k_0 (consequently delay, time-constant, and gain) were estimated by minimising the mean squared error between the model and experimental SpO$_2$ over the window of interest. After estimation of the parameters for all of the adjustments, the goodness of fit between the model and the experimental data was assessed based on R^2 metric. The estimations were done based on the first-order assumption and those responses which did not follow the first order pattern reported a poor fit for the model. This means that first-order responses had a higher R^2 and to discriminate them from the rest, a threshold had to be defined. Selection of a threshold was performed by observing the model output and the experimental data over numerous samples in different ranges of R^2 metric.

Cluster Analysis

In cluster analysis samples in a dataset are divided into several clusters. The number of clusters could be defined in advance or obtained during an iterative process. There are numerous clustering techniques which vary in terms of the model that they use for representing the dataset as well as the search process. The Expectation Maximisation (EM) clustering algorithm (Witten and Frank, 2005) was used in our study to divide the entire set of parameters from the first-order responses into clusters with narrower parameters ranges. In this statistical method the dataset is represented by a mixture of probability distributions each representing one cluster.

A feature of EM algorithm is that rather than strictly dividing the samples into clusters, they are attributed to each cluster by a probability level. Moreover, a probability value is assigned to each cluster defining its likelihood. Gaussian probability distributions are used in this thesis to describe the clusters which can be defined by their mean and standard deviation.

The search process starts from initial guesses for the mean and standard deviation of the distributions as well as likelihood of each cluster e.g. 3n-1 parameters for n clusters. Then, the EM algorithm iteratively updates the probability of clusters (expectation) and parameters of the distributions (maximisation). The iteration continues until the increase in a so called "overall-likelihood" objective function becomes less than a threshold. Further information can be found in (Witten and Frank, 2005).

The algorithm was first applied to determine the optimal number of clusters which described the data set by using cross validation (Witten and Frank, 2005). Using this technique, clustering was performed for different number of clusters and the cross-validation likelihood of the cluster assignments was calculated. The number of clusters for which the likelihood was maximum and its corresponding cluster assignments were then selected as the outcome of the cluster analysis. Also, the clustering

was repeated by setting the number of clusters to 3 and 2 and the adjustments were labelled accordingly. Selecting fewer clusters increases the chance of prediction by tolerating wider variations in each cluster.

Feature Extraction

Since the transfer function parameters express the behaviour of the respiratory system, it was first required to extract features that carried information about the state of the system in order to predict the clusters. SpO_2 gives the current oxygen saturation and was selected as the first input. This parameter is important as it is related to the position on the hemoglobin dissociation curve (Severinghaus, 1979).

The heart rate affects the perfusion of the lungs and may affect the way SpO_2 responds to FiO_2 adjustments; this possible relation comes to mind when considering the fact that sometimes acute episodes of desaturation and apnoea are accompanied by a decrease in heart rate known as bradycardia (Poets *et al.*, 1993). The respiratory rate was also included as it affects the ventilation of the alveoli in the lungs where the oxygen exchange with the blood takes place. Both heart rate and respiratory rate were moving averages over a minute and had a limited capacity in representing the variations of the heart-beat and the respiration dynamics, respectively.

The CPAP pressure at the airway was used as it assists the infant by decreasing the respiration effort and keeping the airspaces open. To account for level of maturity and physical development at birth, four infant-specific parameters were used: gestational age, birth weight, gender and exposure to antenatal steroids (used to enhance lung maturation). Two parameters relating to the time of observation, corrected age (gestational age + age since birth) and current weight were extracted for each adjustment and considered as additional inputs.

The next parameter was the value of FiO_2 at the step position. This parameter was
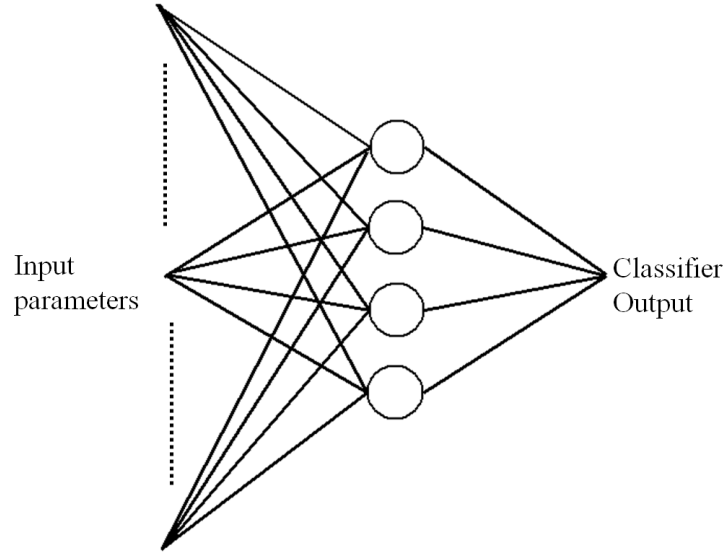
Figure 3.1: Schematic of a typical ANN. Linear combinations of the predictor inputs produce an output after passing throgh nonlinear activation functions.

considered to account for any possibility that the same magnitude of adjustment can cause different consequent changes in SpO_2 given the different absolute values of FiO_2 before the adjustment (Karbing *et al.*, 2007). Recent changes of SpO_2 might contain information that is relevant to the current physiological conditions. For example how rapidly the SpO_2 has fallen before an adjustment might be related to the underlying desaturation mechanism. Thus, having a model of the SpO_2 signal in a window before the adjustment can be useful in prediction of the clusters. A third order autoregressive model of the mean-removed SpO_2 in a 3-minute window before the adjustment was used and is given as

$$x(n) = -a_1 x(n-1) - a_2 x(n-2) - a_3 x(n-3). \tag{3.4}$$

The coefficients a_1, a_2, a_3 were used as the inputs for prediction. The disadvantage of using a low order model is under-modelling of the signal dynamics, while a large order could potentially model the noise. The order 3 was selected using Akaike Information Criterion (AIC) which is given as

$$AIC(p) = \frac{2p}{N} + logV, \tag{3.5}$$

where p is the order of the model, N is the number of samples used in the estimation and V is the noise variance. The model order for which AIC was minimum was considered the best order for modelling the signal (Blinowska and Zygierewicz, 2011). It should be mentioned that sometimes there were missing values in the recorded signals; this was more commonly observed in the SpO_2 signal related to sensor drop-outs. Since the samples were required to fit the autoregressive model, it was not possible to have $a_1 - a_3$ for all of the adjustments.

Thus the 14 selected features are listed here:

- SpO_2 and FiO_2,

- heart rate, respiratory rate and CPAP pressure,

- gestational age, birth weight, gender and steroid exposure,

- corrected age and current weight,

- parameters $a_1 - a_3$.

Missing values of any given feature were filled with random numbers in the range of the available samples for that feature. This allowed a sample to be used for prediction when a few of its relevant features were not available.

Parameter Classification

Classification was performed using artificial neural networks (figure 3.1). Networks with a single hidden layer and a hyperbolic tangent sigmoid activation function

in both hidden and output layers were trained to classify the parameters. To train the classifier, networks with different number of neurons (from 1 to 50) in the hidden layer were trained. For each selection of the number of neurons, the network was trained 20 times and its performance was recorded in terms of mean and standard deviation of the True Positive Rates (TPRs) (correctly classified samples in a cluster/all of the samples in that cluster) and accuracies (overall number of correctly classified samples/number of all of the samples) over the 20 runs in the unseen test set which comprises 15% of the entire dataset.

During the training if a run caused all of the samples in the test set to be classified in only one class, that run was eliminated from the study and replaced with a new one. This was done to avoid obtaining high accuracies by classifying all of the samples in the class that has the most number of members. The remaining samples of the dataset included 70% training set and 15% validation set that were used during the process of training. To compare the performance of the networks with different number of neurons in the hidden layer the formula given as

$$score = \frac{\sum\limits_{i=1}^{N} TPR_{i(\mu-\sigma)}}{NC} + accuracy_{(\mu-\sigma)}, \tag{3.6}$$

was used to score each classifier. In this equation, NC is the number of classes.

TPR for each class defines the sensitivity of the classifier to that class. However, since a high sensitivity can be obtained by assigning all the samples to one or a few of the classes, it doesn't guarantee a high precision. The overall accuracy of the classifier should also be considered to have a better judgement of the classification performance. On the other hand, accuracy describes the overall success of the classification and TPR is defined for each class.

To define the score formula shown in equation 3.6 that gives the same weight to the accuracy and TPR, the latter was averaged over the classes and summed with

the accuracy of the network. Evaluation of the score was performed over the test set to avoid selecting an over-fit network. The classifier with the highest score was then selected and its performance was reported. Area under the receiver operating characteristic curve (AUC) was also investigated as an additional measure of the performance for each classifier.

3.4   Results

3.4.1   Parameter Estimation

Bound and linear inequality constraints were set during the application of the genetic algorithm for estimating the parameters. Parameter k_0 was constrained to integer numbers in the range 0-90 seconds and the time-constant was limited to 120 seconds that upper bounds d to $exp(-1/120)$. d and c were lower bounded to zero and finally the gain was limited to 30 which means $c/(1-d) < 30$. Three examples of modelling for four different ranges of R^2 are shown in figure 3.2.

Observing numerous examples in each group, $R^2 > 0.7$ was selected as the threshold. As observed in figure 3.2, the difference between the experimental data and the model has increased for smaller values of R^2. Table 3.1, presents the number and percentage of the adjustments that have fallen into each group based on the goodness of fit as well as the number and percentage of the positive adjustments in each group.

As seen in table 3.1, only 869 of 2369 adjustments (37%) had $R^2 > 0.7$, and were thus first order by our definition. Among the adjustments defined as first order, 507 (58%) were positive, compared with 44% for the entire dataset. χ^2 test was applied to the observed and expected incidences of the positive adjustments for different levels of fitness among the first-order responses. The expected number of positives in each group was obtained as the rounded product of the number of members in
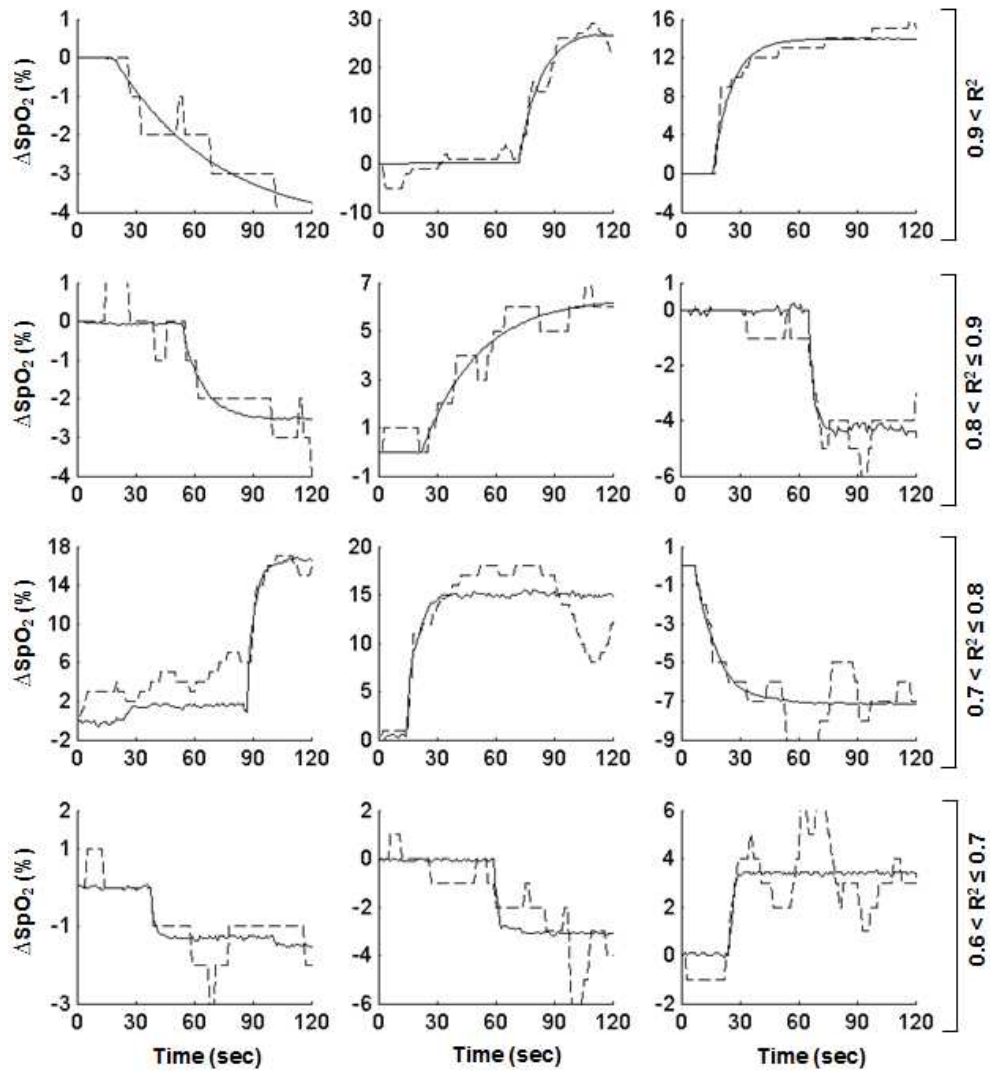
Figure 3.2: Examples of fit for different values of R^2 (solid line: model output, dashed line: experimental data).

that group and the ratio of positive adjustments in the entire dataset.

Histograms of the transfer function parameters for three different ranges of R^2 are presented in figure 3.3 and the median and interquartile ranges of the parameters for different ranges of R^2 among the first order responses are presented in table 3.2. These results show that the gains and the time-constants have concentrated around smaller values as the goodness of fit has decreased, while time delays have become more widespread within the possible range.

Several examples of SpO$_2$ responses following FiO$_2$ adjustments are presented in

Table 3.1: Number and percentage of samples for different fitness levels and the p value for the χ^2 test.

Fitness level (R^2)	No. of members	% of of all	No. of positives	% of positives	P value
(0.95, 1]	126	5.3	107	85	
(0.9, 0.95]	166	7.0	113	68	
(0.85, 0.9]	149	6.3	100	67	
(0.8, 0.85]	156	6.6	74	47	<0.001
(0.75, 0.8]	130	5.5	54	42	
(0.7, 0.75]	142	6.0	59	42	
(0.7, 1]	869	37	507	58	
all	2369	100	1034	44	

figures 3.4-3.9.

3.4.2   Cluster Analysis

Applying the clustering algorithm with cross-validation on the set of parameters for the 869 first order adjustment, 6 clusters were identified as shown in table 3.3(a). Table 3.3(b) and table 3.3(c) present the characteristics and the number of samples in each cluster when the number of clusters was set to 3 and 2, respectively. Different mean values of the parameters in the clusters show how the clusters have divided the entire dataset into smaller subsets and the standard deviations in the clusters indicate to the level of variations in each subset.

3.4.3   Feature Extraction

The ranges of the features are presented in table 3.4. Missing values were most commonly observed in the SpO_2 signal (432 cases) related to sensor drop-outs. Additionally 82 samples of respiratory rate and 2 samples of heart rate in the entire data set (2369 adjustments) were missing. It should be mentioned that all of the features were later normalised to fall into the range of $[-1, 1]$ for training the

classifier.

3.4.4 Classification of the Parameters Using Artificial Neural Networks

For each classifier TPRs and AUCs corresponding to each class and the overall accuracy of the classifier were obtained for both the test set and the whole data. In the case of two clusters, the second class is the alternative of the first class and only one AUC value exists. These results which are presented in table 3.5 showed that the extracted features had limited capability in explaining the variations of the parameters. This limitation was reflected in the small values of TPRs, AUCs and accuracies. The classification accuracy increased by decreasing the number of clusters, where the maximum average classification accuracy was 64% for 2 clusters. However, the average TPR was only 7.5% for the second class in this case and the mean AUC was only 0.47.

