Non-invasive venous oximetry through venous blood volume modulation

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NON-INVASIVE VENOUS OXIMETRY THROUGH VENOUS BLOOD VOLUME MODULATION

BY

FANG-CIAT DANIEL CHAN, BEng

A doctoral thesis

submitted in partial fulfilment of the requirement for the award of

doctor of philosophy of Loughborough University

JULY 2002

Supervisor: Professor Peter R. Smith, Ph.D

Department of Electronic and Electrical Engineering

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For Sheit Lan,

who cheered me on with every page that I completed.
For decades, the monitoring of mixed venous oxygen saturation has been done invasively using fibre-optic catheters. This procedure is not without risk as complications may arise from catheterization. This thesis describes an alternative and novel means of monitoring venous oxygen saturation. The technique outlined involves inducing regular modulations of the venous blood volume and the associated measurement of those modulations using an optical sensor. Just as pulse oximetry utilizes the natural arterial pulse to perform spectral analysis of the peripheral blood in order to estimate the arterial blood oxygen saturation, the new venous oximetry technique uses the artificially generated pulse to perform the task of measuring peripheral venous oxygen saturation.

This thesis explores and investigates the feasibility of this new venous oximetry technique. A heuristic model was first developed to predict the effects of introducing an artificially generated pulsatile signal in the venous system. The effect on the underlying natural arterial pulsation was also examined. Experiments were then conducted to justify and interpret the model developed. Other experiments were also conducted to optimize the design of the artificial pulse-based venous oximeter, to explore the effects of prolonged modulation of the venous system and to establish evidence that the measurements made were indeed related to venous oxygen saturation.

It is concluded that the new venous oximetry technique is indeed feasible and with further research and development would one day replace the current invasive method.
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Daniel Chan
Loughborough, Leicestershire
Summer 2002
CONTENT

ABSTRACT ...........................................................................................................i

ACKNOWLEDGEMENTS .....................................................................................ii

CONTENT ...........................................................................................................iii

CHAPTER 1

1. INTRODUCTION ............................................................................................1

1.1 THESIS OVERVIEW ..................................................................................2

1.2 IMPORTANCE OF OXYGEN TO THE HUMAN BODY ..................................4

1.2.1 Oxygen Transport ...................................................................................4

1.2.1a The Human Cardiovascular System ......................................................5

1.2.1b The Binding of Oxygen to Haemoglobin Molecules ............................7

1.2.1c The Release of Oxygen into Tissues ......................................................7

1.3 INTRODUCTION TO VENOUS OXIMETRY ..............................................7

1.3.1 Principle of SvO₂ Monitoring .................................................................8

1.3.2 Mixed Venous Oxygen Saturation (SvO₂) .............................................9

1.3.3 Peripheral Venous Oxygen Saturation .................................................10

1.3.4 The Importance of Venous Oximetry ...................................................11

1.4 INTRODUCTION TO VENOUS OXIMETRY TECHNIQUES ..................12

1.4.1 Continuous Invasive Venous Oximetry Method ....................................13

1.4.1a Limitations of SvO₂ and Central Venous Catheters ............................15

1.4.2 Continuous Non-invasive Venous Oximetry Method ............................16

1.4.2a Limitations of NIRS ...........................................................................18
1.5 INTRODUCTION TO PHOTOPLETHYSMOGRAPHY ........................................ 19
  1.5.1 Principle of Operation .............................................................................. 20
    1.5.1a Transmission and reflection modes .................................................... 20
    1.5.1b PPG Signal Components ..................................................................... 21
    1.5.1c The PPG Waveform .......................................................................... 23
  1.5.2 Major Applications of Photoplethysmography ....................................... 24

1.6 PULSE OXIMETRY ..................................................................................... 25
  1.6.1 Principle of Operation ........................................................................... 26
  1.6.2 The Beer-Lambert Law .......................................................................... 27
    1.6.2a The Logarithmic Solution .................................................................... 29
  1.6.3 Calibration ................................................................................................ 30
  1.6.4 Limitations of Present Pulse Oximeters ............................................... 31

1.7 SUMMARY ................................................................................................. 32

CHAPTER 2
2. MODELLING .............................................................................................. 33

2.1 ARTIFICIAL VENOUS PULSATILE SIGNAL ........................................... 34
  2.1.1 A Heuristic PPG Model ........................................................................ 34
  2.1.2 Definition of the model ......................................................................... 35
  2.1.3 Applicability ......................................................................................... 36
  2.1.4 Interpretation of the Model ................................................................... 36

2.2 ARTIFICIAL PULSATILE SIGNAL HEURISTIC MODEL .......................... 37

2.3 BEER-LAMBERT MODEL FOR VENOUS OXIMETRY ............................. 41
  2.3.1 Generalized Arterial and Venous Pulse Oximetry ................................. 42
  2.3.2 Beer-Lambert Model Interpretation ...................................................... 44
    2.3.2a Separation of Signal Components ...................................................... 44
2.4 SUMMARY ......................................................................................................... 47

CHAPTER 3
3. IMPLEMENTATION .................................................................................. 49

3.1 NEW VENOUS OXIMETRY METHODOLOGY ................................................. 50

3.1.1 Methods In Generating The Pulsatile Signal .............................................. 51

3.1.1a Digit Pressure Cuff for Generating Artificial Pulse ................................. 52

3.1.1b Air Source for the Digit Cuff .................................................................... 53

3.1.1c Pinch Valve to Control Inflation and Deflation of the Digit Cuff ............. 55

3.1.2 Recording of the Artificial Venous Pulsatile Signal ................................... 58

3.1.3 Software for Artificial Pulse Generator and PPG System ....................... 58

3.2 SUMMARY ......................................................................................................... 61

CHAPTER 4
4. EXPERIMENTAL INVESTIGATION .......................................................... 63

4.1 CONFIRMATION OF THEORETICAL RESULTS ........................................ 64

4.1.1 The Artificial Pulsatile Signal has an Additive Effect ............................... 65

4.1.2 The Appearance of the Multiplicative Term .............................................. 72

4.2 EFFECT OF MULTIPLICATIVE TERM ON SaO2 MEASUREMENT ............ 76

4.3 OPTIMIZATION OF THE DESIGN .............................................................. 79

4.3.1 Modulation Depth Optimisation ............................................................... 79

4.3.1a Data Analysis of the Recorded Data ....................................................... 80

4.3.2 Modulation Frequency Optimisation ........................................................ 84

4.4 PROLONGED APPLICATION OF ARTIFICIAL PULSE ............................... 93

4.5 RELATIONSHIP BETWEEN SaO2 and SvO2 ............................................. 95
1. INTRODUCTION

Venous oximetry or venous oxygen saturation monitoring is an essential tool for assessing the patient’s oxygenation both at the systemic and regional levels. It is also used to derive other hemodynamic parameters indirectly, such as Cardiac Output (CO) measurement through the Fick method. Although the technology involved in venous oximetry has been around for decades, venous oximetry is still not widely adopted as the end point in guiding therapy. Currently, one of the main disadvantages of the venous oxygen saturation monitoring technique is the invasive nature of the method. In order for progress to be made in the field, it is postulated that a new non-invasive method is needed to supplant the current technique to help venous oximetry with achieving its optimal clinical impact.
1.1 Thesis Overview

Venous oximetry has been noted for decades to potentially be of clinical value in the assessment of oxygenation. One of the main obstacles in limiting the wide application of venous oximetry in clinical environments is the invasive nature of the method. In view of the limitation in the present venous oximetry technology, it is the aim of this thesis to explore the possibility of developing a new non-invasive method that is able to monitor venous oxygen saturation in real time. This new technology would result in a more acceptable and risk free technique for monitoring venous oxygen saturation.

The first chapter begins by introducing the importance of oxygen to the human body; on how the limited reserve we have in our body requires us to have a continuous input through breathing. The physiological aspect of how oxygen is transported to various parts of the body where it is needed will also be discussed briefly. A brief synopsis on the history of oximetry and the various techniques that are currently available will also be included. Lastly, there will be an introduction to photoplethysmography (PPG) and pulse oximeter (since they are closely related to the new proposed method).

Chapter 2 will be devoted to the mathematical modelling of the introduction of an artificial venous pulsation to the venous system. The new venous oximetry mathematical model will describe both the PPG signal and the induced artificial pulsatile signal of the vascular system. A heuristic PPG model developed by SmithHayes (upon which the new method is based) will also be presented here. This chapter will also discuss the effects of introducing an artificial pulsatile signal into the vascular system from the heuristic model’s perspective and the nature of the active pulse in its relation to the underlying PPG signal. The multiplicative term derived from the model is the measure of the degree of coupling between the two signals and this will also be examined closely. Finally, a discussion of how the model can be modified to interpret venous oxygen saturation will also be included.

Chapter 3 discusses the implementation of the new non-invasive and continuous venous oximetry technique. Emphasis will be placed on the theoretical and practical issues affecting the overall performance. The chapter will provide an overview of the electronic implementation of the new technique in venous oximetry.
It will also include an introduction to the software required to control the hardware and to coordinate data acquisition.

In chapter 4, experiments that were conducted to investigate the feasibility of the new method in measuring venous oxygen saturation will be outlined, followed by discussions on the experimental results. Some of the investigations that will be described are the experimental justification of the heuristic model, the optimisation of the design and the verification of the measurements taken as truly related to venous oxygen saturation. The protocol of the experiments and the data analysis that followed will be described in detail. Finally, a discussion of the results and its implications will also be included.

Chapter 5 briefly reiterates the major achievements of the work and provides concluding remarks. Recommendations are also made for further studies in this area.

The references are collected in a common section following the main body of the report. Appendices are included, which offers technical details about the electronic design of the new method of venous oximetry and the program listings used for conducting the experiments.
1.2 IMPORTANCE OF OXYGEN TO THE HUMAN BODY

Hippocrates (460-377 B.C.) suggested that the purpose of respiration was to cool the heart. However, it is unequivocally established that the main purpose of respiration is to supply oxygen; \( \text{O}_2 \) to cells for their metabolic needs and to remove carbon dioxide (\( \text{CO}_2 \)) from cells. Living cells need energy for maintenance, growth, defence and replication. The energy required to facilitate this process is obtained through aerobic respiration. This is a process that requires oxygen and produces carbon dioxide.

Food, water, and air constitute the essentials of life. Energy derived from the oxidation of food can be used immediately or it can be stored in high energy chemical bonds for later use. A readily available energy supply is required both for physical activity and, more importantly, to maintain order and to keep the organism displaced from equilibrium or death. However, the ability of the organism to store these essentials varies considerably. For example, humans can survive for weeks without the intake of food; this suggests that the body has relatively large energy stores or reserves. Human beings can also survive for days without water or \( \text{H}_2\text{O} \); suggesting the body has considerable water reserves. However, human beings can survive for only a few minutes without air or \( \text{O}_2 \). This indicates that life is dependent on the minute-to-minute transfer of air (\( \text{O}_2 \)) from the environment to the tissue cells. This also indicates that, unlike energy (food) or \( \text{H}_2\text{O} \), human beings have relatively little storage capacity or reserve of \( \text{O}_2 \) in the body.