3.5 Discussion

Central to optimal automatic control of FiO_2 in newborn infants is an understanding of the SpO_2-FiO_2 transfer function. In a dataset from preterm infants we found that using an R^2 threshold of 0.7 to define validity of the transfer function, only 37% of FiO_2 adjustments were followed by a first order SpO_2 response. Applying EM clustering to the gains, time-constants and delays of the transfer function of first order responses, these parameters were divided into two clusters. With input of a panel of 14 features relevant to the time of each adjustment, in a binary classification using an artificial neural network, it was possible to predict the clusters correctly for 64% of the adjustments.
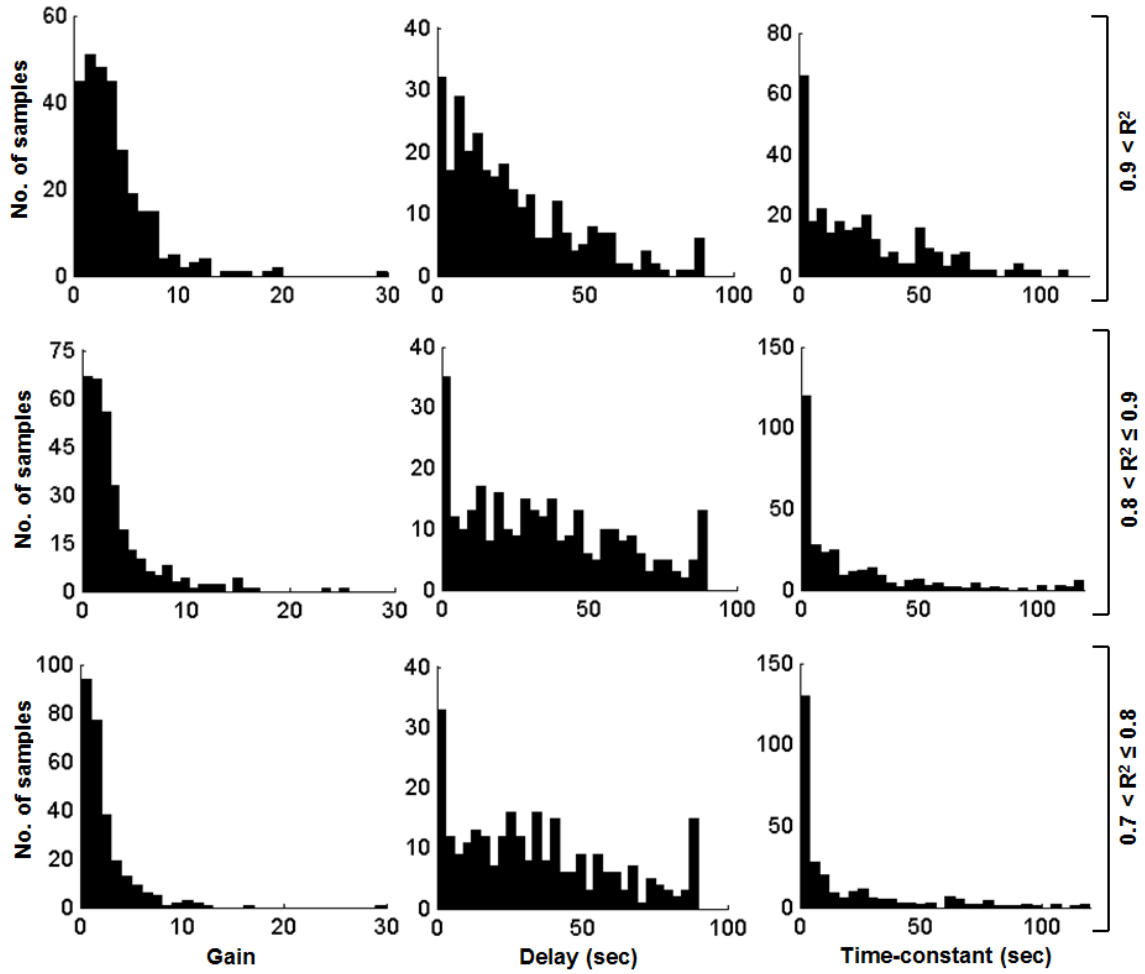
Figure 3.3: Histograms of gain, delay, and time-constant for different ranges of R^2.

3.5.1 The Transfer-Function Model and Dataset

One of the issues regarding developing controllers for automatic control of inspired oxygen is that there is a gap between the language which is used in control theory and the one used by clinicians in dealing with the gas exchange system (Karbing *et al.*, 2011). This chapter attempts to fill this gap by interpreting the physiological system into technical terms using a large set of experimental data obtained from preterm infants. A first order transfer function was the model utilised for this purpose. Investigations performed on this representation would provide a solid experimental background and conclusions which are usable in control theory.

Although transfer functions have been previously used to design oxygen controllers

Table 3.2: Values of the transfer-function parameters for different levels of fitness. Data are presented as median (interquartile range).

Fitness level (R^2)	Gain	Time-constant (seconds)	Delay (seconds)
$(0.9, 1]$	3.2 (1.6 - 5.2)	21 (5.0 - 45)	20 (9 - 39)
$(0.8, 0.9]$	2.1 (1.1 - 3.8)	9.5 (1.2 - 28)	32 (13 - 55)
$(0.7, 0.8]$	1.4 (0.75 - 2.9)	4.6 (0.91 - 25)	30 (13 - 51)
$(0.7, 1]$	2.2 (1.1 - 4.1)	11 (1.6 - 32)	27 (12 - 48)

(Yu *et al.*, 1987; Sano *et al.*, 1988; Keim *et al.*, 2009, 2011; Krone, 2011), using them as a proxy for interpreting a large set of experimental data into technical terms in order to assess validity and predictability of the model is novel. Assessment of validity is important since it provides a basis for designing controllers. Investigating the predictability of the model parameters on the other hand, clarifies whether it is technically possible to predict the variations of the response based on the currently available measurements. Answering this question is valuable since accurately predicting the model variations would make it possible to adapt a controller to the infant over time and make the oxygen delivery safer and more optimal.

The dataset used in this work was a pooled set of FiO_2 adjustments obtained from 34 infants during manual control of oxygen. The adjustments performed during manual control were, in terms of timing, size and adequacy, not necessarily optimal, and were not assumed or required to be so. This is because the adjustments and their consequent responses were used to extract the system properties (or transfer function parameters) under a wide range of infant conditions. Having these parameters for variable conditions gives a realistic image of the situation that a potential controller would face in practice.

3.5.2 Implications of the Results

We observed that the first order model was only valid for 37% of the adjustments. Further, positive FiO_2 alterations were over-represented amongst the first order

Table 3.3: Values of the transfer-function parameters for different clusters (a) 6 clusters selected by cross-validation (b) fixed number of 3 clusters (c) fixed number of 2 clusters. Data are presented as mean $\pm$ standard deviation.

(a)

Cluster label	1	2	3	4	5	6
Gain	1.5 ± 1.1	1.7 ± 1.1	7.9 ± 6.5	4.1 ± 2.6	3.7 ± 2.2	1.4 ± 0.72
Delay	44 ± 18	21 ± 13	42 ± 29	48 ± 25	7.4 ± 6.6	46 ± 19
Time-constant	0.48 ± 0.19	17 ± 8.9	49 ± 32	6.7 ± 4.6	48 ± 26	2.0 ± 1.1
No. of members	145 (17%)	170 (20%)	91 (10%)	133 (15%)	205 (24%)	125 (14%)

(b)

Cluster label	1	2	3
Gain	2.9 ± 2.0	1.5 ± 1.1	6.0 ± 5.2
Delay	12 ± 9.7	45 ± 19	45 ± 28
Time-constant	37 ± 28	1.6 ± 1.5	26 ± 27
No. of members	363 (42%)	309 (36%)	197 (23%)

(c)

Cluster label	1	2
Gain	4.1 ± 3.9	1.5 ± 1.0
Delay	25 ± 25	45 ± 20
Time-constant	33 ± 28	1.6 ± 1.5
No. of members	558 (64%)	311 (36%)

adjustments. The use of exclusively positive adjustments for parameter estimation in previous studies (Keim *et al.*, 2009; Krone, 2011) is thus explained by our finding. Under-representation of negative adjustments is one of the reasons of the limited validity of the model.

Positive and negative adjustments of FiO_2 are related to low and high levels of SpO_2 respectively and it is known that PaO_2 widely varies for high levels of SpO_2 (Castillo *et al.*, 2008). This means that when a negative adjustment is made the PaO_2 might be very high so that its reduction is not reflected in SpO_2 and the expected first order response is not observed. This limitation could be overcome using in-dwelling sensors suitable for long-term monitoring of PaO_2, thus providing more precise measurements of oxygenation at high SpO_2 levels.

Apart from the issue of validity, parameters of the transfer function presented in figure 3.3 for FiO_2 changes followed by first order responses depict wide variations which reflect the difficulties of automated control of oxygen therapy in preterm

Table 3.4: Ranges of the features in the entire dataset.

feature	range
SpO_2 (%)	31-100
FiO_2	21-83
heart rate (min^{-1})	55-207
respiratory rate (min^{-1})	10-143
CPAP pressure (cmH_2O)	5-10
gestational age (weeks)	25-37
birth weight (Kg)	0.6-3.6
gender	0,1(M,F)
steroid exposure	0,1 (False/True)
corrected age (weeks)	26-43
current weight (Kg)	0.6-3.5
a_1	-1.29,-0.63
a_2	-0.58,0.35
a_3	-0.25,0.61

infants. Despite a few instances of long delay and large gain, these two parameters were mostly concentrated around smaller values while time constant was more widespread in its range.

From the physiological point of view during the oxygen control, a large value of the gain parameter means that a given adjustment in FiO_2 may cause a significant overall change in SpO_2. This change could start after a short or long delay and the transition from the current level of SpO_2 to the new level could be slow or fast corresponding to large and small values of time constant, respectively. Thus, a closed loop controller design based on incorrect values of the model parameter might be unstable or sub-optimal in delivering the oxygen.

The cluster analysis performed in the chapter divided the adjustments into groups with less variability of parameters in each one as shown in table 3.2 so that a potential controller has to deal with less variation at any given time. These clusters provide a basis for an adaptive control approach in which the controller switches between the clusters as required. The classifiers developed for predicting the clusters based on the available parameters performed poorly which means it was not possible to accurately define the cluster of transfer-function parameters at each moment of time

Table 3.5: Performance of the artificial neural networks in predicting the clusters (a) a network with 12 neurons obtained the best performance for 6 clusters (b) a network with 27 neurons obtained the best performance for 3 clusters (c) a network with 4 neurons obtained the best performance for 2 clusters. Data are presented as mean $\pm$ standard deviation.

(a)

	Test set			Whole data		
Cluster label	TPR	AUC	Accuracy	TPR	AUC	Accuracy
1	13 ± 9.7	0.38 ± 0.20	22 ± 3.2	19 ± 11	0.42 ± 0.23	29 ± 2.7
2	23 ± 15	0.48 ± 0.10		31 ± 16	0.57 ± 0.10	
3	5.9 ± 5.8	0.49 ± 0.13		12 ± 10	0.58 ± 0.15	
4	15 ± 10	0.54 ± 0.08		20 ± 11	0.60 ± 0.06	
5	49 ± 19	0.53 ± 0.16		54 ± 17	0.57 ± 0.17	
6	13 ± 12	0.43 ± 0.23		18 ± 12	0.48 ± 0.25	

(b)

	Test set			Whole data		
Cluster label	TPR	AUC	Accuracy	TPR	AUC	Accuracy
1	64 ± 17	0.50 ± 0.17	42 ± 4.5	69 ± 12	0.56 ± 0.19	48 ± 4.7
2	38 ± 16	0.47 ± 0.17		43 ± 19	0.57 ± 0.20	
3	8.7 ± 9.5	0.39 ± 0.21		15 ± 11	0.50 ± 0.26	

(c)

	Test set			Whole data		
Cluster label	TPR	AUC	Accuracy	TPR	AUC	Accuracy
1	94 ± 4.6	0.47 ± 0.17	64 ± 3.6	96 ± 3.3	0.51 ± 0.18	65 ± 1.1
2	7.5 ± 8.0			8.7 ± 7.5		

based on the selected features and classifier.

This conclusion about predictability of the clusters emphasises the limitations of the available inputs in explaining the variations of the response and the necessity to measure more relevant inputs to improve the prediction performance. Obtaining such measures could also provide insight into the underlying reasons of non-first order responses apart from shortcomings of the SpO_2 signal.

The study revealed the validity and predictability of the transfer function using a large set of experimental data however; performing similar studies on larger datasets may provide even more robust conclusions. Also, one of the inherent weaknesses of using a time-invariant transfer function as the system representation is that it does not reflect the dynamic changes of the system's behaviour during the modelling window which could be another reason for limited validity of the model.

The chapter has a technical look at the transfer function parameters. This is while the transfer function model is a representation of the characteristics of the SpO_2 response to FiO_2 adjustments. Investigation of the oxygenation characteristics and their relationships with lung disease, SpO_2 disturbances and baseline oxygenation level could have important clinical implications if the transfer function parameters are clinically interpreted. Study of intra- and inter-infant transfer function variability is also of interest. These studies are the topic of Chapter 4.

3.6   Conclusion

The outcomes of this chapter quantify the characteristics of oxygenation response in preterm infants which can be a basis for developing automated FiO_2 controllers. The results indicate that there is a need for measuring more physiological inputs to achieve higher performance in predicting the clusters due to shortcomings of the existing predictors. Because of the non-liniearity/inaccuracies in SpO_2 which can affect the shape and predictability of the oxygenation response to FiO_2 adjustments, using a more precise measure of the oxygen level in the blood as the feedback signal could also help to improve the quality of control.
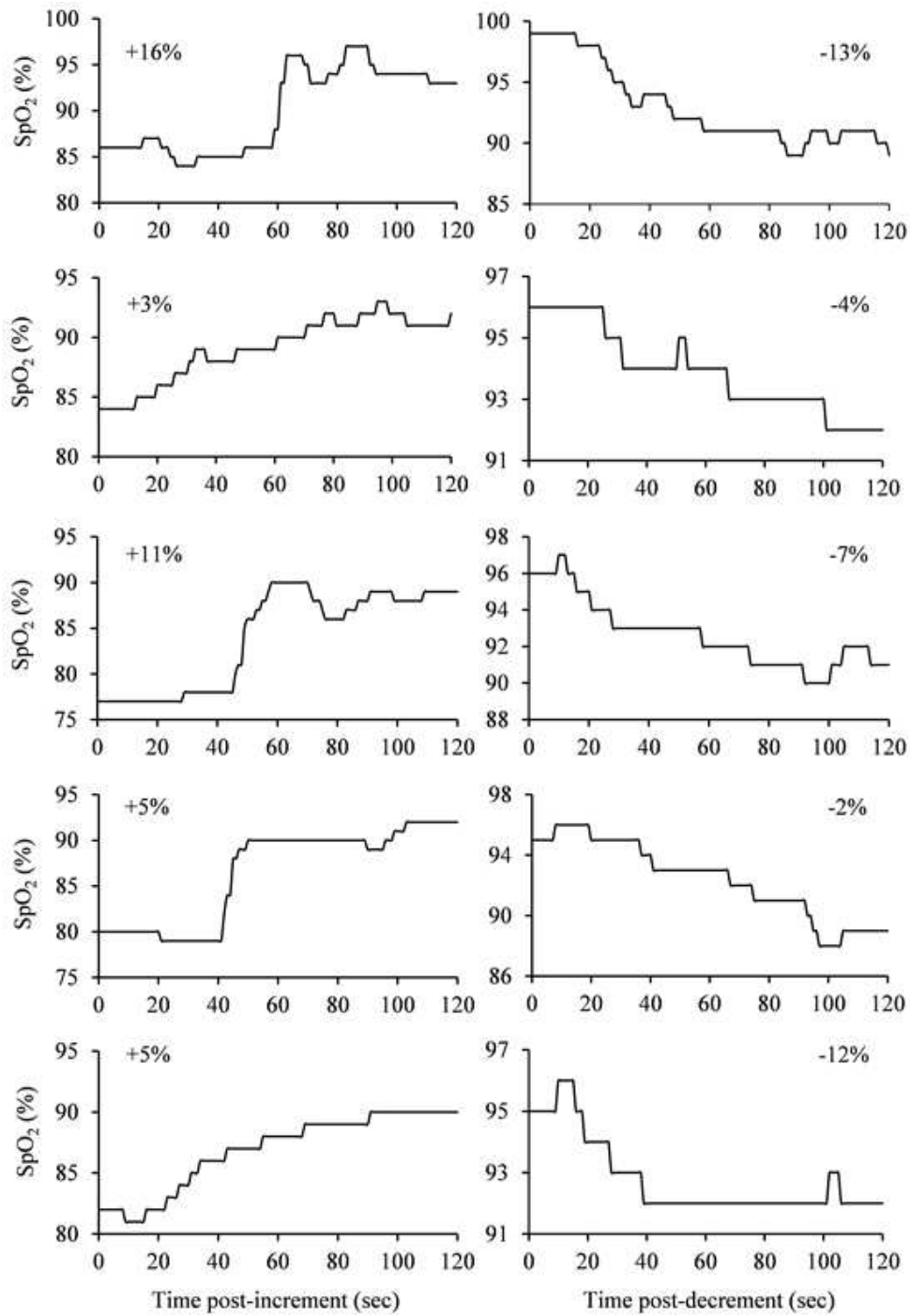
Figure 3.4: Examples of SpO$_2$ responses with $R^2 > 0.9$ following FiO$_2$ adjustments.
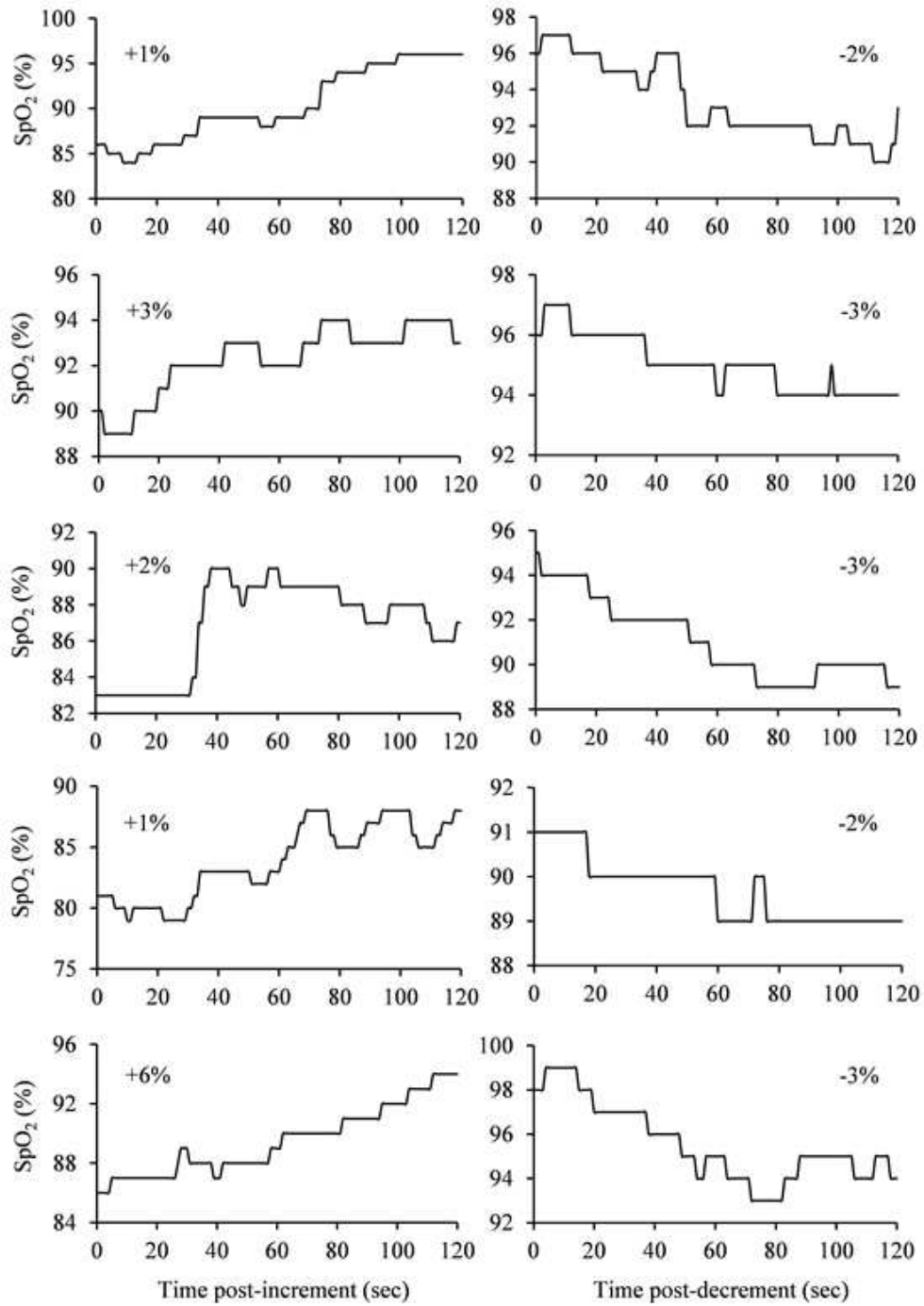
Figure 3.5: Examples of SpO$_2$ responses with $0.8 < R^2 \leq 0.9$ following FiO$_2$ adjustments.

64
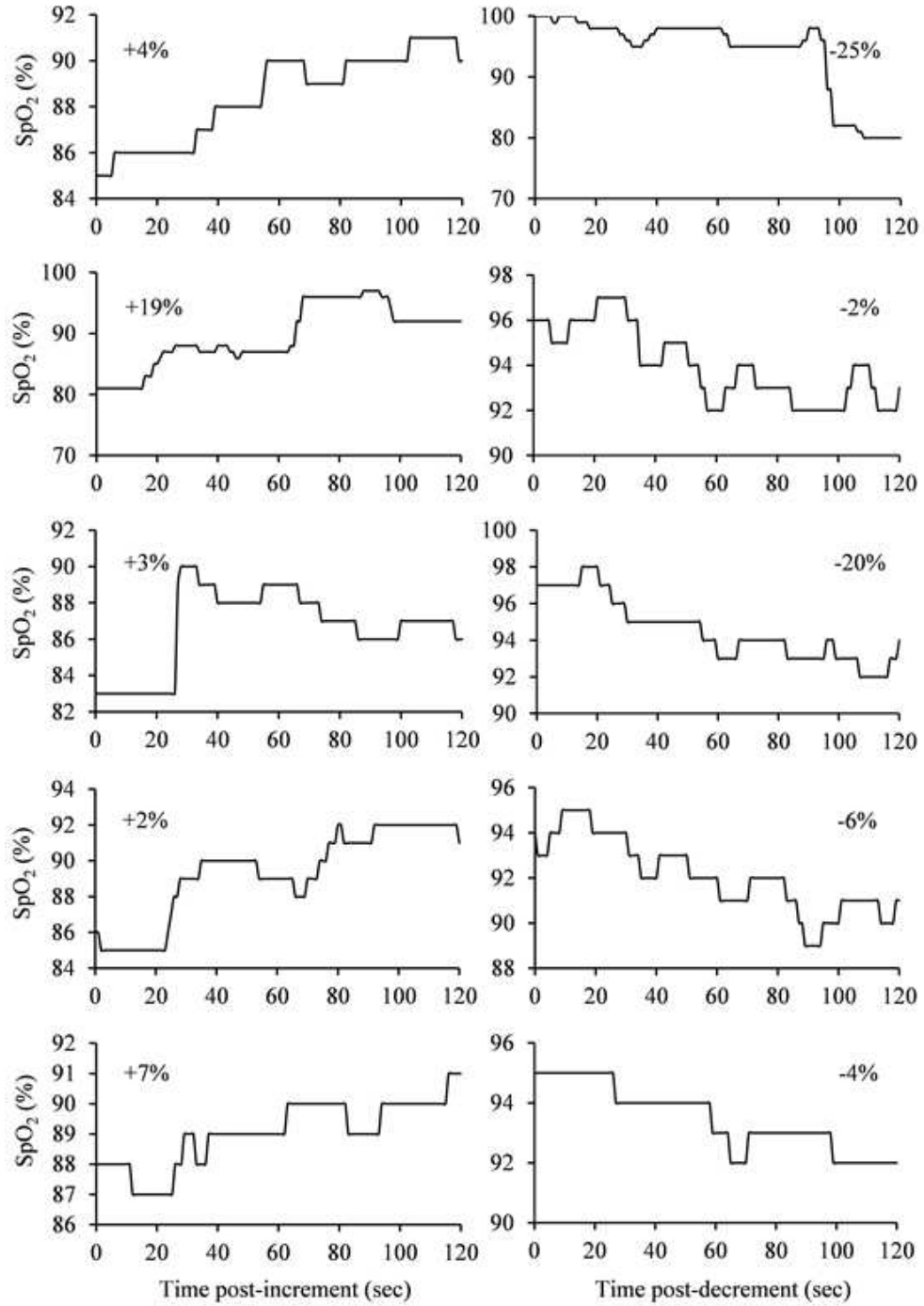
Figure 3.6: Examples of SpO$_2$ responses with $0.7 < R^2 \leq 0.8$ following FiO$_2$ adjustments.
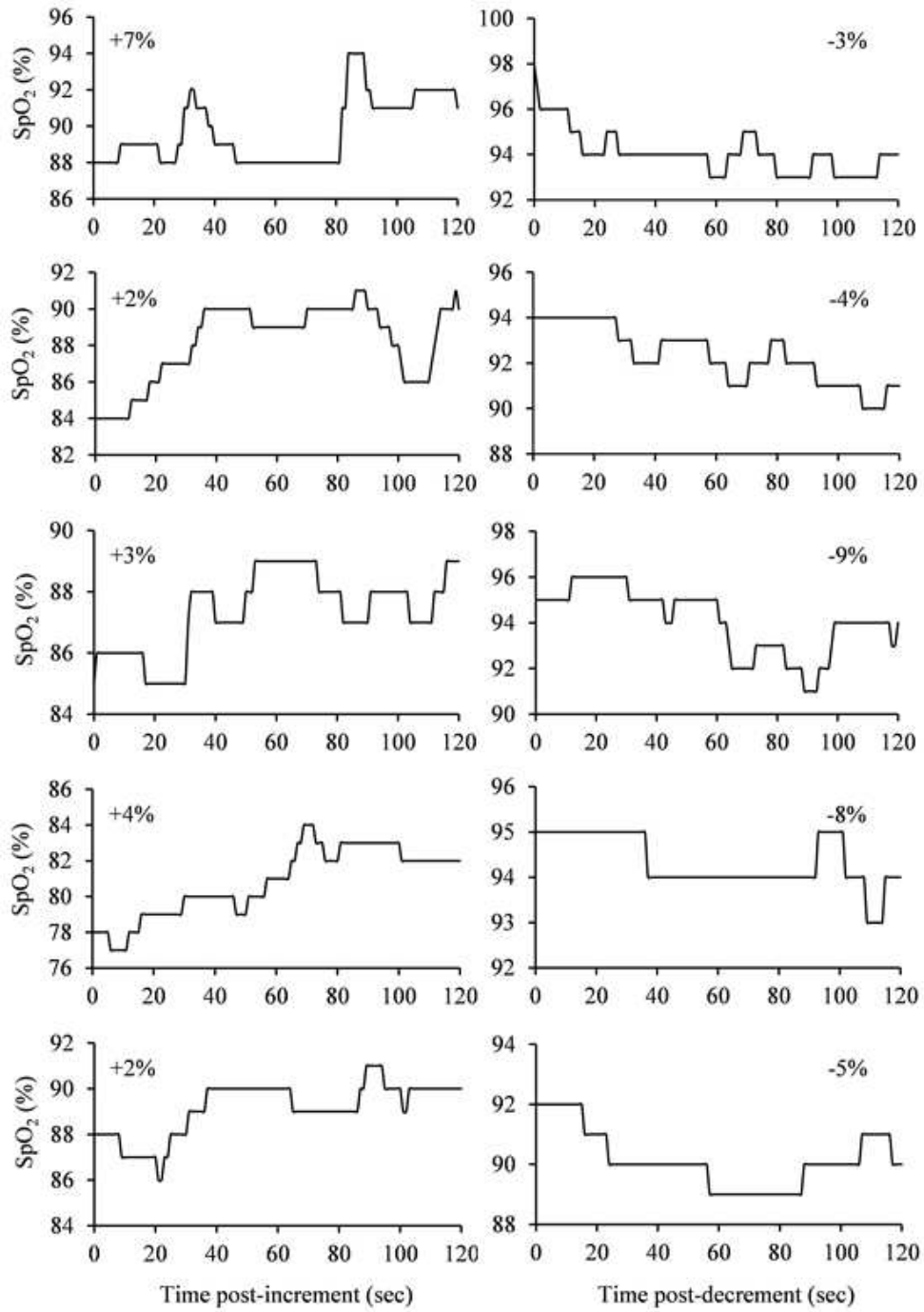
Figure 3.7: Examples of SpO$_2$ responses with $0.6 < R^2 \leq 0.7$ following FiO$_2$ adjustments.
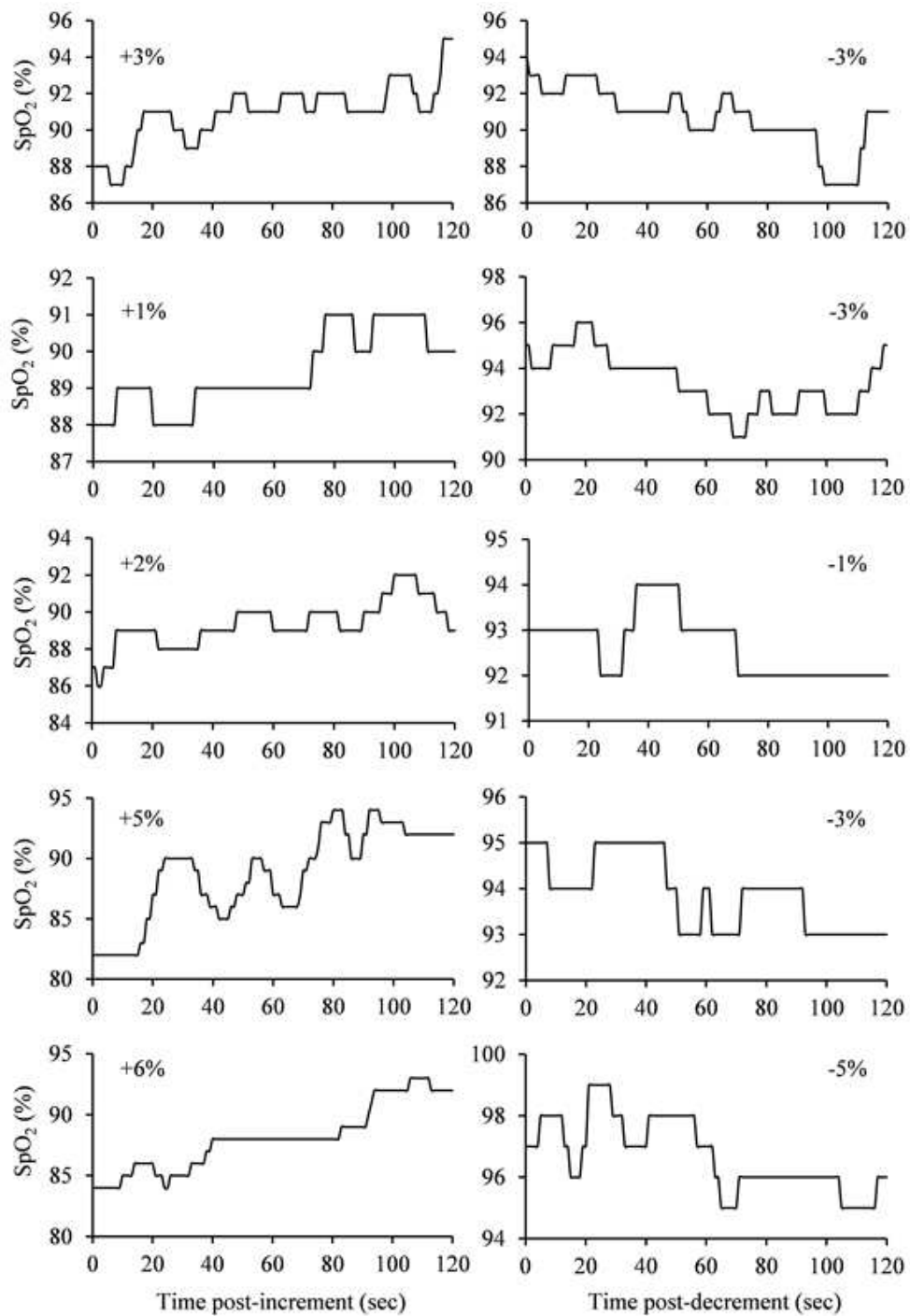
Figure 3.8: Examples of SpO$_2$ responses with $0.5 < R^2 \leq 0.6$ following FiO$_2$ adjustments.
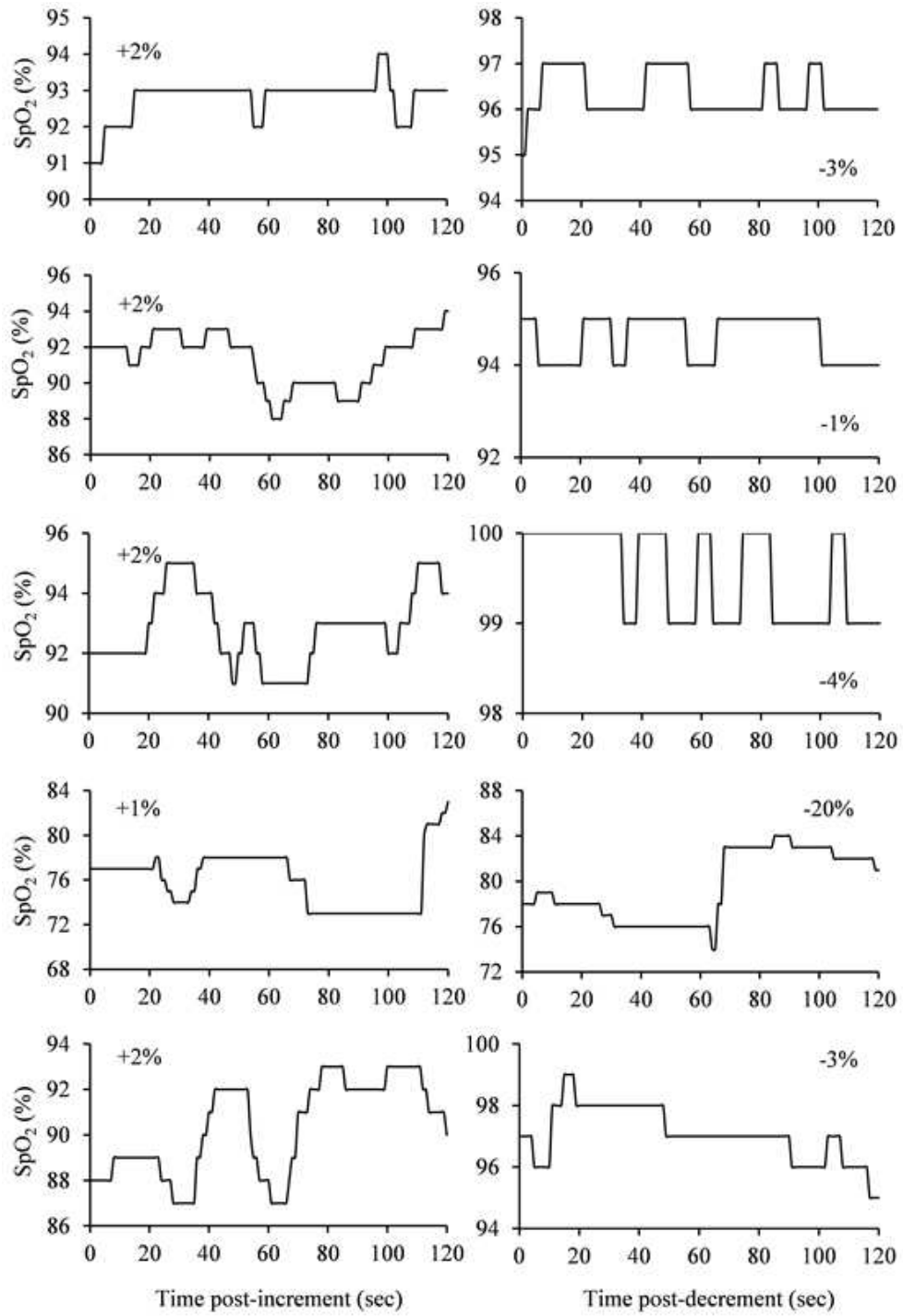
Figure 3.9: Examples of SpO$_2$ responses with $R^2 \leq 0.5$ following FiO$_2$ adjustments.