1.2.1 Oxygen Transport

In order to illustrate the role of both venous and arterial blood in the transportation of oxygen, it helps to look at how gaseous exchange is achieved through respiration. The lung is mobilized by contractions of respiratory muscles, which create a pressure gradient to move \( \text{O}_2 \) from the atmosphere to the gas exchange sites within the lungs. Airways and alveoli of the lung comprise the conduits that direct gas from the atmosphere to the blood. From the alveoli, oxygen diffuses into the blood and the cardiovascular (C-V) system then transports \( \text{O}_2 \) from the lung to the cells of the body (tissues).
Therefore, there is an interdependence of the pulmonary and cardiovascular system in delivering O₂ to and removing CO₂ from cells of the body. The interdependence is illustrated in the figure below:

![Figure 1.1 - The anatomical design of respiration.](image)

The blood delivered by the pulmonary arteries has a higher level of carbon dioxide partial pressure (PCO₂) and a lower level of oxygen partial pressure (PO₂) than alveolar air. Diffusion between the alveolar air and the pulmonary capillaries thus elevates the PO₂ of the blood as oxygen enters the bloodstream whilst lowering its PCO₂ as carbon dioxide leaves it.

### 1.2.1a The Human Cardiovascular System

In the human cardiovascular system, the arteries and veins serve as conduits for delivering nutrients and oxygen (O₂) to cells far removed from the source, whilst simultaneously removing and transporting waste and carbon dioxide (CO₂) from the immediate area of the cells to organs designed to eliminate them from the body. An illustration of the human body cardiovascular system is shown in Figure 1.2.

The oxygenated blood is carried back to the heart (left atrium) through the pulmonary veins and is emptied into the left ventricle during diastole. Oxygenated blood is then pumped into the arterial system during systole; that is, when the left ventricle contracts.

---

**CHAPTER 1**

5
The arteries serve as conduits to transport blood and thus, oxygen from the heart to peripheral vessels (arterioles and capillaries). In this way, oxygen is being transported to various parts of the body where it is needed. Arterioles are short vessels composed almost exclusively of smooth muscle. They serve as "stopcocks" or valves that regulate the flow of blood from arteries to capillary beds. The vessels can redistribute flow by constricting or dilating; thus increasing flow to tissues undergoing high levels of activity (exercise) and reducing flow to areas where less flow is needed.

The capillaries are short, thin-walled vessels that provide a large total cross-sectional area (considering all capillaries as a unit) for exchange of materials with interstitial fluid and cells. Normal interstitial fluid has a oxygen partial pressure ($PO_2$) of 40 mm Hg and a carbon dioxide partial pressure ($PCO_2$) of 45 mm Hg. As a result, oxygen diffuses out of the capillaries and carbon dioxide diffuses in until the capillaries’ partial pressures are the same as those found in the adjacent tissues. Venules are low-pressure vessels that collect blood from capillaries and return it to the veins. The blood is then transported to the heart.
1.2.1b The Binding of Oxygen to Hemoglobin Molecules

Only 1.5 percent of the oxygen content of arterial blood consists of oxygen molecules in solution. The remaining oxygen content of arterial blood is bound to the hemoglobin (Hb) molecules and specifically to the iron atoms in the centre of heme units. This reversible reaction can be summarised as follows:

\[ Hb + O_2 \leftrightarrow HbO_2 \]

1.2.1c The Release of Oxygen into Tissues

The amount of oxygen retained by hemoglobin depends primarily on the PO\textsubscript{2} in its surroundings. As a result, the lower the oxygen content of a tissue, the more oxygen is released by hemoglobin molecules as they circulate through the region. At a normal tissue PO\textsubscript{2} of 40 mm Hg, hemoglobin releases approximately 25 percent of its stored oxygen. Active tissues consume oxygen at an accelerated rate. When PO\textsubscript{2} declines, it automatically increases the amount of oxygen released by hemoglobin molecules passing through local capillaries. In addition to the effect of PO\textsubscript{2}, the amount of oxygen released is also influenced by pH and temperature. The hemoglobin molecules release their bound oxygen molecules more readily when the pH declines. Hemoglobin also releases more oxygen when the temperature rises.

1.3 INTRODUCTION TO VENOUS OXIMETRY

Venous oximetry refers to the range of techniques that are employed to measure the oxygen saturation in the venous blood. It can be further divided into two categories; mixed venous oxygen saturation (SvO\textsubscript{2}) and peripheral oxygen saturation. Mixed venous oxygen saturation (SvO\textsubscript{2}) is a reflection of the body's total oxygen consumption, or the end result of both oxygen delivery and consumption at the tissue level. Peripheral oxygen saturation is the measure of oxygen saturation in specific regions of the human body, such as the forearm or cerebral oxygenation in the brain.
1.3.1 Principle of SvO₂ Monitoring

SvO₂ monitoring is based on the premise that hemoglobin releases oxygen to the cells in a manner which is dependent on the cellular need for oxygen and the amount of oxygen that is being delivered. As discussed in the previous section, hemoglobin can unload oxygen and allow the cells to extract oxygen from the blood. It is dependent upon cellular oxygen demand and partial pressures of oxygen, as shown in Figure 1.3. As the cells unload oxygen, hemoglobin desaturates according to cellular oxygen requirement, as illustrated in Figure 1.4.

![Figure 1.3 - Saturation of hemoglobin on arrival to the cells](image)

![Figure 1.4 - Desaturation of hemoglobin at the cellular level](image)
The desaturation of hemoglobin is never complete; that is, hemoglobin never releases all of its oxygen. Under normal circumstances, hemoglobin releases approximately one fourth of the oxygen attached to hemoglobin, releasing enough for cellular need and resulting in a normal venous oxygen saturation of approximately 75%. If oxygen delivery is inadequate or cellular demand increases, hemoglobin carries a reserve of oxygen in the sense that approximately 40-50% more oxygen can be extracted off hemoglobin\(^1\). Generally speaking, hemoglobin can never totally release all of the oxygen content attached to hemoglobin molecules, but can release levels up to nearly 70-80%\(^2\). This equates to a mixed venous oxygen saturation of about 20-30%. The only oxygen reserve that is truly present in the body is hemoglobin’s ability to release more oxygen than the 25% that is released during a normal oxygen pass by the tissues. If the cells require more oxygen, hemoglobin can release more, which would result in a decreased venous oxygen saturation level.

### 1.3.2 Mixed Venous Oxygen Saturation (SvO\(_2\))

Mixed Venous Oxygen Saturation or SvO\(_2\) monitoring is the measurement of the amount of oxyhemoglobin returning to the lungs after all tissues have extracted the required oxygen\(^3\). Normally, SvO\(_2\) levels are obtained from the pulmonary artery. This allows for a mixing of blood from all parts of the body to reveal a mixed sample of oxygen in the blood. The SvO\(_2\) level is determined by various factors, namely oxygen delivery or DO\(_2\) (CO - Cardiac Output, hemoglobin, arterial oxyhemoglobin and arterial oxygen tension) and oxygen consumption (VO\(_2\)). Oxygen consumption can be defined as the amount of oxygen consumed by the body and is related to cardiac output, the oxygen carrying capacity of the blood, the amount of exercising skeletal muscle and the ability of the muscle to utilise supplied oxygen. The relationship can be expressed in the following modified Fick equation:

\[
SvO_2 = SaO_2 - \frac{VO_2}{1.306 \times CO \times Hb}
\]

Where SaO\(_2\) is the arterial oxygen saturation, Hb is the hemoglobin concentration and 1.306 is the oxygen combining power of hemoglobin\(^4\).
The SvO₂ level is also a reflection of the balance between oxygen delivery and utilisation. It is also a good indicator of the overall cardiopulmonary system. Since it consists of a mixture of blood returning to the lungs, SvO₂ is a global reflector of tissue oxygenation.

Although SvO₂ values do not reflect a change in any single component of DO₂ or VO₂ (unless all other components are held constant), SvO₂ values do however, reflect when an imbalance in DO₂ and VO₂ exists. When such an imbalance occurs, SvO₂ values change rapidly to reflect this imbalance⁵.

Under normal conditions, the SvO₂ is 68% to 77%, indicating that the tissues will extract approximately 25% of the oxygen delivered. An increase in the VO₂ or a decrease in the arterial oxygen content (SaO₂ × Hb) is compensated for by increasing the cardiac output or tissue oxygen extraction.

A normal SvO₂ however, does not ensure a normal metabolic state. In certain situations, a normal SvO₂ may be present due to regional hypoperfusion, left-to-right systemic shunts, or poisoned mitochondria from cyanide poisoning⁶. However, SvO₂ is the best single measurement to use in assessing the overall adequacy of oxygenation in the critically ill patient.

1.3.3 Peripheral Venous Oxygen Saturation

Peripheral venous oxygen saturation monitoring is mostly done on specific regions of the human body such as in the adult human forearm⁷. The availability of oxygen to the peripheral tissues in animal models of shock and in critically ill adults have been studied by measuring tissue PO₂⁸. These studies have shown that the measurement of peripheral oxygenation is a sensitive method of studying the progress of shock and resuscitation. Peripheral oxygen saturation or tissue oximetry (in conjunction with various exercise protocols) have an application in the diagnosis of peripheral vascular disease⁹.
Specialised algorithms have also been developed to allow the assessment of muscle oxygenation and regional blood flow during submaximal and maximal exercise, as well as under other pathophysiological conditions including cardiovascular disease and sepsis\textsuperscript{[10]}.

1.3.4 The Importance of Venous Oximetry

As there is currently no gold standard available for the measurement of tissue oxygenation, traditional assessments of the adequacy of oxygenation have relied on parameters such as blood pressure (BP), cardiac output (CO) and physical assessment. However, several studies have shown that these traditional assessments are limited\textsuperscript{[11]}. Furthermore, traditional hemodynamics such as BP, cannot reflect tissue oxygenation reliably and are not the best physiological parameters for assessing the impact of therapy\textsuperscript{[12]}.

\(\text{SvO}_2\) overcomes these traditional assessment limitations by offering the following advantages:-

- A rapid, virtually immediate, indicator of a threat to global tissue oxygenation. It detects the threat by noting an increase in oxygen extraction from hemoglobin.
  1. It replaces BP and CO as the initial indicators for the adequacy of blood flow to the tissues.
  2. It indicates at what point parameters affecting oxygen delivery and consumption causes a threat to tissue oxygenation.
  3. When used in conjunction with lactate, it indicates the severity of the threat to tissue oxygenation.
- It allows for the real time measurement of intrapulmonary shunting.
- It helps to correctly attribute changes of arterial oxygenation to intrapulmonary shunting or tissue oxygenation.
- It detects changes in oxygen consumption during weaning, movement and sedation control.
- \(\text{SvO}_2\) has been indicated as a prognostic indicator, such as in the case of patient with congestive heart failure (CHF)\textsuperscript{[13]}. 