Chapter 4

Characterisation of the Oxygenation Response to Inspired Oxygen Adjustments

4.1 Summary

Oxygen saturation (SpO_2) targeting in the preterm infant may be improved with a better understanding of the SpO_2 responses to changes in inspired oxygen (FiO_2). We investigated the first-order FiO_2-SpO_2 relationship, aiming to quantify the parameters governing that relationship, the influences on these parameters, and their variability. In recordings of FiO_2 and SpO_2 from preterm infants on continuous positive airway pressure and supplemental oxygen, we identified unique FiO_2 adjustments and mapped the subsequent SpO_2 responses. For responses identified as first-order, the delay, time constant, and gain parameters were determined. Clinical and physiological predictors of these parameters were sought in regression analysis, and intra- and inter-subject variability were evaluated.

In 3788 h of available data from 47 infants at 31 (28-33) post-menstrual weeks [median, (interquartile range)], we identified 993 unique FiO_2 adjustments followed by a first-order SpO_2 response. All response parameters differed between FiO_2 increments and decrements, with for increments a shorter delay, longer time constant and higher gain [2.9 (1.7-4.8) vs. 1.3 (0.58-2.6), $P < 0.05$]. Gain was also higher in less mature infants and in the setting of recent SpO_2 instability, and was diminished with increasing severity of lung dysfunction. Intra-subject variability in all parameters was prominent. First-order SpO_2 responses show variable gain, influenced by the direction of FiO_2 adjustment and the severity of lung disease, as well as substantial intra-subject parameter variability. These findings should be taken into account in adjustment of FiO_2 for SpO_2 targeting in preterm infants.

4.2 The Necessity and Benefits of Characterisation

Despite many decades of oxygen therapy for preterm infants, there is no accepted algorithm to determine suitable adjustment of FiO_2 in clinical practice, and the success of SpO_2 targeting thus remains largely a function of the approach taken by individual bedside caregivers. The characteristics of an infant's SpO_2 response after FiO_2 adjustment are not well understood and yet knowledge of the key parameters governing this response might well aid in titrating oxygen delivery. Observational studies under controlled conditions in adults (Cakar *et al.*, 2001; Weinreich *et al.*, 2013), along with the few data in neonates (Keim *et al.*, 2011; Sano and Kikucki, 1985; Versmold *et al.*, 1978), found FiO_2 change to produce an exponential oxygenation response typical of systems modelled mathematically using first-order differential equations (figure 4.1a).

This first-order relationship has held regardless of whether oxygenation was measured as partial pressure of oxygen (PaO_2) or SpO_2 (Cakar *et al.*, 2001; Weinreich *et al.*, 2013; Keim *et al.*, 2011). For FiO_2 alterations occurring as part of routine practice, we recently noted that 37% of SpO_2 responses could be considered first-order, with ongoing system instability and the complexities of the sigmoidal PaO_2-SpO_2 relationship acknowledged as potential interfering factors (Fathabadi *et al.*, 2014).

Notwithstanding the documented unpredictability of the SpO_2 response to FiO_2 adjustment under standard clinical conditions, in the development of an algorithm for control of oxygen therapy, the assumption of a first-order relationship appears reasonable, and this form of modelling has long been used in the design of automated FiO_2 controllers (Sano and Kikucki, 1985; Keim *et al.*, 2011; Yu *et al.*, 1987; Lopez *et al.*, 2014; Luepschen *et al.*, 2007). With the assumption of first-order behaviour comes the requirement to further investigate the relevant parameters of the first-order FiO_2-SpO_2 response, these being delay, time constant and gain (figure 4.1a).

Knowledge of these parameters would potentially assist in determining the optimal timing and magnitude of FiO_2 adjustments. The factors influencing delay, time constant and gain also deserve investigation, including the starting position on the SpO_2 sigmoid curve, and the severity of lung dysfunction (Claure *et al.*, 2001; Quine *et al.*, 2006). Establishing the degree of intra- and inter-individual variability is also clearly important. Such information would be valuable whether FiO_2 adjustments are being made manually, or by an automated control device.

In this study, we investigated the parameters of the first-order relationship between FiO_2 adjustment and observed SpO_2 response in preterm infants receiving supplemental oxygen. We aimed to examine whether the response parameters were a) similar for FiO_2 increments and decrements, b) influenced by infant characteristics, markers of disease severity and physiological instability, or by position on the SpO_2 sigmoid curve, and c) subject to variability both within and between infants.

4.3   Dataset, Predictor Variables and the Approach

The physiological dataset used in this work was collected prospectively over a 10 month period from preterm infants <37 weeks gestation in the Neonatal Intensive Care Units (NICUs) of the Royal Hobart Hospital, Hobart and the Royal Women's Hospital, Melbourne. All infants were being managed with continuous positive airway pressure (CPAP) and supplemental oxygen. SpO_2 target range was 88-92% in all cases. Further details of the study design and infant selection are reported previously (Lim *et al.*, 2014).

Repeated physiological recordings of 24 h duration (maximum 25 recordings) were made in preterm infants < 37 weeks gestation whilst they were on continuous positive airway pressure, in supplemental oxygen and less than 4 months corrected gestational age. During each recording, clinical management including FiO_2 ad-
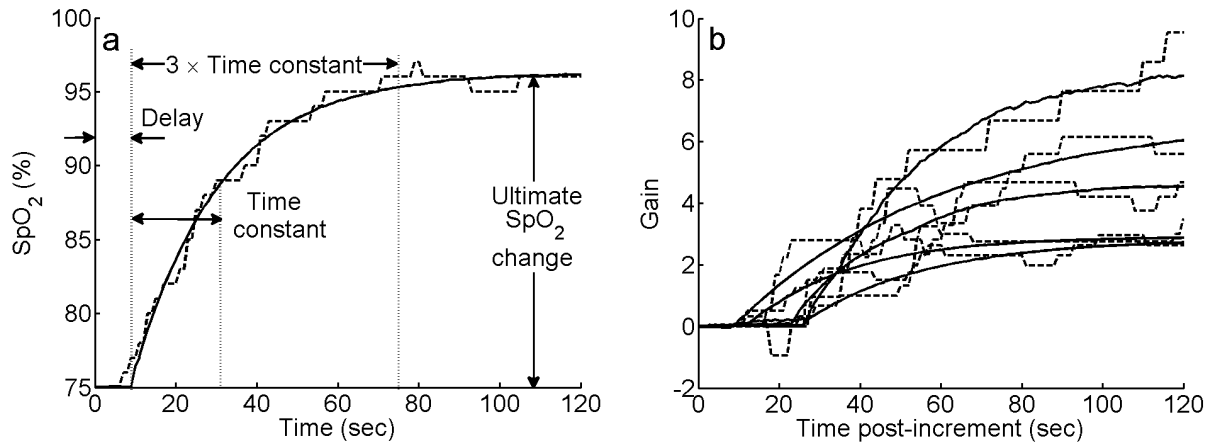
Figure 4.1: First-order modelling of the FiO_2-SpO_2 relationship Panel a. Example of a first-order SpO_2 response after a FiO_2 increment from 21.3% to 26.6% at time zero in a 24 week gestation infant at 22 days of age. Dashed line: recorded data (raw values for SpO_2), solid line: fitted first-order model, with SpO_2 following an exponential trajectory to a new steady state, with the rate of change of SpO_2 being proportional to the distance from steady state. The modelled first-order response fits well to the recorded data ($R^2 > 0.90$). The response parameters are indicated: delay = elapsed time from FiO_2 adjustment until first detected change in SpO_2; time constant = time to achieve 63% of the overall SpO_2 change; gain = ratio between ultimate SpO_2 change and FiO_2 increment (expressed as %). In this case delay = 9 sec, time constant = 22 sec and gain = 21% / 5.3% = 3.9. Panel b. Examples of first order SpO_2 responses after FiO_2 increments at time zero in a single infant. Y-axis: gain (as defined above). The SpO_2 responses show variability in all 3 response parameters (delay, time constant and gain).
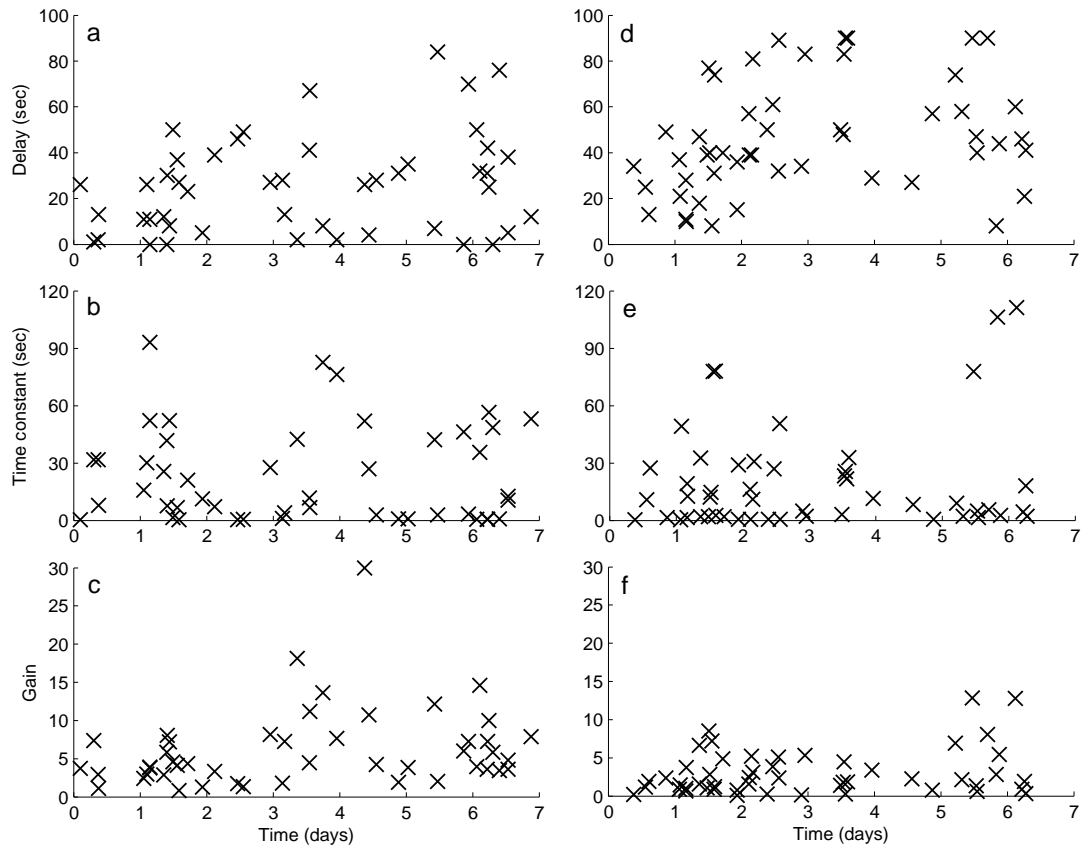
Figure 4.2: Intra-subject variability in response parameters. Model parameters in sequential adjustments with a first-order SpO_2 response in one infant over a 1 week period. Separate plots of delay, time constant and gain for increments (a, b, c) and decrements (d, e, f). For FiO_2 increments, quartile coefficients of variation for the delay, time constant and gain were 0.67, 0.90, and 0.41, respectively, and 0.34, 0.86, and 0.65 respectively for decrements.

justment was performed as usual. SpO_2 data were sourced from either a Dräger Infinity Monitor (Dräger Medical Systems Inc., Notting Hill, Australia) or a Masimo Radical v4 oximeter (Masimo Corp, Irvine, California), in both cases with minimum averaging time (2-4 sec).

FiO_2 was continuously measured with an inline oxygen analyser (MX300-I; Teledyne Analytical Instruments, Industry, California). Both SpO_2 and FiO_2 signals were input to a laptop computer with a sampling frequency of 0.5 or 1 Hz using purpose-built software (LabVIEW 8.6, National Instruments, Austin, USA). From 24 h data recordings, SpO_2 and FiO_2 signals were input to a laptop computer using purpose-built software (LabVIEW 8.6, National Instruments, Austin, USA). The data collection was approved by institutional ethics committees at both sites and parental consents were obtained.

For this study, unique FiO_2 adjustments with magnitude of at least ±0.01 and clear by at least 120 sec of any other FiO_2 alterations were first identified. Increments and decrements in FiO_2 were considered separately throughout, given that their SpO_2 start points would potentially be in different regions of the sigmoid curve. Comparisons were made between the two groups as appropriate. The SpO_2 response to the FiO_2 adjustment was examined over the 120 sec period after the FiO_2 change. Each SpO_2 response was fitted to a first-order model (figure 4.1a), with best fit values for the response characteristics determined, and a goodness of fit was evaluated using the R^2 metric. FiO_2-SpO_2 responses with $R^2 > 0.70$ were considered first-order (Fathabadi *et al.*, 2014) and their values for delay, time constant and gain were used in this study as response parameters.

In seeking factors influencing (i.e. predicting) the response parameters, clinical and physiological data were collected. Gestation at birth, birth weight z score and corrected gestational age at the time of each recording (post-menstrual weeks) were ascertained. For each FiO_2 adjustment, SpO_2 instability was defined as the standard

deviation in the SpO_2 recording in the previous 2 min. Severity of lung dysfunction and position on the SpO_2 sigmoid curve were defined as the FiO_2 and SpO_2 values immediately prior to each adjustment, respectively.

Univariate regression analysis of putative predictor variables was performed against each of the response parameters, and the direction of the relationship (sign of the regression coefficient), as well as its strength (P value), were noted. Multiple linear regression analysis was used to identify which input variables were independently predictive of each response parameter. This analysis was performed using the in-built functions of the statistical software package NCSS. Input variables found to be independently predictive of the outcome parameter ($P < 0.05$) are reported.