Considering these advantages and its indication of the threat to tissue oxygenation which is unmatched by other parameters, venous oximetry is fast becoming an indispensable tool in the area of medical diagnosis. Its ability to give a real time indication of tissue oxygenation makes it a preferred parameter for monitoring the adequacy of hemodynamics. Its use as an end point for determining the adequacy of hemodynamics, measurement of intrapulmonary shunting and prediction of potential hemodynamic instability, make this parameter invaluable for the knowledgeable clinician. Used in context with the complete physiological profile, SvO2 is helping to revolutionise our understanding of tissue oxygenation and our related patient management\[^{14}\]. There are no ‘short cuts’ to critical care, but SvO2 monitoring may represent the best alternative that is currently available.

1.4 INTRODUCTION TO VENOUS OXIMETRY TECHNIQUES

All venous oximetry techniques can be categorised into two areas; methods that are invasive and those that are non-invasive. Each area is further divided into continuous and non-continuous. The differences are illustrated in Figure 1.5. Among the first method available is that of a blood gas analyser. A sample of pulmonary artery blood is taken and then analysed for its oxygen saturation in a blood gas analyser. However, the invasive nature of the measurement and its lack of real time monitoring capability limit its usefulness in the clinical environment.

![Figure 1.5 - Different types of venous oximetry techniques](image_url)
1.4.1 Continuous Invasive Venous Oximetry Method

Invasive continuous mixed venous oxygen saturation (SvO$_2$) monitoring is a technique that has been in existence for about 25 years$^{[15]}$. The technique is a variation of the standard Swan-Ganz Pulmonary Artery Catheter (PAC). The PAC was introduced in the 1960s and became a standard by the 1970s. The second variation of the technique arrived in the early 1970s and evolved to become a standard in the 1980s. The PAC is used within the Intensive Therapy Unit (ITU) for various diagnostic purposes such as to evaluate heart failure, monitor therapy after a heart attack, check the fluid balance of a patient with serious burns, kidney disease or after heart surgery.

After receiving a local anaesthetic, the catheter is placed through the skin into a vein. This can be a vein under the collar bone, a vein in the neck, a vein in the arm or in the leg. The catheter is essentially a long, thin plastic tube that contains multiple channels within it. The catheter is then advanced through the vein, through the right sided heart chambers and into the pulmonary artery. It is usually left in place for 1 to 3 days, depending on the patient's clinical situation. It gives valuable information about the pumping ability of the heart and the pressure within the chambers of the heart which can help to guide further therapy.

In the late 1980s, two fibre-optic bundles were inserted in the PAC. This permitted the transmission of a light to the tip of the catheter in the pulmonary artery via one of these two fibre-optic bundles. The second bundle was used to reflect back the redness seen with this light into a photodetector cell. The redness of the light could then be translated into mixed venous oxygen saturation (SvO$_2$), thus providing a clinician with a quantitative measurement of oxygen transport. This instrument used the principle of reflection spectrophotometry to make this measurement. This modified PAC was slow to become popular and is still not used in all hemodynamic monitoring, despite SvO$_2$ being rather valuable in its ability to make judgements about the balance of total body oxygen supply and demand. The modified PAC was then named SvO$_2$ catheters. A sketch of a SvO$_2$ fiber optic catheter is shown on Figure 1.7.
Central Venous Catheterization (CVC) is a variation of the PAC technique. This method is sometimes preferred because it is relatively less risky and costly than PAC. In CVC, the catheter is inserted into the large veins and the tip of the catheter is advanced into the superior vena cava (SVC) which is more accessible than the Pulmonary artery (Figure 1.7).

There are currently studies being made on whether the venous oxygen saturation measurement obtained using these two methods are interchangeable. In one of the studies by Ladakis et al., it was found that S\textsubscript{vO\textsubscript{2}} can be estimated with great accuracy by central venous oxygen saturation (ScvO\textsubscript{2}) using a power model\textsuperscript{[16]}. However, a separate study observed a poor correlation between ScvO\textsubscript{2} and S\textsubscript{vO\textsubscript{2}}\textsuperscript{[17,18]}. 

![Figure 1.6 - Sketch of a S\textsubscript{vO\textsubscript{2}} fibre optic catheter](image)

![Figure 1.7 - Insertion of Central venous catheter.](image)
Until further studies could be made to compare the two variants of the technique, mixed venous oxygen saturation monitoring through Central Venous Catheterization remains a questionable alternative.

1.4.1a Limitations of SvO₂ and Central Venous Catheters

Although the new technology offers real time monitoring capability, it is more limited than laboratory measurements that are obtained by co-oximetry. One key limitation of the two-wavelength system is the potential to have elements in the blood other than oxyhemoglobin and reduced hemoglobin reflect light. For example, the presence of excess lipids or dye can alter the SvO₂ signal\textsuperscript{[19]}\textsuperscript{19}. This limitation of the two-wavelength system was finally addressed when Baxter improved the optical processing method of the system and several studies now support its accuracy\textsuperscript{[20]}\textsuperscript{20}.

The primary concern now, with the two-wavelength system, is its inability to control and account for hemoglobin changes. Changes of more than 2 g/dL (grams/decilitre) would cause the two-wavelength system to be suspect in accuracy. However, current literature does not appear to identify or support this concern.

The cost of special SvO₂ catheters has been a controversial issue in clinical care. A special fibre-optic SvO₂ catheter cost about £66 more than a normal PAC catheter (£110 versus £44) and as such, clinicians are not in agreement as to the cost-benefit and the cost-effectiveness of the SvO₂ catheter. As a result, SvO₂ monitoring utilising a fibre-optic catheter is not widely adopted in ITU.

Another limitation of the present invasive method of venous oxygen saturation monitoring is that the time needed to set up the catheterization might not be suitable for patients in critical conditions where an immediate assessment of venous oxygen saturation is needed. A non-invasive SvO₂ monitoring device would be useful in ambulatory settings as it allows SvO₂ assessment without the need for pulmonary catheterization.
Research does support how SvO₂ monitoring allows more rapid termination of drug therapies, reduces the incidence of mechanical ventilator manipulation and may improve the movement of patients out of Intensive Therapy Units. What is needed in place of this present invasive method, is a system which is non-invasive; one that would negate the complications that might arise with Pulmonary Artery Catheterization and a method that could provide an immediate assessment of SvO₂.

1.4.2 Continuous Non-invasive Venous Oximetry Method

Near Infrared Spectroscopy (NIRS) is a relatively new venous oximetry technique and has shown much promise, as evident in the vast literature on its applications. The first observations using NIRS were made by Jöbsis (1977). Subsequently, the technique has been refined and applied to the study of cerebral hemodynamics in new born babies\textsuperscript{21}, children\textsuperscript{22} as well as adults\textsuperscript{23}.

In NIRS, the light emitted by appropriate sources (typically laser diodes), at wavelengths in the range of 650-900nm, is conveyed to the skin of the subject. Whilst propagating through the tissues, the light undergoes both scattering and absorption\textsuperscript{24}. Scattering is due to the discontinuities in the refractive index, which typically take place at the membranes and organelles. The optical absorption is generally due to a large number of substances present in the tissues. In near infrared, the dominant species are water, cytochrome $a$ and $a_3$, myoglobin and hemoglobin in its oxygenated and reduced forms. Between the wavelength of 700-850nm, the absorption is mostly due to oxyhemoglobin and deoxyhemoglobin. After travelling through the tissues, part of the light would be diffusely reflected from the skin and can be detected at a distance from the source. The spacing between the source and the detector is known as optrode spacing. Increasing the optrode spacing improves the sensitivity. However, in order to achieve a sufficiently high signal-to-noise ratio, it was necessary to limit this distance\textsuperscript{25}.

Specific algorithms have been developed to calculate the concentration changes of the species. Algorithms that involve using three wavelengths and solving three simultaneous equations\textsuperscript{26} will be highlighted here.
INTRODUCTION

NIRS is based on a modified version of the Beer-Lambert law. The Beer-Lambert law (or Beer’s law) is the linear relationship between the absorbance and the concentration of an absorbing species. The general Beer-Lambert law is usually written as:

\[ A = \mu(\lambda)rC \]  \hspace{1cm} 1.3

where \( A \) is the measured absorbance, \( \mu(\lambda) \) is a wavelength-dependent absorptivity coefficient measured in \( \text{L mol}^{-1}\text{cm}^{-1} \), \( r \) is the path length measure in \( \text{cm} \), and \( C \) is the analyte concentration in \( \text{mol L}^{-1} \). Changes in the concentrations of the three different species (or chromophores) can be measured from changes in the absorbance of light transmitted into the tissues, using a modified Beer-Lambert law, the following can be derived:

\[ A = \mu(\lambda) \times r \times C \times G \]  \hspace{1cm} 1.4

The addition of \( G \) is used to accommodate the tissue properties and it varies with the type of tissues and geometry of the optrode positioning. \( G \) is also known as the path length modifier. By assuming that \( G, r \) and \( \mu(\lambda) \) are constants, changes in the absorbance of light should only be due to:

\[ \Delta A = l \times \mu(\lambda) \times \Delta C \]  \hspace{1cm} 1.5

Where we made the substitution, \( l = r \times G \). There are three different chromophores involved; oxyhemoglobin (\( \text{HbO}_2 \)), deoxyhemoglobin (\( \text{Hb} \)) and cytochrome \( a_3 \) (\( a_3 \)). By assuming that the absorption at each wavelength is a linear summation of the effects of these 3 compounds then:

\[ \frac{A(\lambda_n)}{l} = \mu^{\text{Hb}}(\lambda_n)C_{\text{Hb}} + \mu^{\text{HbO}_2}(\lambda_n)C_{\text{HbO}_2} + \mu^{a_3}(\lambda_n)C_{a_3} \]  \hspace{1cm} 1.6

Where \( A(\lambda_n) \) is absorption measurement at wavelength \( n \), \( \mu^x(\lambda_n) \) is absorption coefficient of compound \( x \) at wavelength \( n \) and \( C_x \) is concentration of compound \( x \).
In order to calculate the change in concentration of the three chromophores, three different light sources were used to measure the absorption changes such that three simultaneous equations can be constructed. By doing a matrix inversion, a multiplying factor, $\sigma$, for each wavelength and compound is then obtained. The concentration changes are then calculated as:

$$
\begin{bmatrix}
    C_{Hb} \\
    C_{HbO_2} \\
    C_0
\end{bmatrix}
= \begin{bmatrix}
    \sigma^{Hb}(\lambda_1) & \sigma^{Hb}(\lambda_2) & \sigma^{Hb}(\lambda_3) \\
    \sigma^{HbO_2}(\lambda_1) & \sigma^{HbO_2}(\lambda_2) & \sigma^{HbO_2}(\lambda_3) \\
    \sigma^{a^3}(\lambda_1) & \sigma^{a^3}(\lambda_2) & \sigma^{a^3}(\lambda_3)
\end{bmatrix}
\begin{bmatrix}
    A(\lambda_1) \\
    A(\lambda_2) \\
    A(\lambda_3)
\end{bmatrix}
$$

The calculated concentration changes are then expressed in mol L$^{-1}$ multiplied by the optical path length, $l$. For example, for oxyhemoglobin:

$$
l.C_{HbO_2} = \sigma^{HbO_2}(\lambda_1)A(\lambda_1) + \sigma^{HbO_2}(\lambda_2)A(\lambda_2) + \sigma^{HbO_2}(\lambda_3)A(\lambda_3)
$$

The algorithm was used to calculate cerebral oxygenation. The results can also be related to venous oxygen saturation when used in conjunction with other protocols.