Intra-subject variability in each first-order parameter was quantified using the quartile coefficient of variation (QCV) (Feinstein, 2001); the ratio of interquartile range to the sum of the first and third quartiles. QCV values greater than 0.5 were taken to represent considerable dispersion, with values of 0.2-0.3 indicative of relative homogeneity in biological systems (Aliverti *et al.*, 2013). Inter-subject variability was examined initially by comparing first-order parameter subsets between subjects (Kruskal-Wallis ANOVA, minimum 10 observations per individual).

4.4   Recognised Differences, Associations & Variations

A total of 3788 hours of recorded data was available, from 47 infants of median gestational age 30 weeks (interquartile range, IQR, 27-32 weeks) and birth weight 1.3 (0.9-1.8) kilograms. At the commencement of each recording, the infants were 6 (2-28) days of age, at a corrected gestation 31 (29-33) post-menstrual weeks, with CPAP level 7 (6-8) cmH_2O and FiO_2 25 (22-29)%. In all, 2715 unique FiO_2 adjustments were identified with no other FiO_2 alteration for 120 sec on either side. Of these 993 (37%) were identified as having a first-order SpO_2 response, including 580 increments and

Table 4.1: First-order modelling of FiO_2-SpO_2 relationship FiO_2 adjustment details and values for the parameters from first-order modelling of the SpO_2 response to FiO_2 adjustments. Includes only episodes for which goodness of fit of the first-order model was $R^2 > 0.70$. Median (IQR). Values for each model parameter differ between increments and decrements, $P<0.05$, Mann-Whitney test. *absolute values.

		FiO_2 increments	FiO_2 decrements
	N	580	413
FiO_2 adjustment	FiO_2 (%)	3.8 (2.3, 7.1)	3.6 (2.1, 6.3)*
details	Pre-adj. SpO_2 (%)	79 (72, 84)	97 (95, 99)
	Pre-adj. FiO_2 (%)	28 (24, 33)	33 (28, 41)
	Delay (seconds)	22 (8.0, 40)	34 (17, 57)
Model	Time constant (sec)	13 (2.2, 35)	9.4 (1.2, 32)
Parameters	Gain	2.9 (1.7, 4.8)	1.3 (0.58, 2.6)
	R_2 for model	0.88 (0.81, 0.94)	0.81 (0.75, 0.89)

413 decrements.

Analysis of the parameters derived from first-order modelling of SpO_2 responses revealed a shorter delay, longer time constant and higher gain after FiO_2 increments compared to decrements (table 4.1). In univariate analysis, the gain was the parameter most strongly predicted by input variables, with gestation at birth and severity of lung dysfunction predictive of gain for both FiO_2 increments and decrements, and SpO_2 instability and position on the sigmoid curve being additional predictors for FiO_2 increments (table 4.2). Relationships with other first-order parameters were inconsistent, although for FiO_2 increments, lung dysfunction was predictive of delay and time constant as well as gain. For these relationships, the sign of the regression coefficient showed more severe lung dysfunction to be associated with a longer time delay, shorter time constant and lower gain (table 4.2). The univariate relationships largely persisted in multivariate analysis (table 4.2), with lung dysfunction remaining as a strong predictor of gain, both for FiO_2 increments and decrements (regression coefficients -0.055 and -0.064, respectively).

Table 4.2: Relationships of predictor variables with first-order model parameters. Shows regression coefficient and P value in parentheses for linear regression of predictor variables against first-order model parameters. Pooled data from all individuals (580 increments, 413 decrements). See text for definition of SpO_2 instability, severity of lung dysfunction and position on sigmoid curve.

Predictor variable	FiO_2 increments			FiO_2 decrements		
	Delay	Time constant	Gain	Delay	Time constant	Gain
Gestation at birth (completed weeks)	0.80(0.036)†	1.38(0.0016)†	-0.21(<0.001)†	-1.1(0.028)†	-0.42(0.46)	-0.17(0.011)†
Birth weight z score	0.71(0.45)	-0.48(0.65)	0.048(0.71)	0.82(0.53)	-0.060(0.97)	0.079(0.65)
Gestation at recording (post-menstrual weeks)	0.064(0.77)	0.039(0.88)	-0.018(0.57)‡	-0.21(0.50)	-0.29(0.41)	-0.033(0.44)
SpO_2 instability	-0.39(0.14)	-0.58(0.058)	0.21(<0.001)†	1.3(0.011)†	-0.75(0.20)	-0.056(0.42)
Severity of lung dysfunction	0.24(0.0066)†	-0.27(0.0070)†	-0.031(0.015)†	-0.048(0.66)	0.13(0.30)	-0.049(0.0010)†
Position on sigmoid curve	0.038(0.69)	0.12(0.28)	-0.064(<0.001)	0.092(0.86)	-0.10(0.87)	0.023(0.74)

† Remained as a significant predictor in multivariate analysis, with coefficient of same sign.
‡ Became significant in multivariate analysis, with opposite sign coefficient (0.095).

Considerable intra-subject variability was noted in all response parameters, both for FiO_2 increments and decrements (figure 4.2). The average QCV for delay, time constant and gain among increments were 0.66, 0.79, 0.38, respectively and 0.57, 0.87, and 0.59 for decrements. Values for response parameters also showed inter-subject variation, with median values for delay (decrements only), time constant (increments only) and gain (both) differing between subjects (P<0.05, Kruskal-Wallis ANOVA, minimum 10 observations per subject).

4.5   Interpretation of the Outcomes and Their Implications

A requisite step towards improvement of SpO_2 targeting in the preterm infant is to better understand the vagaries of the FiO_2-SpO_2 relationship. In this study of FiO_2 adjustments made during routine clinical practice, we found that the nature of the SpO_2 response differed with FiO_2 increments and decrements, most notably in the gain and thus ultimate SpO_2 change. The gain was higher in less mature infants and in the setting of recent SpO_2 instability, and diminished with increasing severity of lung dysfunction. All parameters of the SpO_2 response showed substantial intra-individual variability, along with variability between individuals in particular in the gain parameter.

From a clinical perspective, our findings suggest the following:

1. Because of the take-off point on the steeper, linear section of the sigmoidal PaO_2-SpO_2 curve, increasing FiO_2 from a state of hypoxia is associated with a greater gain in the SpO_2 response than decreasing FiO_2 from hyperoxia. This means that FiO_2 decrements in a state of hyperoxia must be of greater magnitude to achieve the same ultimate SpO_2 change compared with FiO_2

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increments during hypoxia.

2. The SpO_2 response to a FiO_2 adjustment is affected by severity of lung dys-
   function, with more severe disease being associated with substantial reduction
   in gain. This means that FiO_2 must be changed by a greater amount to achieve
   the same ultimate SpO_2 response in the diseased lung, with the gain being
   reduced by 30-50% (based on the multivariate regression coefficients) for an
   infant requiring 40% oxygen compared to one in room air.

3. The response parameters of the FiO_2-SpO_2 relationship show significant vari-
   ability, both within and between individuals. Whatever the cause, this vari-
   ability must be taken into account when adjusting FiO_2, and has implications
   in automated control, suggesting that adaptive (i.e. changing) and robust
   (i.e. resilient to variation) algorithms may perform better than unchanging
   algorithms designed to operate based on a constant set of model parameters.

Our study examined a large number of FiO_2-SpO_2 responses with first-order be-
haviour, recorded in a group of preterm infants under standard clinical conditions.
The data obtained are thus subject to the variability implicit in real-time recordings
from multiple subjects in uncontrolled circumstances, but on the other hand faith-
fully represent the challenges faced by caregivers (and control devices) attempting
to target an SpO_2 range.

The values we obtained for first-order SpO_2 response parameters in standard clinical
conditions are largely similar to those obtained from limited experimental data
by Keim *et al.* (2011), and also to what would be predicted from physiological
modelling and first principles (Yu *et al.*, 1987; Severinghaus, 1979). Using data from
preterm infants after FiO_2 increments, Keim et al noted gains ranging from 0.23 to
8.4 compared with a median value in our study of 2.9.

The Severinghaus equation linking PaO_2 with SpO_2 (Severinghaus, 1979) indicates

that for FiO_2 increments occurring on the steeper part of the haemoglobin dissociation curve (below SpO_2 90%) a gain of 10 or more may be expected. Time constants in the study of Keim *et al.* (2011) were in the range 32-122 sec, and somewhat longer than we observed after FiO_2 increments (median 13 sec, 75th centile 35 sec). Differences in the degree of prematurity and severity of lung disease may explain the relatively shorter time constants we observed.

The reduction in gain in association with increased lung dysfunction is an important finding of our study. As reduced ventilation-perfusion ratio is not associated with a change in slope of the FiO_2-SpO_2 curve (Appendix 8.2), the attenuated SpO_2 response would appear to be at least in part explained by an increase in the degree of shunt (Quine *et al.*, 2006; Karbing *et al.*, 2007). The assumption of a contribution of shunt to the SpO_2 response to FiO_2 adjustments has long been incorporated in modelling of oxygenation in preterm infants (Sano and Kikucki, 1985; Tehrani and Bazar, 1994; Morozoff and Saif, 2008) but only one controller incorporates differences in gain associated with differing severity of lung dysfunction (Claure *et al.*, 2001).

Our findings have implications not only for manual FiO_2 adjustments but also for the design of automated control devices. The algorithm governing the response to SpO_2 deviations should ideally handle hypoxic and hyperoxic situations separately, and have the capacity to alter gain depending on severity of lung disease. Ideally the algorithm would be adaptive beyond these simple measures, and thus equipped to accommodate the considerable intra- and inter-infant variability that was demonstrated in our study group. A response to rapidly changing SpO_2 should also be incorporated.

Undoubtedly the underlying cause of fluctuation in SpO_2 (e.g. apnoea, circuit pressure loss) will be a determinant of the response after an FiO_2 adjustment. Our data did not allow an analysis along these lines, but this is clearly an important area for future study. Similarly, a more complete analysis of the impact of severity and

nature of lung disease on the FiO_2-SpO_2 relationship should be undertaken.

4.6   Conclusion

In conclusion, characterisation of first-order SpO_2 responses to FiO_2 adjustments reveals a variable gain, influenced by the direction of FiO_2 adjustment and the severity of lung disease, as well as substantial intra- and inter-subject variability. These findings should be taken into account in adjustment of FiO_2 for SpO_2 targeting in preterm infants.

Chapter 5

Hypoxic events and concomitant factors in preterm infants on non-invasive ventilation

5.1 Summary

Automated control of inspired oxygen for newborn infants is an emerging technology, currently limited by reliance on a single input signal (oxygen saturation, SpO_2). This is while other signals that may herald the onset of hypoxic events or identify spurious hypoxia are not usually utilised. We wished to assess the frequency of apnoea, loss of circuit pressure and/or motion artefact in proximity to hypoxic events in preterm infants on non-invasive ventilation. Hypoxic events (SpO_2 <80%) were identified using a dataset obtained from preterm infants receiving non-invasive ventilation. Events with concomitant apnoea, loss of circuit pressure or oximetry motion artefact were annotated, and the frequency of each of these factors was determined. The effect of duration and timing of apnoea on the characteristics of the associated hypoxic events was studied. Among 1224 hypoxic events, 555 (45%) were accompanied by apnoea, 31 (2.5%) by loss of circuit pressure and 696 (57%) by motion artefact, while for 224 (18%) there were no concomitant factors identified. Respiratory pauses of longer duration (>15 seconds) preceding hypoxic events, were associated with a relatively slow decline in SpO_2 and more prolonged hypoxia compared to shorter pauses. Hypoxic events are frequently accompanied by respiratory pauses and/or motion artefact. Real-time monitoring and input of respiratory rate may thus improve the function of automated oxygen controllers, allowing pre-emptive responses to respiratory pauses. Furthermore, use of motion-resistant oximeters and plethysmographic waveform assessment procedures will help to optimise feedback control of inspired oxygen delivery.

5.2 Why Concomitant Factors Matter

In preterm infants needing respiratory support the fraction of inspired oxygen (FiO_2) is controlled to decrease the risk of consequences of both high and low levels of oxygen delivery, including lung damage, retinopathy of prematurity and mortality (Bhandari, 2010; Chen *et al.*, 2010; SUPPORT, 2010). Currently the task of controlling FiO_2 in preterm infants is in the hands of bedside caregivers, who make adjustments based on the level of oxygen saturation (SpO_2), measured transcutaneously and displayed in real-time. Targeting a desired range of SpO_2 readings by manual FiO_2 control is known to be difficult (Hagadorn *et al.*, 2006; Laptook *et al.*, 2006; Lim *et al.*, 2014), and for that reason the concept of automated control was first explored many years ago (Beddis *et al.*, 1979; Sano and Kikucki, 1985; Bhutani *et al.*, 1992).

More recently, the field has entered a new phase, with the introduction of several new control algorithms, some of which have been tested in clinical trials (Claure *et al.*, 2001; Urschitz *et al.*, 2004; Morozoff and Smyth, 2009; Lopez *et al.*, 2014). These algorithms appear to show some promise, resulting in more time in the target SpO_2 range compared with manual control. The algorithms also appear to limit the amount of time spent with inappropriately high SpO_2 readings, but in several cases this is at the expense of a greater time spent hypoxic (i.e. with low SpO_2 levels) (Claure *et al.*, 2009, 2011). This is while a recent study (Poets *et al.*, 2015) suggests that prolonged episodes of SpO_2 <80% increase the risk of death and disability at 18 months corrected age for extremely preterm infants.

A major challenge in the design of an automated control algorithm is how to predict, detect and respond to the relatively frequent hypoxic events that occur in preterm infants. The difficulty stems in large part from the reliance on a single input to the algorithm - SpO_2 - without other contextual information. This is a limitation of all recent control algorithms, and one that has several important consequences. Firstly, the SpO_2 reading from a probe on the limb of a premature infant is prone to motion

artefact, with the potential for an incorrectly low SpO_2 reading to be input to the algorithm (Poets and Southall, 1994), and an inappropriate increase in FiO_2 called for.

Second, with SpO_2 as the only input, in the case of true hypoxia an FiO_2 adjustment can only occur when the hypoxic event is underway, even though there may be identifiable preceding or concurrent events that might predict the occurrence and severity of hypoxia. Such predictive events might include transient cessation of breathing (apnoea) or loss of pressure within the circuit of a respiratory support device. Finally, having other inputs to the algorithm such as respiratory rate and circuit pressure might also avoid an over-vigorous FiO_2 adjustment in situations in which there is a remediable cause of hypoxia. This in turn might prevent an overshoot in SpO_2 and exposure to unnecessarily high levels of oxygen once the issue is resolved (Urschitz *et al.*, 2004).

In this study we explored the relationship between hypoxic events in preterm infants and concomitant factors, such as apnoea and circuit pressure drop, that might be predictive of hypoxia and also interfere with the initial response to increases in FiO_2. We also explored the occurrence of motion artefact, potentially indicative of spurious hypoxia. In physiological recordings from preterm infants receiving respiratory support with continuous positive airway pressure (CPAP) we aimed to identify hypoxic events, and determine the frequency of concomitant apnoea, loss of CPAP circuit pressure or motion artefact.

5.3   Hypoxia Detection and Annotation

Physiological recordings were taken in preterm infants of median (IQR) 25 (25-27) weeks gestational age and 830 (693-949) grams birth-weight, receiving respiratory support with either CPAP or nasal intermittent positive pressure ventilation (NIPPV).

The infants were admitted to the Royal Women's Hospital in Melbourne, Australia. The dataset, partially used elsewhere (Owen *et al.*, 2010, 2011), was obtained from 20 infants and comprised of 136 recordings of 40 (30-45) minutes duration (5184 minutes overall).

Recordings of SpO_2, saturation plethysmographic waveform, CPAP circuit pressure, FiO_2, and respiratory motion were made with a sampling frequency of 200 Hz. SpO_2 was recorded from a Masimo Radical SET pulse oximeter (Masimo, Irvine, California, USA), CPAP pressure with a Florian respiratory function monitor (Acutronic Medical Systems, AG, Zug, Switzerland), FiO_2 with an MX300 oxygen analyser (Teledyne Analytical Instruments, City of Industry, California, USA) and respiratory motion with an abdominal capsule linked to a respiration monitor (MR10; Graseby Medical, Watford, England).

Video images of the infant's head and torso were recorded at six frames per second and synchronised with the physiological data using Spectra software (Grove Medical, London, UK). The data collection was approved by the hospital Research and Ethics Committees and informed written parental consent was obtained prior to the recordings. A hypoxic event was defined as an episode starting with a fall in SpO_2 and including SpO_2 <80% for minimum duration of four seconds.