1.4.2a Limitations of NIRS

Applications of the modified Beer-Lambert law to living tissues are difficult because the optical path length cannot be determined precisely$^{[27]}$. The means of determining the optical path length remains problematic in NIRS and presently, the problem is attempted by time-of-flight and phase modulation of the light source. The factor, $G$ in the modified Beer-Lambert model is not constant for all subjects as it varies with different skin types. Furthermore, the method is very sensitive to blood flow. These factors greatly affect the calibration of the instrument for venous oximetry.

NIRS is currently not widely used in clinical environments for measuring venous blood oxygen saturation. It is generally considered more as a research equipment.
It is hoped that the development of NIRS would one day provide information on regional and global cerebral oxygenation, as well as total cerebral blood volume by measuring changes in total Hb over time.

Due to its limitation, NIRS is a poor candidate to replace the traditional method of venous oximetry using $\text{SvO}_2$ and central venous catheters.

The proposed new method of venous oximetry is closely related to plethysmography and pulse oximetry. The rest of this chapter will be devoted to both of these topics as they are crucial to understanding the new proposed method of venous oximetry.

1.5 **INTRODUCTION TO PHOTOPLETHYSMOGRAPHY**

Photoplethysmography (PPG), which was developed by Hertzman in 1938\[^{[28]}\], is the electro-optic technique for the non-invasive monitoring of peripheral blood volume changes. It is a simple and useful method of measuring the cardiovascular pulse wave found throughout the body, which is caused by the periodic pulsations of arterial blood volume and is measured by the changing optical absorption which this induces. Clinicians have since used the PPG for diverse applications when there are questions arising out of changes in blood volume, blood pulsatility and tissue perfusion by blood.

The ease of use, simplicity and non-invasive nature of the technique has resulted in the dominance of the optical methods as the preferred technology in a number of biomedical monitoring situations. The introductory notes here will briefly explain the basic principles of the operation of PPG systems and its current major applications.
1.5.1 Principle of Operation

Photoplethysmography\textsuperscript{[29]} refers to optical plethysmography (the registration of blood volume change), and was originally used to describe the electro-optic technique of measuring the cardiovascular pulse wave. The pulse wave is discernible by the dynamic optical absorption that the periodic arterial pulsations induce in well-perfused peripheral tissues.

1.5.1a Transmission and reflection modes

PPG signals could be observed by illuminating a suitable pulsating vascular bed; for example, by trans-illumination of the fingers or toes. The most commonly used light source is Infrared light since it is well absorbed in blood and weakly absorbed in tissue. This property of Infrared light causes the pulse wave to be observed in reasonable contrast. As the illuminated vascular bed pulsates, the optical path length through it alters and therefore the transmitted light is modulated throughout the cardiac cycle. This transmission mode PPG is limited to monitoring sites that are well-perfused and sufficiently transparent for the transmitted light to be detected (such as the finger tips, toes, ear lopes and in the case of infants, the foot or palm of the hand).

In reflection mode PPG, both the source and detector are positioned at the skin surface as shown in Figure 1.8, with back scattering light returning from a range of depths within the highly scattering tissue.
In the near infrared region, light penetrates several centimetres into tissues\textsuperscript{30}, where the dynamic absorption of the pulsating vascular bed modulates the total reflected light. Reflectance PPG enables monitoring on other peripheral sites such as the forehead, limbs and chest\textsuperscript{31}.

### 1.5.1b PPG Signal Components

PPG systems differentiate between light absorption due to blood volume and that of other fluids and tissue constituents by observing that arterial blood flow pulsates whilst tissue absorption remains static. There are therefore two components in the PPG signal; the rapidly alternating signal (AC component) which is caused by the arterial pulsations and the steady signal (DC component) due to other fluid constituents, together with bone and tissues which do not modulate the light but have a fixed level of absorption. The pulsatile component accounts for a small proportion (1 – 5%) of the total intensity\textsuperscript{32}. The small arterial blood volume changes will induce a parallel change in optical path length and also function to modulate the macroscopic absorption of the vascular bed (Figure 1.9).
The arterial pulse amplitude has been physiologically interpreted as the measure of the blood supply to the skin. Since blood circulation in the body undergoes a transition from high-pressure arteries to low-pressure veins, much of the non-pulsatile blood will be venous. This non-pulsatile intensity has been found to be useful in comparative venous testing. Any PPG realisation will consist of both the AC and the DC signal. The former being the dynamic component representing the arterial pulsations and the latter being the slowly, changing quasi-static component, which is indicative of the venous blood volume.
1.5.1c The PPG Waveform

Although it is an implicit assumption that in PPG, changes in measured light intensity are due to changes in blood volume, no direct relationship has been formulated between the observed pulsations and the underlying physiological dynamics. However, a significant correlation has been reported between dynamic (AC) PPG signal and strain-gauge plethysmography\textsuperscript{[37]}\textsuperscript{[37]}. The over simplistic Beer-Lambert law of optical transmission through tissue is often employed to aid physical understanding\textsuperscript{[38]}\textsuperscript{[38]}, with broader theoretical applicability afforded by the diffusion theory\textsuperscript{[39,40]}\textsuperscript{[39,40]}. Whilst the received light intensity depends on many factors (both physiological and geometric), appropriate sensor designs coupled with compensation for skin absorption by control of the source intensity\textsuperscript{[41]}\textsuperscript{[41]} can result in a quasi-static (DC) PPG signal which is governed to a large extent by the total illuminated blood volume. Dynamic changes in the optical properties of the tissue, such as the arterial pulsations, can be further used to isolate absorption by dynamic blood from absorption by static blood. In this way, non-invasive characterisation of blood may be performed despite the complex optical interactions and the inherent variability in both subjects and geometry.

Analysis of the PPG waveform can be used to infer physiological information. For example, the presence of a second, smaller pulse within the arterial pulse called a \textit{dichrotic notch} (Figure 1.10) is due to the pressure wave reflection from the lower body at the bifurcations of the arterial tree\textsuperscript{[42,43]}\textsuperscript{[42,43]}.

![Figure 1.10 - Dichrotic notch in PPG (AC) waveform](image-url)
INTRODUCTION

Studies have shown that the dichrotic notch slowly disappears from the PPG waveform with age. This has been explained by reduced wave reflection\textsuperscript{[44]} . The dichrotic notch is the most noticeable feature that changes with age\textsuperscript{[45]} . Low frequency trends in the quasi-static PPG level and arterial pulsations amplitude have been attributed to the effects of respiration and vasomotion\textsuperscript{[46]} .

1.5.2 Major Applications of Photoplethysmography

One of the major applications of PPG is in the area of pulse oximeter\textsuperscript{[47]} which measures the oxyhemoglobin saturation in the arterial blood. It relies on the knowledge that when two compounds with differing absorption spectra are together in a given solution, the ratio of the two concentrations can be determined from the ratio of the light absorbed at two different wavelengths. PPG is also used for the studies of peripheral vascular compliance\textsuperscript{[48]} and more recently, for monitoring the oxygen status of the foetus during labour and delivery\textsuperscript{[49]} . Others have used PPG to measure physiological variables such as respiratory rates\textsuperscript{[50]} and peripheral arterial pressure\textsuperscript{[51]} . The pulsatile microcirculation was also studied in its relation to hypertension\textsuperscript{[52]} . Bilateral PPG pulse waves at multi-sites were used to diagnose vascular patients with asymmetrical disease\textsuperscript{[53]} . Venous PPG signals have been used in a variety of functional venous hemodynamics testing situations\textsuperscript{[54]} , with recent advance in calibration of these signals\textsuperscript{[55]} spawning increased clinical interest.

Here, we shall hereby examine the main application of PPG signal, namely, pulse oximetry. Pulse oximetry remains the dominant clinical application of PPG but also serves to demonstrate the use of arterial pulsations to isolate the absorption due to arterial blood, thus, enabling a non-invasive spectral blood analysis.
1.6 **PULSE OXIMETRY**

Pulse oximetry is arguably the greatest advance in patient monitoring since electrocardiography. It enables oxygenation, an important physiological variable that is poorly detected in clinical means, to be monitored continuously, simply, and non-invasively. This methodology relies on the knowledge that deoxyhemoglobin and oxyhemoglobin absorb light at varying degrees as a function of wavelength\[^{56}\].

Currently, most commercially available pulse oximeters use two wavelengths of light; one in the red band (660nm) and the other in the infrared band (940nm).

Since at 660nm deoxyhemoglobin absorbs more light than oxyhemoglobin, and at 940nm, oxyhemoglobin absorbs more light than its reduced form (Figure 1.11), pulse oximetry relates this differential measurement to the arterial oxygen saturation.

---

**Figure 1.11** - Absorption spectra of oxyhemoglobin and deoxyhemoglobin, showing the two most commonly used wavelengths

\[^{56}\] Reference 56
A consideration of the optical spectra highlights that a choice of wavelengths on the opposite sides of the Isosbestic point, that is, the wavelength at which the absorption of the hemoglobin species are identical (around 800-815nm), will give the greatest contrast possible. In living tissues, however, light is also being absorbed by the tissues and by the hemoglobin in venous and capillary blood.

The breakthrough was the realisation that the light absorbed varied with each pulse. In addition, if the absorption was measured at one point of the pulse wave and compared with the absorption at another point, then the difference between the values was due to arterial blood alone; the contribution of other absorbers could thus be eliminated.

1.6.1 Principle of Operation

The degree at which oxygen is chemically combined with hemoglobin is referred to as the functional arterial oxygen saturation or SaO2. It is the ratio of the concentration of oxyhemoglobin (HbO2) to the sum of oxyhemoglobin and deoxyhemoglobin (HbO2 + Hb) that is present in the arterial blood stream:

\[
SaO_2 = \frac{HbO_2}{Hb + HbO_2} \times 100\% \]

SaO2 is closely related to fractional arterial oxygen saturation, which is the ratio of oxyhemoglobin to the total hemoglobin of all species including carboxyhemoglobin and methemoglobin. Since the amount of oxygen physically dissolved in blood is small in comparison with oxygen being chemically combined with hemoglobin, functional or fractional arterial oxygen saturation gives a good measure of the oxygenated state of hemoglobin in the blood stream.