The detection algorithm detected the onset of a hypoxic event as the first point where SpO_2 fell by minimum 3% following a stable period or a local maximum (Poets and Southall, 1991). If the onset was followed by an episode with SpO_2 < 80% for minimum 4 seconds in a 30 second time window the event was considered in the analysis.

A graphical user interface was developed to investigate and annotate the hypoxic events using MATLAB R2012a (The MathWorks, Inc., Natick, Massachusetts, United States). A detailed description of the detection method as well as images of the graphical user interface can be found in Appendix C in section 8.3. For each detected

event, identification and annotation of concomitant apnoea and loss of pressure was performed automatically (figure 5.1). Apnoea was defined as a pause in respiration of 4 seconds or greater (Poets *et al.*, 1991; Stebbens *et al.*, 1991; Adams *et al.*, 1997).

For apnoea detection, the search started form the end of the episode with SpO_2 < 80% (maximum 30 seconds after the onset) by deriving the standard deviation (SD) of the respiratory motion signal in a 4 second moving time window, with a frameshift of 20 msec. The standard deviation was compared with an adjustable threshold to identify cessation of breathing, with the onset of the respiratory pause then located secondarily (maximum 30 seconds prior to the onset).

In cases with repeated respiratory pauses, those closest to the onset of hypoxia were used in the analysis. Identified pauses were categorized as preceding the hypoxic event if their onset was at least two seconds prior to onset of hypoxia (Poets *et al.*, 1991; Stebbens *et al.*, 1991), or otherwise considered to be concurrent/subsequent. Identified pauses were further sub-categorized by duration (<10 sec, 10-15 sec, >15 sec). The SpO_2 slope from the onset of the hypoxic event to its detected minimum, and the duration for which SpO_2 was <80 %, were compared between respiratory pauses of different timing of onset and duration (Kruskall-Wallis ANOVA with Dunn's post hoc test).

Loss of circuit pressure lasting for at least four seconds was detected using a similar moving window to that described above, in this case identifying if pressure was < 4 cmH_2O. Detected episodes of pressure loss were further investigated by examination of the video recording looking for evidence of a detached CPAP interface or circuit tubing.

Motion artefact associated to hypoxic events was detected by visual examination of the plethysmographic waveform (Poets and Southall, 1994; Poets and Stebbens, 1997), looking for evidence of disturbance (a non-pulsatile tracing and/or baseline fluctuation). This step was followed by review of video images by one of the authors,

exploring whether there were observable infant movements in association with the waveform disturbance.

Hypoxic events during which there was concurrent motion artefact in the waveform were annotated as being potentially spurious. Finally, the co-existence of apnoea, loss of circuit pressure and motion artefact was investigated by categorising the hypoxic events into groups representing all possible combinations of concomitant factors. The frequencies of the events in different groups were then analysed.

5.4   Frequency of Factors and Relevance of Apnoea

Overall, 1275 hypoxic events from 96 recordings met the criteria for study and were analysed using the graphical user interface. Fifty-one events were later excluded, 39 because of presence of FiO_2 decrements within 60 seconds preceding the onset of hypoxia, 9 because of missing signals, and 3 because of being the extension of a previous episode of hypoxia. For the 1224 remaining events, median SpO_2 at onset was 82% (interquartile range, IQR, 79-87%), and duration <80% was 8.0 (6.0-17) seconds. The overall rate of hypoxic events in all 86 hours of recordings was 14 events per hour.

Detection of apnoea was optimised with an SD threshold of 0.075 applied to the respiratory motion signal. Apnoea occurred concomitant with the hypoxic event in 555 (45%) cases, including 495 (40%) in which apnoea preceded the event and 165 events in which it occurred concurrently/subsequently. Comparisons between the slope and duration of periods of hypoxia among different categories of apnoea (table 5.1) were performed for preceding apnoea of differing duration, and separately for concurrent/subsequent apnoea.

Among apnoeic events preceding periods of hypoxia, the SpO_2 slope was of lesser magnitude but the hypoxia duration was longer for apnoea >15 sec compared with
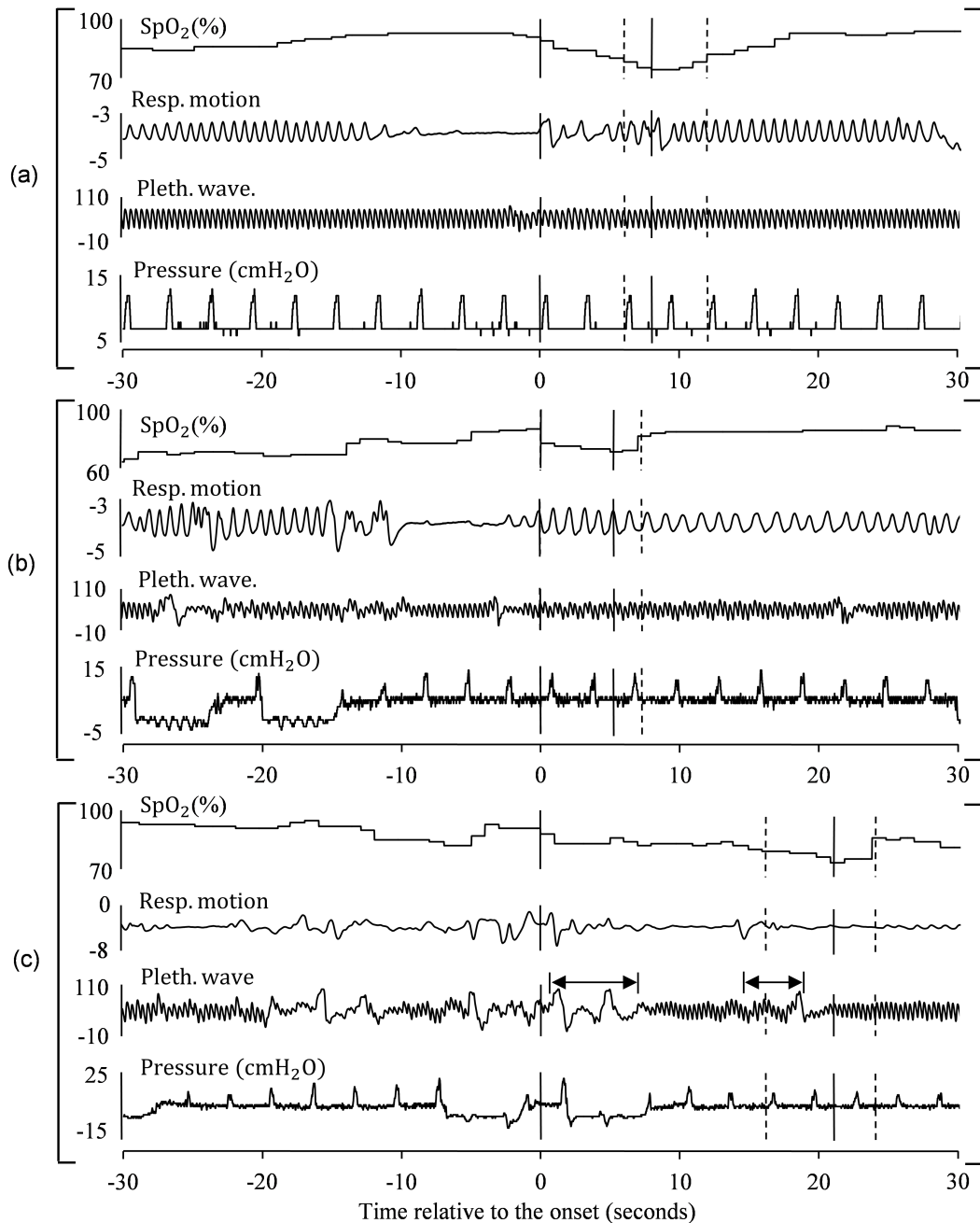
Figure 5.1: Representative hypoxic events with concomitant factors. Vertical solid lines define the onset and minima of the hypoxic events; vertical dashed lines indicate the period with SpO_2 <80%. (a) Hypoxia preceded by apnoea at -9.1 seconds. (b) Hypoxia preceded by loss of pressure at -29 sec and -20 sec, and also by apnoea at -10 sec. (c) Hypoxic event with circuit pressure loss at -6.6 sec and 2 sec, and a disturbed plethysmographic waveform. Movements observed in the video recordings at time points marked by arrows. Resp. motion: respiratory motion; Pleth. wave: oxygen saturation plethysmographic waveform; Pressure: CPAP circuit pressure.

shorter respiratory pauses (table 5.1). Among the concurrent/subsequent apnoeic events the slope was again of lesser magnitude for pauses with >15 sec compared with those with <10 sec duration, while pauses with 10-15 sec duration were not different from either. Duration of hypoxia was also longer among pauses >10 sec duration compared with shorter pauses.

Loss of circuit pressure was detected in 31 (2.5%) hypoxic events mostly occurring preceding the event (table 5.2). Of which 22 were detected in a single 36 minute recording in association with functional limitations of the NIPPV device. In other cases an obvious tube disconnection or detachment of the prongs from the nostrils was observed. In one case, the detected end-point for loss of pressure was adjusted because of noisy data and inappropriate detection.

Disturbance of the plethysmographic waveform was present in the time window of interest during 696 of 1224 hypoxic events (57%), with detectable body motion present in the video recordings in 439 of these (67%). Analysis of the videos during hypoxic events also revealed that there were occasions when the nasal prongs were dislodged from nostrils but the prongs were obstructed against the infant's face, preventing loss of circuit pressure but providing no respiratory support.

Table 5.1: Hypoxic events with concomitant apnoea.

	Preceding apnoea (N=495)			Concurrent/subsequent apnoea (N=165)		
	Apnoea duration			Apnoea duration		
	<10 s	10-15 s	>15 s	<10 s	10-15 s	>15 s
n (%)	389 (79%)	64 (13%)	42 (8%)	145 (88%)	12 (7%)	8 (5%)
Hypoxia duration(s)	8.0(6.0, 15)	9.9(6.0, 18)	23(13, 28)*	13(6, 28)*	26(17, 29)	26(21, 28)
SpO$_2$ slope (%/s)	-2.6(-4.0,-1.7)	-2.5(-3.7,-1.5)	-1.5(-2.0,-0.8)*	-2.6(-4.3,-1.5)	-2.0(-2.5,-1.7)	-1.2(-1.9,-0.7)[+]

Median (IQR). *Differs from other sub-groups, $P<0.05$, Kruskal-Wallis ANOVA with Dunn's post hoc test. [+]Differs from sub-group with apnoea duration <10 sec.

Table 5.2: Hypoxic events with loss of circuit pressure.

	Preceding	Concurrent/Subsequent
No.	30	9
Pressure loss duration (s)	5.5 (5.4,5.8)	5.6 (5.4,5.7)
Hypoxia duration (s)	10 (6.9,17)	17 (8.9,20)
	Median (IQR)	

Table 5.3: Classification of 1224 hypoxic events.

	Loss of pressure	Apnoea	Motion artefact	No obvious category
All	31 (2.5%)	555 (45%)	696 (57%)	224 (18%)
+No other factor	2 (0%)	297(24%)	429 (35%)	
+Motion artefact	14 (1%)	243 (20%)		
+Apnoea	5 (0%)			
+Motion artefact & Apnoea	10 (1%)			

Occasions where two or more factors were associated with a hypoxia were common (table 5.3). In total 998 (82%) hypoxic events were collectively associated with either apnoea or motion artefact, with an additional 2 instances including circuit pressure loss. Only 224 (18%) of events were not associated with any of the three unwanted factors. When an apnoea was present (555 events), the proportion of hypoxic events concomitant with motion artefact (253/555) was 46%, less than for hypoxic events overall (57%). Around 62% of the cases of motion artefact (429/696) occurred without apnoea or loss of pressure.

5.5 Indications for Automated Control

Currently, automated control of inspired oxygen is based around detection of hypoxic events, without regard to factors that may cause or mimic hypoxia. Apnoea and loss of pressure could hinder appropriate respiratory support particularly during automated control, and motion artefact on the other hand may mislead the control algorithm. Hypoxic events were frequent among our infants with the overall average rate of hypoxic events being 14 per hour.

This rate fits into the range of the rate of desaturations (0.0-45 per hour) in a report studying artefact-free episodes of SpO_2 in preterm infants receiving CPAP and NIPPV and including shorter hypoxic events (Pantalitschka *et al.*, 2009). We found a high probability of apnoea preceding hypoxic events, and of motion artefact

concurrent with such events. Long respiratory pauses were associated with a slower decline in SpO_2, but longer duration of hypoxia.

5.5.1 Apnoea and Loss of Pressure

Previous studies have found high rates of association between preceding apnoea and hypoxic events ($SpO_2 < 80\%$) in the newborn. Stebbens and coworkers found 98% and 65% of hypoxic events in healthy term infants were related to a respiratory pause during regular and non-regular breathing, respectively (Stebbens *et al.*, 1991). However, their study included very short episodes of hypoxia, with the median duration of events being around 1 second. In separate studies of spontaneously-breathing preterm infants, hypoxic events of at least 4 seconds have been found to be preceded by respiratory pauses in 83% (Poets *et al.*, 1991) and 97% (Adams *et al.*, 1997) of cases.

For the preterm infants on non-invasive respiratory support in our study, the proportion of hypoxic events preceded by apnoeic pauses appears considerably less than for those breathing spontaneously. We noted a respiratory pause $\geq$ 4 sec preceded the onset of hypoxia in 40% of cases. The use of CPAP, known to increase lung volume (Elgellab *et al.*, 2001), may lessen the frequency of apnoea as an antecedent to hypoxic events, as has previously been noted in infants during active sleep (Tourneux *et al.*, 2008). Our results indicate that although the likelihood of apnoea related to major hypoxic events in infants receiving non-invasive support is less than previous reports, it still remains a major concern for automation of oxygen control.

A key finding of our study is the association of longer preceding respiratory pauses (>15 sec) with a slower decline in SpO_2 but ultimately more prolonged hypoxia. Studies on the slope and duration of hypoxic events in association with respiratory pauses in infants are limited. A report on spontaneously breathing preterm infants found an association between periodicity of apnoea and faster slope of desaturation

(Poets and Southall, 1991). Another study in term infants suggested that duration of hypoxic events increased when breathing was non-regular (Stebbens *et al.*, 1991).

Our findings suggest that for short apnoeic pauses and a rapid decline in SpO_2, the optimal response may be a brief increase in FiO_2 to prevent or treat hypoxia. Longer pauses may require another form of intervention (e.g. stimulation), with hypoxia being refractory to FiO_2 increases until respiratory effort has normalised. Thus far, no automated oxygen controller has included a real-time measurement of respiratory movement as an additional input, in part due to the practical difficulties associated with such monitors.

We found circuit pressure loss to be much less common than apnoea as a factor influencing hypoxic events. As we observed, respiratory support can be compromised without loss of circuit pressure. Nevertheless, given the relative simplicity of measurement of circuit pressure, it could easily be incorporated as an input in an automated oxygen control device.

5.5.2 Motion artefact

A high proportion (57%) of hypoxic events in our study had concomitant motion artefact identified in the plethysmographic oximetry waveform. Along with erroneous readings induced by low perfusion, motion artefact is well known to result in falsely low SpO_2 readings (Poets and Southall, 1994). Without another measure of oxygenation, for any given hypoxic episode it may be difficult to discern whether the low SpO_2 values are spurious or not.

In a previous study (Poets and Stebbens, 1997), 31% of the recording segments of plethysmographic waveform from preterm infants contained motion artefact, and for episodes with $SpO_2 \leqslant 80\%$, this proportion increased to 88%. The authors thus concluded that a significant proportion of perceived hypoxic episodes may actually

be related to motion artefact and not represent true hypoxia.

The recommended approach in such cases has been to identify the motion, for instance by comparing the plethysmographic extracted and electrocardiographic heart rates (Poets and Stebbens, 1997), and then to consider the SpO_2 readings valid only when the two heart rates correlate. For an automated oxygen controller with continuous SpO_2 feedback this means there may be long episodes with no reliable reference data on which to base decisions.

The high proportion of hypoxic events in which there is motion artefact necessitates the design of automated oxygen controllers that can make a decision on the reliability of the recorded hypoxic events. Motion tolerant oximeters (Goldman *et al.*, 2000) have been developed to extract SpO_2 in the presence of motion (Petterson *et al.*, 2007). Even with motion-tolerant oximetry, there is still potential for spurious SpO_2 readings to compromise the performance of automated control devices.

Accordingly, it is crucial to design control algorithms that use all possible avenues to determine whether low SpO_2 values are related to motion artefact. Beyond the use of perfusion index and also comparison of heart rate as described above, we recommend that waveform analysis software should be incorporated to identify motion artefact, in much the same way as was done visually in this study.