In order to distinguish between the two species of haemoglobin, mainly oxyhemoglobin and deoxyhemoglobin, two separate wavelengths, \( \lambda_1 \) and \( \lambda_2 \), are used to illuminate the vascular bed. The transmitted light is then measured.
The pulse oximeter first determines the AC component of the absorbance at each wavelength and then divides it by the corresponding DC component to obtain a “pulse added” absorbance that is independent of the incident light intensity. The ratio of ratios (R) of the pulse added absorbances are related to arterial oxygen saturation (SaO₂):

\[
R = \frac{AC_{\lambda_1} / DC_{\lambda_1}}{AC_{\lambda_2} / DC_{\lambda_2}}
\]

In practice, the two light sources must be multiplexed so that each source provides illumination for a discrete time period during which the intensity may be measured.

1.6.2 The Beer-Lambert Law

The Beer-Lambert law states that the transmission of light through a turbid medium is a logarithmic function of the density or concentration of the absorbing molecules in the solution. The intensity of the transmitted light is also a function of the length of the path the light travels through the solution and the absorbance constant for a given absorbing particle at a given wavelength. This law may be written as the equation:

\[
I(\lambda) = I_o(\lambda) \exp(-\mu_{eff}(\lambda)r)
\]

Where \( r \) is the path length, \( \mu_{eff}(\lambda) \) is the effective absorbance. The constant \( I_o \) can be interpreted here as the source intensity, and has wavelength dependency to account for the discrete narrow-bandwidth sources used in pulse oximetry. The pulse oximeter also used the Beer-Lambert law, but with important empirical corrections. For the Beer-Lambert law to be valid, both the solvent and the cuvette must be transparent. The length of the light path must be known exactly and no other absorbers can be present in the solution. However, it has been shown that this approximation to the complex optical interactions that occur in living tissue can give a good first order solution\[^{57}\].
INTRODUCTION

The primary assumption of the Beer-Lambert formulation is that the optical path through tissue may be separated into a static component and a small dynamic component that depends solely on the wavelength-dependent absorbance of the pulsating arterial blood.

This can be expressed by decomposition of the macroscopic optical density:

\[ \mu_{\text{eff}}(\lambda) r = \mu_{\text{blood}}(\lambda) d(t) + \mu_{\text{tissue}}(\lambda) l \] ........................................ 1.12

where \( \mu_{\text{blood}}(\lambda) \) and \( \mu_{\text{tissue}}(\lambda) \) are effective absorbance for the blood and tissue respectively, \( d(t) \) is the dynamic path length through the pulsating blood (assumed to be identical for all wavelengths) and \( l \) is the constant path length through all other anatomical components.

The dynamic component is further decomposed by virtue of the absorbance differences between oxyhemoglobin and deoxyhemoglobin at the illuminating wavelength:

\[ \mu_{\text{blood}}(\lambda) = S \mu_{\text{HbO}_2}(\lambda) + (1 - S) \mu_{\text{Hb}}(\lambda) \] ........................................ 1.13

\( S \) is the proportion of hemoglobin that is oxygenated (or in other words, the desired arterial oxygen saturation, \( \text{SaO}_2 \)). This allows us to write the received intensity at a particular wavelength, \( \lambda \), in terms of the oxygen saturation, the constant effective absorbances and the path lengths:

\[ I(t, \lambda) = I_o(\lambda) \exp\left\{ (S \mu_{\text{HbO}_2}(\lambda) + (1 - S) \mu_{\text{Hb}}(\lambda)) d(t) + \mu_{\text{tissue}}(\lambda) l \right\} \] ........................................ 1.14

It is therefore possible to generate instances of the above equations at different wavelengths and solve these to obtain a value for the oxygen saturation. The following example solution is conceptually based on one of the most predominant used algorithms and serves to introduce both common methodology and terminology.
In order to obtain a linear equation in \( S \), the natural logarithm of the intensity can be used to isolate the multiplicative source constant, \( I_o(\lambda) \),

\[
\ln I(t, \lambda) = \ln I_o(\lambda) - \left( S \mu_{HbO_2}(\lambda) + (1 - S) \mu_{Hb}(\lambda) \right) d(t) - \mu_{tissue}(\lambda) \] ............1.15

Since both the source constant and the tissue absorbance are time invariant, we can eliminate them by considering the time derivation of the equation,

\[
\frac{d[\ln I(t, \lambda)]}{dt} = -\left( S \mu_{HbO_2}(\lambda) + (1 - S) \mu_{Hb}(\lambda) \right) \frac{d[d(t)]}{dt} \] .................1.16

The derivative of \( d(t) \) is an unknown dynamic but according to this standard model, is not wavelength dependent. Thus, the two instances of the equation above may be generated at two wavelengths and a ratio constructed to eliminate any dependence on \( d(t) \):

\[
\frac{d[\ln I(t, \lambda_1)]}{dt} = \frac{S \mu_{HbO_2}(\lambda_1) + (1 - S) \mu_{Hb}(\lambda_1)}{S \mu_{HbO_2}(\lambda_2) + (1 - S) \mu_{Hb}(\lambda_2)} \frac{d(d(t))}{dt} = R \] ...............1.17

The ratio \( R \), determined from the measured intensities at the two wavelengths, is the ratio of ratios and is defined as the ratio of the absorbance of blood at the two illuminating wavelengths. This unknown oxygen saturation, \( S \), may be determined from the measured \( R \) and knowledge of the four effective absorbances:

\[
S = \frac{R \mu_{Hb}(\lambda_2) - \mu_{Hb}(\lambda_1)}{R \left( \mu_{Hb}(\lambda_2) - \mu_{HbO_2}(\lambda_2) \right) - \left( \mu_{Hb}(\lambda_2) - \mu_{HbO_2}(\lambda_2) \right)} = \frac{SaO_2}{100\%} \] ...............1.18
1.6.3 Calibration

The simple model of the relationship between $S$ and $R$ presented in the last section is only approximately true. For example, the two wavelengths do not necessarily have the exact same path length changes, and second-order scattering effects have been ignored. In practice, the four effective absorbances will not be derived theoretically, but will be based upon an empirical calibration through the employment of induced hypoxia experiments\[^{58}\]. A typical empirical calibration versus the Beer-Lambert model is illustrated in Figure 1.12. The final empirical calibration will ultimately depend on the details of an individual sensor design, but these variations can be determined for each sensor and included in unique calibration parameters.

![Figure 1.12 - Empirical Calibration versus Beer-Lambert model](image-url)
1.6.4 Limitations of Present Pulse Oximeters

Pulse oximeters suffer the same limitation as any two-wavelength system for measuring oxygen saturation in the blood. Adult hemoglobin typically contains four different species; oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin and methemoglobin. As most commercially available pulse oximeters use only two wavelengths, only two Hb species can be measured. Carboxyhemoglobin (COHb) looks like HbO₂ at 660nm, whereas COHb is relatively transparent at 940nm. In the presence of large amounts of COHb (such as in the case of carbon monoxide poisoning), the pulse oximeter SaO₂ saturation readings could be indicated incorrectly. Motion artefact occurs when the oximeter sensor is subjected to excessive motion and at present, the problem is tackled using proprietary signal processing techniques, mechanical designs of a new finger probe and more recently, through signal equalisation with an extra control source.

Poor blood perfusion is also commonly encountered in clinical settings when using pulse oximetry. Oximeters depend on an identifiable arterial pulse to operate properly. Conditions such as hypotension, hypothermia and hypovolemia can act to block sensor readings for oxygenation. Other factors that affect pulse oximetry accuracy include ambient light artefacts experienced in the operating theatres and nail polish. Studies have shown that changes in the volume fraction of blood contained in the tissue can affect the slope and offset of the oximeter calibration curve. However, within clinical situations during which a patient’s arterial oxygen saturation is greater than 70%, errors introduced by blood-volume fluctuations are not likely to exceed one or two percent if the pulse oximeter is calibrated for a blood volume fraction in the normal physiological range.

If the venous blood volume changes within the tissues are comparable or less than that of the pulsatile component, it would not affect the accuracy of the pulse oximeter drastically. However, in cases whereby the change of blood volume is due to some physiological factors which leads to significant redistribution of venous blood in the tissues (such as during exercise), pulse oximetry readings will be affected.
1.7 **SUMMARY**

The importance of oxygen to the human body has been presented in this chapter. Due to the small reserve of oxygen within the human body, we need to constantly replenish its supply through respiration. It is therefore also even more vital, that we have a minute-to-minute monitoring of the oxygen saturation in the blood during intensive care. The role of the arterial and venous blood in oxygen transport has been outlined with an illustration of the human cardiovascular system.

Venous oximetry is important within a clinical environment in assessing a patient’s oxygenation. The extant techniques used in venous oximetry are mainly through using fibre-optic catheters in the pulmonary artery and Near Infra Red Spectroscopy (NIRS). The present non-invasive technique (NIRS) is not suitable for replacing the invasive method due to its calibration problems.

The current invasive technique has limited the use of venous oximetry in clinical environments. Therefore a new non-invasive method is needed to supplant the current technology and help venous oximetry with achieving its best clinical impact.

The last portion of this chapter was devoted to introducing photoplethysmography (PPG) and its main application, pulse oximetry. An in-depth look at the PPG waveform and the theory of pulse oximetry based on the Beer-Lambert law were presented. Although there are quite a few factors which could affect the accuracy of pulse oximetry, generally it is accurate and is considered the greatest advance in patient monitoring after electrocardiography\footnote{68}.

The chapter attempts to lay the foundation for understanding the new proposed method of venous oximetry, which is closely related to photoplethysmography and pulse oximetry. The chapter has also sufficiently shown that venous oximetry is an important part of clinical care and the invention of a new non-invasive venous oximetry technique that could be used extensively within a clinical environment would bring about a significantly positive impact in clinical care. Finding a solution for a non-invasive venous oxygen monitoring technique is indeed worthwhile and warrants extensive research.
The new method of non-invasive venous oximetry involves introducing a pulsatile signal into the venous system; the aim of which is to transform the quasi-static venous system into a dynamic, pulsating system. In this way, venous oxygen saturation could be determined in the same way as arterial oxygen saturation in pulse oximetry. The induced artificial pulsation is made to be comparable in amplitude to the PPG signal. At an early stage in the research, a mathematical model was developed which is based on a heuristic model of the PPG signal in order to explore the nature of the artificial pulse, its effect on the underlying PPG signal and any other physiological effects it might produce. It is hoped that any additional artefacts introduced into the system could also be identified here. Another model will also be developed which is an extension of the modified Beer-Lambert law. This model is commonly used as a first order approximation for pulse oximetry. It will be used to demonstrate how the additional artificial pulse can be used to relate to venous oxygen saturation.
2.1 **ARTIFICIAL VENOUS PULSATILE SIGNAL**

An artificial pulsatile signal is externally generated so as to cause the venous blood to pulsate in a given frequency. The aim of inducing a mild perturbation in the venous system is to cause a pulsation that is comparable to the PPG signal present in the arterial system, such that the same principle of measuring arterial oxygen saturation can be similarly applied to the venous system. The actual means of implementing the pulsation shall be examined in later chapters. The effect of introducing a pulsatile signal into the venous system can be viewed as introducing an artefact into the PPG signal, thus a heuristic PPG model\(^{[69]}\) previously developed to examine the effect of motion artefacts on PPG can be used in this case. When the idea of introducing an artificial pulse into the venous system was first conceived, the hypothesis was that the artificial venous pulsatile signal will have an additive effect on the underlying PPG signal, and that the two signals can be separated spectrally. The heuristic model is an intermediate step in proving the hypothesis and it is hoped that the model will also help us to anticipate the behaviour of the artificial pulse and its interaction with both the venous and arterial systems.

2.1.1 **The Heuristic PPG Model**

The most common assumption of PPG studies is that changes in measured light intensity transmitted through or reflected from a vascular bed are induced by changes in blood volume. Due to the fairly uniform distribution of blood volume in vasculature, the heuristic PPG model describes the effect of those blood volume changes as modulations in the homogeneous and macroscopic optical properties of tissue. Certain aspects of the physical behaviour of the PPG can be described as being independent from the chosen model. The heuristic PPG model was formulated according to this behaviour\(^{[70]}\).
2.1.2 Definition of the model

Light is transmitted through or reflected from the anatomy of the patient, resulting in a measured intensity that depends upon the wavelength and intensity of the source, as well as any optical interactions with the subject. The primary assumption of this model is that the received intensity can be separated into components originating from the different optical paths, therefore identifying and specifying distinct optical effects.

We will examine the case when a number of light sources can be used in conjunction with a single receiver to generate one or more PPG signals. The received light intensity as a function of time, \( t \), and wavelength, \( \lambda \), is modelled by,

\[
I(t, \lambda) = \sum_{j=1}^{n} I_j(t) \left[ \alpha_j(t) + \beta_j(t, \lambda) + \gamma_j(t, \lambda) \right] \tag{2.1}
\]

where \( j \) labels the light source of intensity \( I_j \) and \( \alpha_j, \beta_j, \gamma_j \) are coupling coefficients that depend on the geometric, temporal and spectral properties of the source / receiver positioning, artefact, tissue dynamics and the optical properties of both skin, blood and tissue. The coefficient \( \alpha_j \) is interpreted as direct coupling between source and receiver and those labelled \( \beta_j, \gamma_j \) correspond to light coupled via non-pulsatile and pulsatile tissue respectively. The coefficient \( \beta_j \) encompasses the coupling of light from any anatomical components that is not associated with dynamic arterial blood volume.

In many instruments, the light sources emit fixed power levels. Here, however, they will be permitted to vary for the sake of generality. It is assumed that the effects of ambient light have been successfully eliminated by an electronic multiplexing technique. By attributing the dynamic portion of the pulsatile signal tissue coupling coefficient, \( \gamma_j \) to an underlying pulsatile signal \( p_j(t) \),

\[
\gamma_j(t, \lambda) = \gamma_j(\lambda) p_j(t) \tag{2.2}
\]

it can be assumed that the pulsatile signal represents a dynamic change in arterial blood volume and / or macroscopic optical properties of the tissue, which can ultimately be related back to a dynamic change in optical path length.
It is this optical path length change that causes the dynamic modulation of the coupling coefficient expressed in equation 2.2, and therefore the observed intensity fluctuations in equation 2.1.

2.1.3 Applicability

The model developed is underpinned by two fundamental assumptions:

1. The received intensity may be separated into components that can be attributed to the passage of light through various optical paths, with the optical coupling efficiency being free to change between distinct paths. There is no restriction on the physical model, which may vary between paths.

2. The arterial blood pulsations may be modelled as a change in optical path length that ultimately modulates the coupling of light from pulsatile tissue.

Although these assumptions are conceptually similar to those employed in conventional interpretations of PPG signals by technologies such as pulse oximetry, the generality is much improved by the heuristic nature of the model. Within the context of these assumptions, the heuristic model may be used to describe both venous and arterial PPG signals. The model does not dictate physical interpretation of the signal, nor does it attempt to explain the complex optical interactions.

2.1.4 Interpretation of the Model

The model of equation 2.1 is simply a convenient method of describing the observed intensity and its fluctuations. The coupling coefficients identify different optical paths with different optical coupling efficiencies, and therefore, separate the received intensity into optical-path dependent components. In order to attribute physical significance to these coefficients, it is necessary to invoke an analytic optical model that relates the observation of intensity fluctuations to the origin of the optical paths.
The heuristic model has been interpreted previously by two physical models; the Beer-Lambert model and diffusion theory model[70]. Both analyses have shown that the coefficients can be attributed to physical significance.

2.2 ARTIFICIAL PULSATILE SIGNAL HEURISTIC MODEL

The introduction of an artificial pulsatile signal into the venous system can be modelled by modifying the heuristic model. The artificial pulsatile signal can be modelled as a sinusoidal signal,

\[ v_m(t) = v_0 \sin(\omega_m t + \phi_m) \]

where \( v_0 \) is the coefficient of the model, \( \omega_m \) is the modulating frequency and \( \phi_m \) is the phase angle that might be present in the modulating signal. The modulating signal can be generated externally through mechanical and electronic means.

The PPG heuristic model separates the received intensity into different optical-path dependent components, with the coupling coefficients each identifying a separate optical path. With the introduction of an artificial pulse, the following further assumptions are made:

\[ \alpha_j = 0 \]

Due to the design of the finger probe, there is no direct coupling between the source and the receiver. The coupling coefficient, \( \beta_j \) which accounts for light coupled through non-pulsatile anatomical components and within the context of the artificial venous pulsation, can be separated into light coupled through tissue alone and light coupled through both tissue and pulsatile venous blood. The expanded coefficients can be written as:

\[ \beta_j^T(\lambda) - \text{coupling through static tissue only} \]

and

\[ \beta_j^{T+V}(\lambda)[1-v_m(t)] - \text{coupling through static tissue and pulsatile venous blood only} \]
Similarly, the coupling coefficient, $y_j$ can also be separated into two different optical paths and can be written as:

\[ y_j^{T+A} (\lambda)p_j(t) - \text{coupling through static tissue and pulsatile arterial blood only} \]

and

\[ y_j^{T+A+V} (\lambda)p_j(t)[1-v_m(t)] - \text{coupling through static tissue, pulsatile arterial blood and pulsatile venous blood} \]

By combining all these terms, the extended heuristic model can be written as:

\[
I(t, \lambda) = \sum_{j=1}^{n} I_j(t) \left[ \beta_j^{T} (\lambda) + \beta_j^{T+A} (\lambda)\left[1 - v_m(t)\right] + \ldots \right] \]

The model separates the received intensity into all the possible optical paths and accounts for the DC and AC PPG signals, as well as the artificial venous pulsatile signal. Although the model cannot attribute physical significance to each term, it shows the different components that are present resulting from any interactions between the artificial venous pulsatile signal and the underlying PPG signal. Expanding the terms in the equation 2.4 above gives rise to:

\[
I(t, \lambda) = \sum_{j=1}^{n} I_j(t) \left[ \beta_j^{T} (\lambda) + \beta_j^{T+A} (\lambda) - \beta_j^{T+V} (\lambda)v_m(t) + \ldots \right] \]

The first two terms in the expanded model in equation 2.5, $\beta_j^{T} (\lambda), \beta_j^{T+A} (\lambda)$ are independent of the two pulsatile signals and collectively constitute the DC PPG signal as in the original PPG heuristic signal. The next term, $\beta_j^{T+V} (\lambda)v_m(t)$ is the artificial pulsatile signal and its relation with the remaining terms are additive. Therefore, it is possible for it to be extracted spectrally, providing the modulating frequency of the artificial pulse is distinctively different from the PPG signal frequency. Of course this is only an assumption whose validity is only demonstrated in later practical investigations.
The next two terms in the expanded model, \( \gamma_j^{T+A}(\lambda)p_j(t), \gamma_j^{T+A+V}(\lambda)p_j(t) \) constitute the PPG signal since they only consist of the pulsatile coupling coefficient and the underlying pulsatile signal, \( p_j(t) \). The last term of the model, \( \gamma_j^{T+A+V}(\lambda)p_j(t)v_m(t) \) will be referred to as the multiplicative term and is the result of coupling between the two pulsatile signals.

The multiplicative term, which will be explored in more detail in later chapters, is the single most important parameter in optimising the design of artificial-pulse based venous oximetry. The magnitude of the multiplicative term is the measure of the degree at which the arterial system is being disturbed. Such a disturbance can affect the amount of arterial blood being delivered to the tissue and thus, render any measurements of venous oxygen saturation inaccurate.

It would be advantageous to know at what frequencies the multiplicative term would appear. In this way it could be easily identified within a frequency spectrum. This would help in the design of digital filters when separating the two pulsatile signals spectrally. If we model the pulsatile signal, \( p_j(t) \) as:

\[
p_j(t) = \sum_{n=1}^{n} p_n \sin(n\omega_{HR}t + \phi_n^{HR})
\]

where \( p_n \) is the coefficient, \( \omega_{HR} \) is the PPG fundamental frequency, \( n \) represents the harmonics (\( n=1 \) is the fundamental frequency), and \( \phi_n^{HR} \) is the phase involved. This is just a first-order representation of the PPG signal but nevertheless, it is an adequate representation in our present analysis as a PPG-like waveform can be constructed using two sinusoidal waves as illustrated in Figure 2.1.
The multiplicative term due to the fundamental PPG signal can be written as:

\[ p_j(t)v_m(t) = p_t \sin(\omega_{HR}t + \phi_H) \sin(\omega_m + \phi_m) \] ........................................ 2.7

By invoking the following trigonometric identity:

\[ 2\sin A\sin B = \cos(A - B) - \cos(A + B) \] ........................................ 2.8

The multiplicative term in 2.7 can be expanded as:

\[ p_j(t)v_m(t) = \frac{1}{2} p_t v_0 \left[ \cos(\omega_m t - \omega_{HR} t + \phi_m - \phi_H) - \cos(\omega_m t + \omega_{HR} t + \phi_m + \phi_H) \right] \] ........................................ 2.9

By expanding equation 2.7 through invoking the trigonometric identity (equation 2.8), it can be seen that the multiplicative term will appear at frequencies on either side of the artificial pulse modulating frequency as follows; at the difference and the sum of the PPG fundamental frequency, \( \omega_{HR} \) and the artificial venous pulse modulating frequency, \( \omega_m \).
The magnitude of the multiplicative term depends on both the magnitudes of the AC PPG signal and the artificial pulse modulation depth. Since the AC PPG magnitude is small (1-5%) as compared to the total absorption, we can safely assume that the degree of coupling can be minimised if the artificial venous pulse modulation depth is also small.