5.5.3   Other Findings and Limitations

In our study, video images confirmed that a large proportion of the patient movements led to motion artefact. On some occasions detected disturbance in the plethysmographic waveform did not have identifiable movement as a cause, and remained unexplained. The question of the source of disturbance may be far less important than its presence during automated oxygen control. However our observation encourages further study of the cause of oximetry waveform disturbance. Our findings

concerning the reduced frequency of motion artefact during apnoea can be explained by the fact that during a central apnoea an infant is not expected to move and cause artefact in the plethysmographic waveform.

5.6 Conclusion

Incorporating real-time measurements of respiratory rate in automated oxygen controllers would be beneficial in managing hypoxic events appropriately, and measurement of gas pressure in the circuit may be useful. Brief intervals of elevated FiO_2 could be considered in prevention/treatment of hypoxic events following short respiratory pauses and fast SpO_2 declines. The influence of motion artefact on plethysmographic waveforms during hypoxia remains significant and automated oxygen controllers should only receive SpO_2 input from motion-resistant oximeters, and beyond this should implement effective waveform validation algorithms.

Chapter 6

Lost without trace: Oximetry signal dropouts in preterm infants

6.1 Summary

Oxygen saturation (SpO$_2$) signal dropout leaves caregivers without a reliable measure to guide oxygen therapy. We studied SpO$_2$ dropout in preterm infants on continuous positive airway pressure, noting the SpO$_2$ values at signal loss and recovery and thus the resultant change in SpO$_2$, and the factors influencing this parameter. In 32 infants of median gestation 26 weeks, a total of 3932 SpO$_2$ dropout episodes were identified (1.1 episodes/h). In the episodes overall, SpO$_2$ decreased by 1.1%, with the SpO$_2$ change influenced by starting SpO$_2$ (negative correlation), but not dropout duration. For episodes starting in hypoxia (SpO$_2$ <85%), SpO$_2$ recovered at a median of 3.2% higher than at SpO$_2$ dropout, with a downward trajectory in one-quarter of cases. We conclude that after signal dropout SpO$_2$ generally recovers in a relative normoxic range. Blind FiO$_2$ adjustments are thus unlikely to be of benefit during most SpO$_2$ dropout episodes.

6.2 Pulse Oximetry and the Issue of Lost Signal

Pulse oximetry is a widely used monitoring technique, which allows continuous, non-invasive measurement of oxygen saturation (SpO_2) and guidance with supplemental oxygen therapy (Mower *et al.*, 1997). SpO_2 monitoring is indispensable in the neonatal intensive care unit (NICU), in particular for preterm infants highly susceptible to adverse effects at the extremes of oxygenation. NICU caregivers have become heavily reliant on continuous SpO_2 information in preterm infants receiving supplemental oxygen, with the knowledge that avoidance of hypoxia and hyperoxia may improve outcome (Bateman and Polin, 2013).

For a variety of reasons, the photoplethysmography tracing from a pulse oximeter probe may be temporarily lost, meaning that a valid SpO_2 value cannot be displayed. The occurrence of SpO_2 signal dropout is all too familiar to NICU caregivers, and leaves them without a reliable measure to guide oxygen therapy when caring for preterm infants. Previous studies have suggested hypoxia to be the predominant state upon signal return, (Claure *et al.*, 2001) and that an increase in inspired oxygen concentration (FiO_2) should be considered during SpO_2 dropout. The published data are, however, limited to a few hundred dropout episodes in <200 hours of signal recordings (Claure *et al.*, 2001, 2009). Furthermore, no information is available on the pre-dropout SpO_2 values, and thus the trajectory of oxygenation during dropout, which should be taken into account in determining appropriateness of FiO_2 adjustments whilst awaiting signal return.

We studied SpO_2 dropout in a large dataset from preterm infants, aiming to document the context in which SpO_2 dropout occurred, the SpO_2 values at signal loss and recovery and thus the resultant change in SpO_2, and the factors influencing this parameter.

6.3 Eligible Dropouts, Extracted Information and Analysis Details

Repeated 24 h real-time recordings of SpO_2 and FiO_2 at a sampling interval of 1 Hz were made in preterm infants <37 weeks gestation at birth managed in the Royal Hobart Hospital NICU with continuous positive airway pressure (CPAP) and on supplemental oxygen at the start of each recording. SpO_2 target range was 88 to 92%. Methods of data recording and initial analysis have been detailed previously (Lim *et al.*, 2014). In summary, SpO_2 was extracted from bedside monitors (Infinity Monitor, Dräger Medical Systems Inc., Notting Hill, Australia) set to minimum averaging time (2-4 seconds). FiO_2 sourced from an inline oxygen analyser (MX300-I, Teledyne Analytical Instruments, City of Industry, USA). Data were input to a laptop computer using custom software written with labVIEW (National Instruments, Austin, USA). Data collection was approved by our institutional ethics committee as an audit of clinical practice.

For the analysis of signal dropout, in pooled data from all infants episodes throughout which a numerical SpO_2 value was absent were identified. Those with a duration <10 sec or >600 sec were excluded, as were dropout episodes with an FiO_2 adjustment in the preceding 120 sec. Those with a concurrent FiO_2 adjustment were analysed separately. For each episode, the values of SpO_2 prior to signal dropout and at recovery were derived from the average of SpO_2 values over the 10 sec before and after each dropout episode, respectively. From these, SpO_2 change (δSpO_2) and SpO_2 trajectory (δSpO_2/dropout duration) were determined.

Analysis was performed on all episodes combined, and on three sub-groups based on pre-dropout SpO_2: hypoxia (SpO_2 <85%), relative normoxia (SpO_2 85-95%), or hyperoxia (SpO_2 >95%). Median values were compared between these three oxygenation sub-groups (Kruskal-Wallis test), and within each the pre- and post-dropout

SpO$_2$ values were compared (Wilcoxon signed-rank test). Potential predictors of δSpO$_2$ (pre-dropout SpO$_2$, FiO$_2$ and episode duration) were also evaluated using Spearman correlation.

6.4 What Happens After a Dropout

Data were analysed from 32 infants of median gestation at birth 26 weeks (interquartile range, IQR 26-28), birth weight 914 (912-1000) g, and post-natal age at commencement of each recording 23 (7-64) d. Within 3724 h of data recordings, 5709 episodes of SpO$_2$ dropout were identified. 1419 episodes lasted <10 sec, 22 episodes lasted >600 sec, and there were 287 prior and 49 concurrent FiO$_2$ adjustments. After excluding these, 3932 dropout episodes were used for analysis (table 6.1).

SpO$_2$ dropout accounted for 1.7% of the entire recording, and occurred with greater relative frequency during hypoxia (table 6.1). Overall, SpO$_2$ decreased slightly during signal dropout (median δSpO$_2$ -1.1%), but for episodes starting in hypoxia, SpO$_2$ increased by median +3.6% (trajectory +0.09% per sec). Within this hypoxic sub-group, δSpO$_2$ showed negative correlation with pre-dropout SpO$_2$ (lower pre-dropout SpO$_2$ = higher positive value for δSpO$_2$) and positive correlation with FiO$_2$. Across all oxygenation subgroups, slopes of the δSpO$_2$ - duration correlation suggested minimal effect of dropout duration on δSpO$_2$ (table 6.1); for the hypoxia sub-group the slope of 0.019 corresponds to a δSpO$_2$ value only 1% higher for each additional 50 sec of lost signal.

Amongst the episodes of signal dropout in hypoxia, just over one-quarter resulted in a reduction in SpO$_2$ from the starting value, and on 10% of occasions δSpO$_2$ was -6.1% or beyond (figure 6.1 A). When dropout occurred in relative normoxia, there was a 10% risk of SpO$_2$ change by -13% or more (figure 6.1 B).

Table 6.1: oxygenation changes during SpO_2 signal dropout. Data presented for all dropout episodes, and those within oxygenation sub-groups based on pre-dropout SpO_2.

	All episodes	Pre-dropout SpO_2			
		<85%	85%-95%	>95%	P value*
Number of episodes (n)	3932	844	2614	474	NA
Episode freq.(n/hour)	1.1	5.2	1.1	0.42	NA
Proportion of signal (%)	1.7	7.1	1.8	0.77	NA
Drop. duration (sec)	34(19 - 68)	31(18 - 58)	35(19 - 70)	35(22 - 72)	0.0040
FiO_2 at dropout	0.28(0.23,0.42)	0.31(0.25,0.53)	0.29(0.23,0.44)	0.23(0.21,0.28)	<0.0001
Pre-drop. SpO_2 (%)	89(86,92)	79(75,83)	89(87,91)	97(96,99)	<0.0001
Post-drop. SpO_2 (%)	87(82,90)†‡	83(76,87)‡	87(83,90)‡	96(91,98)‡	<0.0001
δSpO_2 (absolute% difference)	-1.1(-5.3,1.7)	3.6(-1.3,9.0)	-2.0(-6.0,0.7)	-2.0(-6.2,0.0)	<0.0001
SpO_2 trajec.(% / sec)	-0.025(-0.14,0.041)	0.090(-0.028,0.26)	-0.043(-0.19,0.013)	-0.042(-0.13,0.0)	<0.0001
δSpO_2 correlation with:					
Pre-drop. SpO_2 slope (95% CI)	-0.50(-0.53,-0.47)	-0.63(-0.71,-0.54)	-0.31(-0.40,-0.22)	-0.16(-0.61,0.30)	NA
FiO_2 slope (95% CI)	+0.058(0.040,0.075)	+0.061(0.020,0.10)	0.031(0.013,0.049)	-0.10(-0.16,-0.042)	NA
Drop. duration slope (95% CI)	-0.004(-0.007,0.000)	0.019(0.010,0.028)	-0.005(-0.009,-0.001)	-0.013(-0.021,-0.006)	NA

Median (IQR) unless otherwise stated. *P value for comparison of different oxygenation sub-groups, Kruskal-Wallis test. †SpO_2 at recovery was <85% in 1376 of 3932 episodes (35%), 85-95% in 2140 (54%) and >95% in 416 (11%). ‡Differs from corresponding pre-dropout SpO_2 value, $P<0.05$, Wilcoxon signed-rank test. δSpO_2: SpO_2 change during dropout; NA: not applicable.
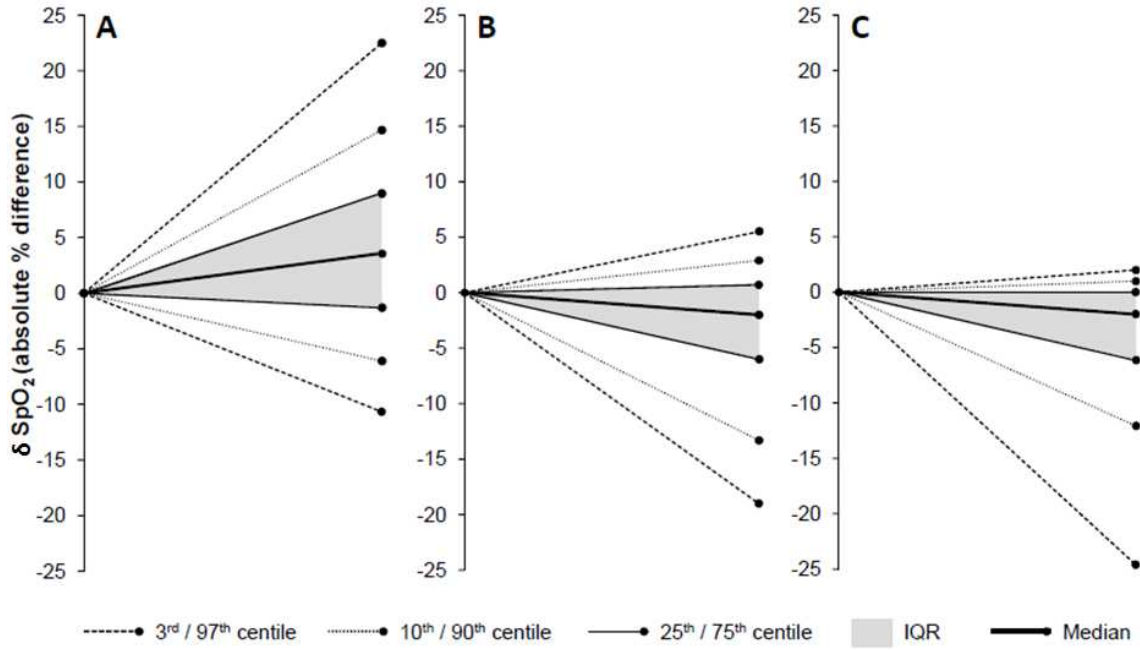
Figure 6.1: Range of δSpO_2 values. 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles for change in SpO_2 (δSpO_2) during signal dropout commencing in hypoxia (<85%, panel A), relative normoxia (85-95%, panel B) and hyperoxia (>95%, panel C). Shaded area indicates interquartile range (IQR).

There were 49 dropout episodes during which an FiO_2 adjustment was made (increased on 42 occasions, decreased on 7). The increases in FiO_2 were by 4.0 (2.4,10)% and the decreases 8.4 (5.5,14)%. Duration of dropout was longer than for episodes in which there was no FiO_2 adjustment [FiO_2 increase 74 (33,184) sec; FiO_2 decrease: 67 (45,150) sec; no FiO_2 adjustment: 34 (19,68) sec, p<0.05, Kruskal-Wallis test]. The FiO_2 alterations occurred relatively early in the dropout episodes, at 20 (7.0,97) and 23 (2.0,34) seconds after signal loss for FiO_2 increases and decreases, respectively. For the most part, δSpO_2 values were as would be predicted by the direction of FiO_2 adjustment [FiO_2 increase: δSpO_2 +0.95 (-4.9, +6.8)%; FiO_2 decrease: -6.3 (-11, 0.0)].

6.5 Comments on Results and Suggestions for Oxygen Control

Episodes of SpO_2 dropout are a common occurrence during NICU monitoring, which in our study occurred at a rate of 1.1 episodes/h, with a higher frequency during hypoxia. Overall, SpO_2 usually recovered in relative normoxia. For episodes starting in hypoxia, SpO_2 recovered at a median of 3.2% higher than at SpO_2 dropout. In most cases, signal dropout lasted <60 secs and SpO_2 on recovery changed by <6%.

To our knowledge, this is the first study to comprehensively examine oxygenation changes and the influence of pre-dropout SpO_2, FiO_2 and dropout duration in a large number of SpO_2 dropout episodes. By design, we focused on dropout episodes of at least 10 seconds duration in preterm infants on CPAP.

Our study findings differ somewhat from previous reports in which there was a preponderance of hypoxic values on signal return, (Claure *et al.*, 2001, 2009) resulting in a suggestion to consider increasing FiO_2 during signal dropout (Claure *et al.*, 2001). Past and present studies concur in the observation that SpO_2 recovery in the hyperoxic range is uncommon (Claure *et al.*, 2001, 2009). Differences in study methodology, including the study population, minimum dropout duration, and definition of hypoxia, preclude further meaningful comparisons.

Although our dataset is the largest examined to date, interpretation is limited having only including infants on CPAP, who were predominantly in supplemental oxygen at the time of signal dropout. Additionally, no video collection was performed in study subjects, no second SpO_2 device was attached, and perfusion indices were not recorded. There is thus a lack of information on the actual cause of signal dropout episode (probe dislodgement/motion artefact/low perfusion) in each case, and some uncertainty regarding the clinical condition preceding or during the event. Future studies of SpO_2 dropout should address these deficiencies.

In conclusion, SpO$_2$ signal dropout occurs frequently in preterm infants on CPAP. In babies with stable FiO$_2$, when the signal recovers, SpO$_2$ is generally in a relative normoxic range. Blind FiO$_2$ adjustments are thus unlikely to be of benefit during most episodes of SpO$_2$ dropout.

6.6 The Final Word

In conclusion, SpO$_2$ signal dropout occurs frequently in preterm infants on CPAP. In babies with stable FiO$_2$, when the signal recovers, SpO$_2$ is generally in a relative normoxic range. Blind FiO$_2$ adjustments are thus unlikely to be of benefit during most episodes of SpO$_2$ dropout.

Chapter 7

Conclusion and Future Directions

7.1 Conclusion

This thesis started with identifying the high level design challenges of automated control of inspired oxygen for preterm infants following a comprehensive overview of the existing algorithms. This part of the study pointed to the variability of oxygenation in preterm infants together with technologic shortcomings of infant monitoring and safety considerations as the major challenges. The thesis then largely focused on investigation of the variability in oxygenation response.