The heuristic model of the artificial pulse-based venous oximetry technique assumes that the effects of introducing an artificial pulse to the venous system on the underlying PPG signal are both additive and multiplicative. The multiplicative effect can be minimised and made insignificant through optimising the different parameters in the actual design of the instrument. The mainly additive nature of the artificial pulse is desirable as it would imply that the artificial pulsation would not affect the arterial system if the modulation depth remains small, and that it can be separated from the PPG signal through filtering techniques such as using a narrow bandpass filter centred at the modulation frequency.

2.3 **Beer-Lambert Model for Venous Oximetry**

The heuristic model of the artificial pulse based venous oximetry technique developed in the last section is a convenient way of describing the observed intensity and its fluctuations. The terms within the heuristic model account for all the different possible optical paths. Thus, the model separates the received intensity into optical-path length dependent components. In order to lend any physical significance to the different terms, it is necessary to recourse to a specific physical model that will relate the observed intensity fluctuations to the origin of the pulsations. We will now consider the Beer-Lambert model to see how the introduction of an artificial pulse could be used to derive the oxygen saturation in the venous blood. We will also see how this physical model can be used as an interpretation of the heuristic model.
2.3.1 Generalized Arterial and Venous Pulse Oximetry

The Beer-Lambert law, which couples physical path length and effective absorbance into a single definition of optical density, is commonly used in arterial pulse oximetry to assign physical significance to changes in the optical path length. Extending the lowest order conventional description of arterial pulse oximetry can make a zeroth order theoretical description of the artificial pulse based venous oximetry. According to this model, we can write the received intensity due to a particular illuminating wavelength, \( \lambda \) in terms of the proportion of arterial hemoglobin that is chemically combined with oxygen, \( S \). Recalling equation 1.14 developed in chapter 1,

\[
I(t, \lambda) = I_0(\lambda) \exp\left\{-\left[(S \mu_{\text{HbO}_2}(\lambda) + (1-S) \mu_{\text{Hb}}(\lambda)) d(t) + \mu_{\text{static}}(\lambda) l\right]\right\} \quad \ldots \ldots \quad 2.10
\]

where \( \mu_{\text{HbO}_2}(\lambda) \), \( \mu_{\text{Hb}}(\lambda) \) are the effective absorbance of oxygenated and deoxygenated hemoglobin respectively, \( d(t) \) is a function of the dynamic physical path length through arterial blood, and \( \mu_{\text{static}}(\lambda) l \) is the optical density of the non-pulsatile tissue and other anatomical components.

By distinguishing optical paths through venous blood, \( d_v(t) \) and arterial blood, \( d_a(t) \) we may generalize equation 2.10 to

\[
I(t, \lambda) = I_0(\lambda) \exp\left\{-\left[\mu_v d_v(t) + \mu_a d_a(t) + \mu_{\text{static}}(\lambda) l\right]\right\} \quad \ldots \ldots \quad 2.11
\]

by making the following substitutions:

\[
\mu_v(\lambda) = \left[S_v \mu_{\text{HbO}_2}(\lambda) + (1-S_v) \mu_{\text{Hb}}(\lambda)\right]
\]

\[
\mu_a(\lambda) = \left[1 - S_a \mu_{\text{HbO}_2}(\lambda) + S_a \mu_{\text{Hb}}(\lambda)\right]
\]

\[
\mu_{\text{static}}(\lambda) = \mu_{\text{static}}(\lambda) l
\]

We will now explore small changes in the received intensity resulting from small changes in the optical paths (resulting from the presence of low amplitude venous and arterial modulations) and consider the resultant changes (AC) normalized by the quasi-static (DC) intensity, namely:
\[
\frac{\Delta I(t, \lambda)}{I(t, \lambda)} = -\mu_a \Delta d_a(t) - \mu_v \Delta d_v(t) \tag{2.13}
\]

The quantities expressed in equation 2.13 can be separated by electronic (or other signal processing methods) since the induced venous modulations are of known origin. One method of separation would be to induce a frequency modulation of the venous system in a band that is distinct from the arterial pulsations. Once the isolation of the arterial and venous dynamics is achieved, the process of calibration can be applied. Inversion of the classical Beer-Lambert model of pulse oximetry is usually achieved by generating two instances of equation 2.13 at two different wavelengths.

These equations are then solved for the quantity, \textit{ratio of ratios}, \( R \), which is defined as the ratio of the absorbance of the illuminated blood at the two wavelengths used.

Assuming each term in equation 2.13 has been isolated, we may form two "ratio of ratios":

\[
R_a = \frac{I(t, \lambda_2) \Delta I(t, \lambda_1)}{I(t, \lambda_1) \Delta I(t, \lambda_2)} = \frac{\mu_a(\lambda_1)}{\mu_a(\lambda_2)} \tag{2.14}
\]

\[
R_v = \frac{I(t, \lambda_2) \Delta I(t, \lambda_1)}{I(t, \lambda_1) \Delta I(t, \lambda_2)} = \frac{\mu_v(\lambda_1)}{\mu_v(\lambda_2)}
\]

Knowledge of the extinction coefficients of oxygenated and deoxygenated hemoglobin at the two wavelengths can then be used to estimate \( S_a, S_v \) from the calculated \( R \) using the formulae as follows:

\[
S_a = \frac{R_a \mu_{Hb}(\lambda_2) - \mu_{Hb}(\lambda_1)}{R_a \mu_{Hb}(\lambda_2) - \mu_{Hb}(\lambda_1) - [\mu_{Hb}(\lambda_1) - \mu_{HbO_2}(\lambda_1)]}
\]

\[
S_v = \frac{R_v \mu_{Hb}(\lambda_2) - \mu_{Hb}(\lambda_1)}{R_v \mu_{Hb}(\lambda_2) - \mu_{HbO_2}(\lambda_2) - [\mu_{Hb}(\lambda_1) - \mu_{HbO_2}(\lambda_1)]} \tag{2.15}
\]
2.3.2 Beer-Lambert Model Interpretation

In order to lend any physical significance to the heuristic model, we will now attempt to interpret the heuristic model using the Beer-Lambert model. The Beer-Lambert model is used here to describe the case of transmission through tissue, as is common in pulse oximetry. With the introduction of an artificial pulse, the resulting measured intensity can be expressed as \( I_0 T(z_a, z_v, \mu) \); where \( I_0 \) is the incident intensity and \( T(z_a, z_v, \mu) \) is the transmittance of the tissue which is dependent on the two optical path lengths through arterial blood \( (z_a) \) and venous blood \( (z_v) \), and the effective absorbance \( (\mu) \). The transmittance is expressed by reference to the modified Beer-Lambert law (equation 2.11):

\[
T(z_a, z_v, \mu) = \exp[-(z_a + z_v)\mu] \quad \text{2.16}
\]

2.3.2a Separation of Signal Components

The transmitted intensity will consist of a static component and two dynamic components that are primarily due to the arterial pulsation and the artificial venous pulsations. Therefore in this interpretation, the dynamics in the homogeneous and macroscopic optical properties of the tissue can be related back to the components in our heuristic model. We can write the total transmittance (through both pulsatile and non-pulsatile components), in terms of the previously defined coupling coefficients:

\[
\beta^T + \beta^{T+V}[1 - v_m(t)] + \gamma^{T+\mu} p(t) + \gamma^{T+\mu+V} p(t)[1 - v_m(t)] = T(z_a + \Delta z_a(t) + z_v + \Delta z_v(t) + \mu + \Delta \mu(t)) \quad \text{2.17}
\]

Where we have assumed that there is no direct coupling between source and receiver, we have attributed some physical significance to the pulsatile signal, \( p(t) \) and \( v_m(t) \). This is achieved by modeling its effect as a dynamic change in optical path length, due to either a dynamic change in the two physical path lengths or in the macroscopic effective absorbance of the tissue.
Because $\Delta z_a(t)$, $\Delta z_v(t)$ and $\Delta \mu(t)$ are small by comparison to their static counterparts, we may linearise equation 2.17 with respect to these small changes using a first order Taylor expansion,

$$T(z_a + \Delta z_a(t), z_v + \Delta z_v(t), \mu + \Delta \mu(t)) \approx$$

$$T(z_a, z_v, \mu) + \Delta z_a \frac{\partial T(z_a, z_v, \mu)}{\partial z_a} + \Delta z_v \frac{\partial T(z_a, z_v, \mu)}{\partial z_v} + \Delta \mu \frac{\partial T(z_a, z_v, \mu)}{\partial \mu} \tag{2.18}$$

which enables us to write:

$$\beta^T + \beta^{T+V}[1 - v_m(t)] + \gamma^{T+V} p(t) + \gamma^{T+AV} p(t)[1 - v_m(t)] \approx$$

$$\exp[-(z_a + z_v)\mu]\left[1 - \left(\Delta z_a(t) + \Delta z_v(t)\right)\mu - \Delta \mu(t)(z_a + z_v)\right] \tag{2.19}$$

Since the heuristic model coefficients can be separated into static and dynamic portions, we can rewrite equation 2.19 as a ratio of the dynamic to the static components as follows:

$$\frac{-\beta^{T+V} v_m(t) + \gamma^{T+V} p(t) + \gamma^{T+AV} p(t) - \gamma^{T+AV} p(t)v_m(t)}{\beta^T + \beta^{T+V}} =$$

$$\frac{-\left(\Delta z_a(t) + \Delta z_v(t)\right)\mu - \Delta \mu(t)(z_a + z_v)}{\beta^T + \beta^{T+V}} \tag{2.20}$$

In equation 2.20, it can be assumed that the multiplicative term, $p(t)v_m(t)$ is small and can therefore be omitted in the equation. Furthermore, the modified Beer-Lambert model for venous pulse oximetry developed in the last section, assumed that the observed pulsations are due to changes in the physical path length through blood only. This implies that the total transmittance may be written as:

$$T(\mu_{\text{tissue}}, r, \mu_{\text{blood}}, z_a + \Delta z_a(t), z_v + \Delta z_v(t)) =$$

$$\exp\left(-\left(\mu_{\text{tissue}} r + \mu_{\text{blood}}(z_a + \Delta z_a(t)) + \mu_{\text{blood}}(z_v + \Delta z_v(t))\right)\right) \tag{2.21}$$
In this case equation 2.20 reduces to

\[ \frac{-\beta^{T+V}v_m(t) + \gamma^{T+A}p(t) + \gamma^{T+A+V}p(t)}{\beta^{T} + \beta^{T+V}} = -(\Delta z_a(t) + \Delta z_v(t))\mu_{\text{blood}} \] ........................................2.22

Since the two pulsatile signals are additive and the effective absorbance of blood can be separated into that of the arterial and venous blood, equation 2.22 could be rewritten as two separate equations; one each for the case of the artificial venous pulsatile signal and the PPG signal,

\[ \frac{-\beta^{T+V}v_m(t)}{\beta^{T} + \beta^{T+V}} = -\Delta z_v(t)\mu_v \] ...................................................2.23

and

\[ \frac{\gamma^{T+A} + \gamma^{T+A+V}}{\beta^{T} + \beta^{T+V}} p(t) = -\Delta z_a(t)\mu_a \] ........................................2.24

When using the physical model and the assumptions employed for deriving both venous and arterial oxygen saturations in section 2.3.1, equation 2.23 and 2.24 tell us that the ratio of coupling coefficients is now equal to the effective absorbance of the venous and arterial blood only. The ratio of ratios used to calculate oxygen saturation is defined as the ratio of the absorbance of the illuminated blood at two wavelengths. It can therefore be seen that the ratio of the two instances of equations 2.23 and 2.24, can be used to rewrite the oxygen saturation in terms of our heuristic coupling coefficients.