In a study assessing the validity and predictability of this model in preterm infants receiving CPAP (Fathabadi *et al.*, 2014) we found that the first order model for the FiO_2-SpO_2 relationship was valid in 37% of 2369 FiO_2 adjustments. We also found that first-order responses were more frequent among FiO_2 increments than decrements, due largely to the non-linearity of the PaO_2-SpO_2 relationship (Castillo *et al.*, 2008).

In a further study, (Fathabadi *et al.*, 2015) we characterised the oxygenation response by evaluating the parameters of the first order model, namely delay, time-constant and gain, among 993 adjustments with first order responses. We found that, notwithstanding significant intra- and inter-infant variability, for both FiO_2 increments and decrements, more severe lung dysfunction (as evidenced by higher baseline FiO_2), was associated with lower value of gain. It is important to note that while our studies (Fathabadi *et al.*, 2014, 2015) explained some of the variability of the SpO_2 response to FiO_2 adjustments, in large part the variability remains unexplained, as does the cause of non-first order responses.

The thesis then investigated the hypoxic events as another aspect of oxygenation variability. Implications of this study were the potential benefits of incorporating real-time measurements of respiratory rate and gas pressure in the circuit in automated oxygen controllers for managing hypoxic events appropriately. Brief intervals

of elevated FiO_2 could be considered in prevention/treatment of hypoxic events following short respiratory pauses and fast SpO_2 declines. We also concluded that the influence of motion artefact on plethysmographic waveforms during hypoxia remains significant and automated oxygen controllers should only receive SpO_2 input from motion-resistant oximeters, and beyond this should implement effective waveform validation algorithms.

The next issue studied in the thesis was the oximetry signal dropouts which can leave an automated controller with no basis to make the adjustments based on. In our recent study (Lim *et al.*, 2015), since a majority of SpO_2 dropouts during hypoxia recovered in relative normoxia, we concluded that blind FiO_2 adjustments when the signal is missing would not be useful in most circumstances.

In a nutshell, although four decades have passed since the first attempts to automate oxygenation control for preterm infants, the number of algorithms developed for this purpose is limited, and much remains to be done. Before heading to the future directions, the conclusions of our work are listed here:

1. The oxygenation system is highly variable within and between preterm infants, manifested in both the variations of the SpO_2 response to an FiO_2 adjustment, as well as in the rapid and repeated fluctuations in SpO_2 that occur. Incorporation of predictors of the SpO_2 response (position on the dissociation curve, severity of lung dysfunction) and of sudden hypoxia (apnoea and hypoventilation) may enhance automated oxygen control algorithms.

2. Given the variability of the oxygenation system, adaptive and intuitive modifications to a rapidly responsive algorithm such as PID are likely to afford more effective control of oxygenation than rule-based or robust algorithms.

3. Automated control of inspired oxygen is currently limited by the technological shortcomings of infant monitoring. Pulse oximetry readings are an imprecise

measure of oxygenation, particularly at high and low values of SpO_2, or in the presence of low perfusion and motion artefact. Current respiratory monitoring devices are not designed for continuous and accurate use during automated control. Future automated controllers will benefit from refined and additional inputs of physiological data.

4. Safety considerations remain essential in the design and application of automated controllers, including appropriate alarms together with signal validity and device functionality checks. Control devices must be viewed as enhancing rather than replacing the skills of the bedside caregiver. Careful selection of the SpO_2 target range also remains crucial.

5. Increased interdisciplinary collaboration, data-sharing, and further experimental and clinical research will be needed in the effort to improve automated oxygen control devices.

The results of the thesis and the conclusions stated above became a basis for development of an automated FiO_2 controller for preterm infants which is the ultimate contribution of the thesis. This controller, for which a patent application has been filed, has been clinically tested in the Neonatal/Paediatrics Intensive Care Unit of the Royal Hobart Hospital. Development of the algorithm and clinical evaluation of the controller in preterm infants are the areas of focus for other members of our research team. Two papers describing features of the algorithm and outcomes of the clinical validation respectively are submitted at the time of writing this thesis with the candidate involved as a co-author.

7.2   Future Directions

In light of the challenges identified in this thesis, a number of directions for future research can be identified. The largely unexplained variability of the oxygenation

system is an area where further research is necessary. Using large datasets to develop a simulation of oxygenation in the preterm infant will potentially help to understand the relationship of predictor variables with response characteristics. A simulation of the oxygenation response would also allow the validity of the assumptions underlying existing adaptive controllers to be tested, and the performance of algorithms to be directly compared. The role of measureable predictors of hypoxic events as inputs to future adaptive control algorithms clearly deserves attention.

As far as technological challenges are concerned, developments in pulse oximetry allowing for more reliable measurements in spite of motion, would directly improve the quality of automated control. Novel approaches such as multi-wavelength, wireless, reflective and in-ear pulse oximetry (Aoyagi *et al.*, 2007; Li and Warren, 2012; Li *et al.*, 2012; Venema *et al.*, 2012, 2014) could be investigated in this regard. Identifying a practical respiratory monitoring technique for preterm infants during automated oxygen control should be studied. The validity and precision of respiratory motion measurement, as well as the feasibility and tolerance of long-term monitoring need to be investigated.

Based on our findings, we propose that future automated control algorithms should accommodate the following features. Firstly, the base algorithm must be capable of responding to fast and frequent hypoxic events. The familiar PID algorithm and other approaches which can make instant and continuous adjustments to FiO_2 are thus preferred to rule-based algorithms making frequent but delayed stepwise adjustments. These algorithms may then be modified or tuned intuitively to match the requirements of infants. Secondly, the controller must be adaptive, so as to overcome the variability in the oxygenation system that might otherwise de-stabilise or at least degrade the performance of the controller. Parameters such as position on the oxygen saturation curve and severity of lung dysfunction should be incorporated in the algorithm.

Thirdly, a controller should ideally utilise additional inputs to assist the algorithm in identifying the cause of hypoxic events, the prediction of response variability as well as validation of oximeter readings. An additional input for identification of apnoea will be an important advance. A sophisticated suite of alarms and/or actions are required, triggered by prolonged apnoea, equipment failure and respiratory deterioration, to name but three. The device must complement but not supplant the clinical acumen and attentiveness of the bedside staff, with the recognition that interventions other than adjustment of FiO_2 may be required.

Chapter 8

Appendices

The research contained within Appendix A (section 8.1) has been published as: Omid Sadeghi Fathabadi, Timothy J Gale, JC Olivier, Peter A Dargaville, Kevin I Wheeler, and Kathleen Lim. "Binary search for time-constant estimation in first order systems, FiO2-SpO2 case study." The 2013 Biomedical Engineering International Conference (BMEiCON-2013), IEEE (Fathabadi et al., 2013). It has been removed for copyright or proprietary reasons.

8.2   Appendix B: Gas Exchange Impairment Mechanisms

Gas exchange impairment mechanisms are called shunting and reduced ventilation : perfusion ratio. These two mechanisms affect the oxygenation curve describing the relationship between arterial partial pressure of oxygen (or saturation) and oxygen pressure in the alveoli in different ways (figure 8.4). While shunting deforms the curve and causes a limit for the maximum level of oxygen in the blood, ventilation-perfusion mismatch shifts the curve (Jones and Jones, 2000; Smith and Jones, 2001; Kjaergaard *et al.*, 2003).

Reduced ventilation:perfusion ratio causes increased levels of alveolar and arterial CO_2 and can be overcome by increasing inspired oxygen pressure. In shunting on the other hand, a proportion of the blood bypasses ventilated areas of the lungs and thus the resulting hypoxia can be resolved by increased inspired oxygen pressure only up to a point where the oxygen carrying capacity of the non-shunted blood is reached (Quine *et al.*, 2006).
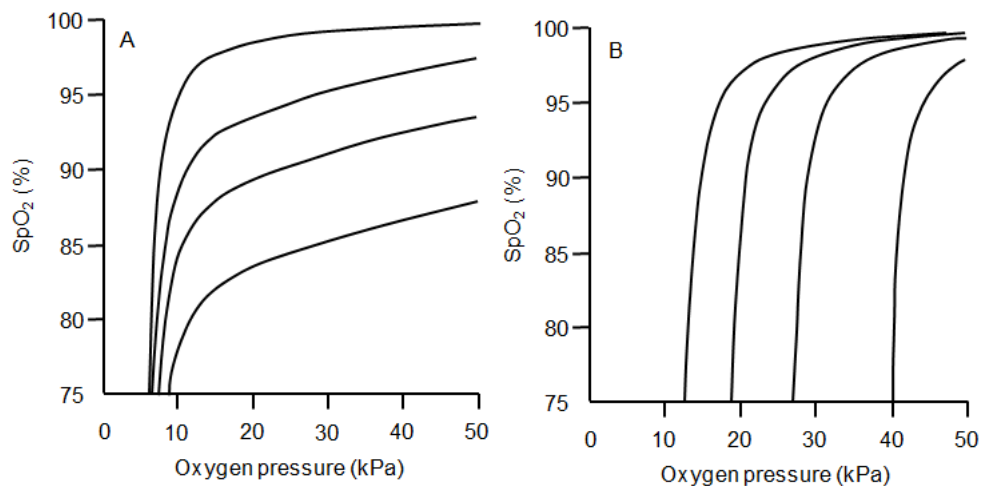

Figure 8.4: Effect of gas exchange impairment mechanisms on the relationship between oxygen saturation and partial pressure of inspired oxygen. A. Increased shunt ratio lowers the curve in high oxygen pressures B. Reduced ventilation:perfusion ratio shifts the curve to the right side. (De Gray *et al.*, 1997; Kjaergaard *et al.*, 2003; Quine *et al.*, 2006)

8.3 Appendix C: Detection of hypoxic Events

For each one of the 136 recordings from 20 patients, after the first 60 seconds (12000 samples) and before the last 20 seconds (4000 samples), at every new sample of the SpO_2 signal (rounded to percentages), it was checked if the signal in that point was equal to the preceding 1001 samples (signal was stable for > 5 s). If this condition was satisfied for a sample, the next 5 seconds of the signal was searched for the first point in which the value was at least 3% less than the stable period. This point (if existent) was considered as the candidate onset point for the hypoxic event. Then, the next 15 seconds after the onset, were looked for a minimum value of the candidate desaturation event.

If such a condition was not met the candidate onset was not considered as a hypoxic events. Also, if during the search for the minimum the signal became larger than the detected minimum so far, the search for the minimum stopped to prevent detecting the minimum of a possible neighbour hypoxic event as the minimum of the current candidate event. At the end of this process, if there was a detected minimum meeting the requirements after the onset, the candidate event was considered as a hypoxic event.

The slope of the desaturation was computed between the onset and the minimum. The search for the next hypoxic event was then continued from the minimum of the current event. Also, if at a point the stability criteria was not met but the value of the SpO_2 signal was not smaller than its neighbouring samples in the previous and the next 2.5 seconds (e.g. a local maximum), the search for the onset and potentially for the minimum was performed as done for the stable periods mentioned above.

8.3.1 Merging the Continuing Desaturations

After implementing the algorithm, it was observed that in some occasions, two separately detected events look like a single desaturation with a bump between them which had probably stopped them from being detected as a single event. Thus, the algorithm was adjusted so that for each detected adjustment in each recording (except for the first one), if its onset was located in less than 10 seconds after the minimum point of the previous desaturation and the SpO_2 at onset was less than or equal to the minimum of the previous desaturation, the two events were merged to form a single event.

8.3.2 Selecting Events with SpO_2<80% and no Overlap

At this stage, among the detected hypoxic events those which were followed by an episode of SpO_2 <80% for 4 seconds or longer during a 30 second window were selected for the analysis. To avoid analysis of a similar time window for more than one event, if the episode of SpO_2<80 for one event extended to after the onset of the next desaturation, the next desaturation was excluded from the analysis. Overall, 1275 hypoxic events were detected. 40 of the 136 recordings included no detected events with the mentioned characteristics.

8.3.3 The Graphical User Interface

Figure 8.5 depicts the graphical user interface developed for analysis of the hypoxic events. The examples are those presented in figure 5.1.
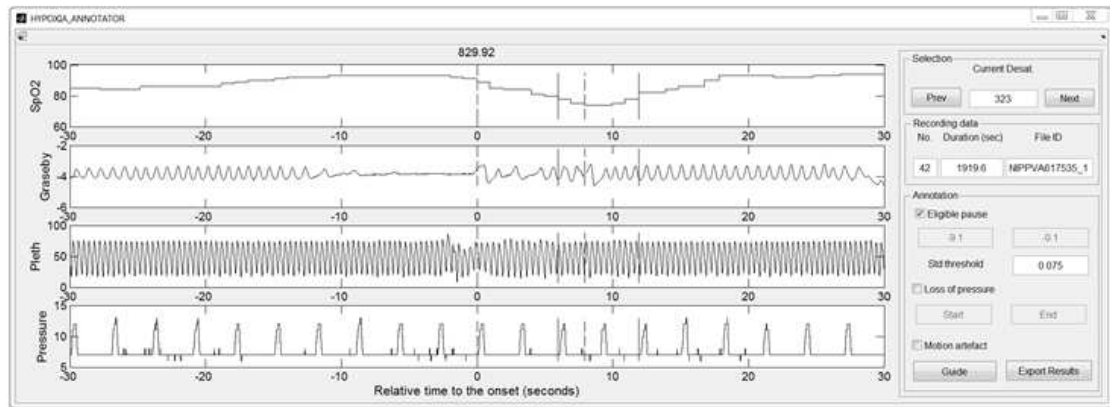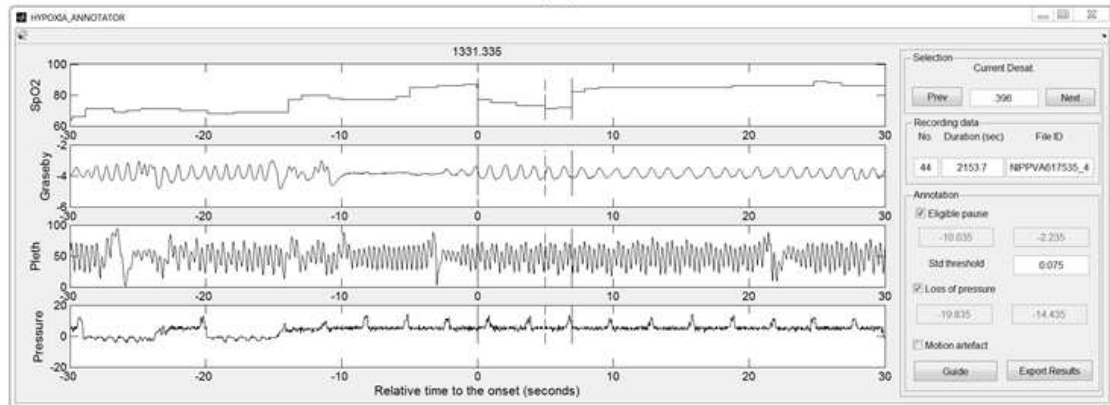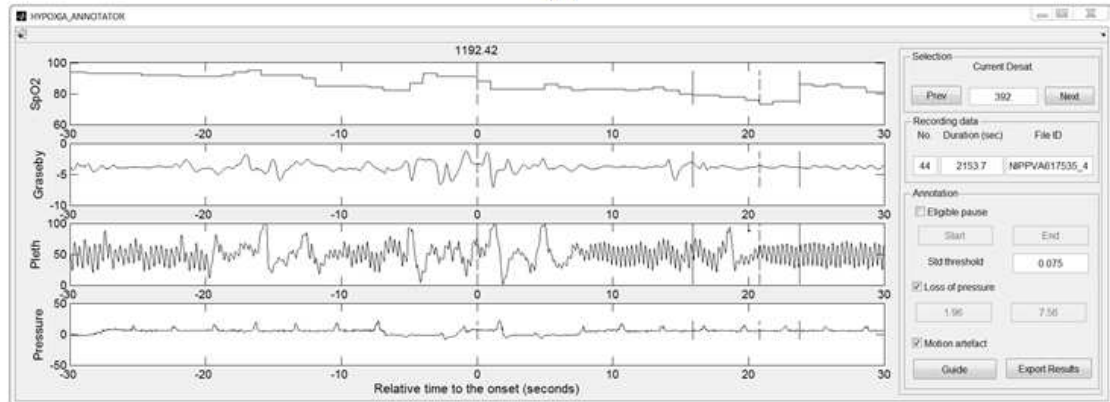
Figure 8.5: Graphical User Interface. (a) Hypoxia preceded by apnoea at -9.1 seconds. (b) Hypoxia preceded by loss of pressure at -29 sec and -20 sec, and also by apnoea at -10 sec. (c) Hypoxic event with circuit pressure loss at -6.6 sec and 2 sec, and a disturbed plethysmographic waveform.

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