This useful method of interpreting the heuristic model through the physical model of Beer-Lambert law illustrates how physical significance can be attributed to the components of our artificial pulse based venous oximetry heuristic model in a specific context. Observations of the behavior of these heuristic components may then be extrapolated back to their physical counterparts, thus providing insights that would be otherwise difficult to obtain.
The use of Beer-Lambert law has served to enable us to place the model within the context of standard oxygen saturation derivation as in pulse oximetry whilst maintaining a high degree of simplicity.

The physical significance of the heuristic model has been illustrated through this analysis of interpreting the heuristic model through the Beer-Lambert law. Other interpretations are possible and in later chapters, the heuristic model will be interpreted through experimental results. The appearance of the multiplicative terms on both sides of the modulation frequency and the additive nature of the artificial pulse (as predicted by the heuristic model), should be evident in the experimental results. In the simplistic Beer-Lambert model, we have related the parameters of our choice of physical model to the parameters of the heuristic model. This enables us to physically interpret the observed intensity dynamics in terms of the model for the origin of the pulsations and characteristic of the tissue.

2.4 SUMMARY

The chapter started with an introduction to the heuristic model of PPG. The model was then modified and expanded to include the introduction of an artificial venous pulsatile signal. The heuristic model’s primary assumption is that the received intensity can be separated into components originating from different optical paths. The new venous oximetry heuristic model helped to identify the different effects of introducing a pulsatile signal into the venous system. The effects of the artificial pulse are mainly additive with respect to the underlying PPG signal. The coupling between the arterial system and the artificial pulse is manifested as a multiplicative term and of which the magnitude will remain insignificant, providing that the modulation depth is small. The heuristic model also enables complex behavior to be expressed in a general manner. The model has been interpreted in terms of the Beer-Lambert law, attributing both the pulsatile components, arterial pulsations and the artificial venous pulsation along with the static parameters of the heuristic model to physical significance.
The Beer-Lambert law has also been modified such that venous oxygen saturation can be derived from it. The derivation does not differ much from the classical way of deriving arterial oxygen saturation. The primary assumption made in using the Beer-Lambert model is that the multiplicative term is small and can be made insignificant through careful design of the instrument and by minimizing the modulation depth of the artificial pulse.
The first two chapters of this thesis laid out the methodology in achieving a non-invasive venous oximetry method that is suitable to be used in a clinical environment. In this chapter, we shall look at how the new technique’s mechanical and electronic designs can be implemented. The hardware involved in this new venous oximetry technique includes a standard PPG system that records PPG waveforms through a transmission mode finger probe, a digit pressure cuff, a pinch valve for modulating the inflation and deflation of the digit cuff, and an air pump that serves as an air source for the digit cuff. The implementation of the electronics, the hardware and the control software for inducing a pulsatile signal in the venous system will be described and outlined in this chapter.
3.1 **NEW VENOUS OXIMETRY METHODOLOGY**

The proposed new method of venous oximetry involves inducing a localised artificial venous pulsation so as to transform the otherwise quasi-static venous system into a pulsatile system. This artificial venous pulsatile signal's magnitude can be made comparable to the PPG. In this way, peripheral venous oxygen saturation can be determined in the same manner as arterial oxygen saturation in pulse oximetry. The figure below shows the block diagram of the new venous oximetry method.

![Block diagram of the new venous oximetry method](image)

*Figure 3.1 - Block diagram of the new venous oximetry method*
First of all, a means of inducing venous blood volume changes was applied to the vascular tissue under test. The localised peripheral venous blood volume was modulated at a given frequency so as to facilitate the recovery of the artificial pulsatile signal during post-processing. The artificial venous pulsation along with the PPG signal were digitized and recorded via an optical probe. The two digitised signals were separated spectrally through signal processing. After the signals were separated, the artificial pulse was analysed to derive parameters relating to venous oxygen saturation.

### 3.1.1 Methods in Generating the Pulsatile Signal

There are various means of generating the artificial pulse. Since we are using a standard transmission mode finger probe to record the PPG signal, it would prove useful to generate a localised artificial venous pulsation near the index finger. In this way, the signal could be recorded via the same finger probe. The small artificial venous pulsatile signal could be generated externally at a site which is proximal or distal from the area through which light is transmitted. Should this distance become too close, the physical perturbation in the area of light transmission can cause changes in the light coupling to the medium under test. If this were to materialise, there will be variations in attenuation which are not due to changes in fluid volume in the area of light transmission. These other variations comprise additional noise that should be removed for accurate measurement.

One way to generate the artificial pulse is to use a jet of air and direct it at a position distal or proximal to the measurement site. Modulation of the venous blood volume can be achieved by directing jets of air onto the tissue under test at a given frequency. This method is feasible but will not be easy to adopt since it is difficult to mount the device onto the hand. The method that was finally adopted is to use a digit pressure cuff to generate the artificial venous pulsatile signal (Figure 3.2).
IMPLEMENTATION

The pressure cuff was wrapped at the base (proximal phalanx) of the index finger and a normal PPG finger probe is also mounted onto the tip of the same finger. A continuous inflation and deflation of the digit cuff will cause a mild perturbation in the peripheral venous system, causing an artificial venous pulsation which will be recorded along with the PPG signal via the finger probe.

3.1.1a  Digit Pressure Cuff for Generating Artificial Pulse

A small digit pressure cuff measuring 9cm by 1.9cm was used to generate the artificial pulse. Due to the small size of the digit cuff, the amount of air needed to inflate it in order to induce a mild perturbation to the underlying tissues is small. Similarly, the digit cuff can be deflated in a relative short time if required, due to the same reason.
The desired frequency of modulation was achieved by controlling the rate of inflation and deflation of the digit cuff. The frequency of modulation is important as it allows the generated artificial venous pulsatile signal to be extracted using filtering techniques.

The depth of modulation depends on the pressure of the air source used to inflate the digit cuff. In the later chapters we will examine the various suitable pairs of modulation frequencies and modulation depths.

The digit cuff was wrapped at the base (proximal phalanx) of the index finger, away from the area of light transmission. This distal position ensured that additional noise sources would not be coupled into the artificial pulse during the recording of the PPG signal and the artificial venous pulse.

3.1.1b Air Source for the Digit Cuff

The air source for the digit cuff must be capable of inflating the cuff within a relative short period of time so as to maintain a relatively high modulation frequency (4 - 7 Hz). The air pressure required was in the range of 60 to 160 mm Hg. This range will enable us to investigate the effect of the different modulation depths on the localised venous system under test. Moreover, the air pump should be relatively simple to control through electronic means. A micro-pressure diaphragm air pump was used for inflating the digit cuff, which was able to maintain an air flow of 6.1 LPM (litres per minute) and a maximum pressure of 260 mm Hg. The air pressure of the micro air pump can be controlled by varying the voltage applied across the DC motor which drives the diaphragm. Due to the fact that it is a motorised air pump, the noise generated can be quite substantial and might not be suitable for a clinical environment. In order to minimize the noise generated, the micro air pump was first encased in an acoustic absorbing material and then the whole artificial pulse generator was put into a metal enclosure. In this way, the noise generated can be minimised to an acceptable level.
The control of the micro air pump was interfaced to the computer through a Programmable Logic Device (PLD) card via the computer’s parallel port. The electronic circuitry for controlling the micro air pump consists of two major parts; the Digital to Analogue (DAC) conversion circuitry and the driving circuitry for the air pump.

The block diagram of the air pump controller is illustrated in Figure 3.3. In order to set the air pump to a desired air pressure, a control word was sent via the computer in the range of 0 to 256 to the micro air pump via the PLD interface (0 being the minimum air pressure and 256 the maximum air pressure). The control word was converted into its corresponding current source through an 8-bit DAC and was then used to drive the air pump.

![Figure 3.3 - Block diagram of micro air pump control circuitry](image)

The circuit diagram for the micro air pump control circuitry is included in the appendix. Although there might not be a linear relationship between the air pressure produced by the air pump and the voltage applied across its DC motor, the air pressure produced at a given voltage can be measured by a pressure sensor. Therefore the desired air pressure can be adjusted according to the pressure sensor reading.
The micro air pump will provide a constant air source to inflate the digit cuff, with the actual modulation of the digit cuff being obtained by using a pinch valve. We shall now look at how the modulation of the digit cuff can be achieved using a pinch valve.

3.1.1c Pinch Valve to Control Inflation and Deflation of the Digit Cuff

The micro air pump and the digit cuff were connected with silicone tubing. Inserted between these two components was a punch valve that was used to control the air flow direction within the digit cuff. When the pinch valve is opened, it lets in air from the micro air pump to inflate the digit cuff. When the pinch valve is pinched, it stops air from entering the digit cuff and releases air in the digit cuff. The block diagram of these three components can be illustrated below,

![Block diagram of the digit cuff inflation and deflation mechanism](image)

The pinch valve is a three-way solenoid-operated device. It has two valves; one is normally open and the other normally closed. The valves' configuration will change over when the solenoid is energised, that is, the normally-opened valve would be closed and the normally-closed valve will be opened. One valve was used to control the tube leading from the micro air pump to the digit cuff and the other was used to control the outlet from the digit cuff. During the inflation of the digit cuff, the tube leading from the micro air pump was opened in order to allow air to enter the digit cuff whilst the tube that was used as an air outlet from the digit cuff was closed. During deflation, the tube leading from the air pump into the digit cuff was 'pinched' and therefore closed. At the same time, the tube leading from the digit cuff (which was used as an air outlet) was opened to allow air within the digit cuff to escape.
By controlling the way the three-way pinch valve opens and closes, different modulation frequencies for generating the artificial venous pulse can be achieved.

The electronic control circuitry block diagram for controlling the pinch valve is shown below.

![Block diagram of pinch valve control circuitry](image)

**Figure 3.5 - Block diagram of pinch valve control circuitry**

The microcontroller was first programmed to output a square wave at the desired frequency of modulation. The square wave was used to either switch on or off the power switch of the pinch valve. As a result, the pinch valve was switched at the rate of the square wave’s frequency. This causes the digit cuff to inflate and deflate at that frequency. In this way, the venous blood volume changes can be induced by the inflation and deflation of the digit cuff that was wrapped at the base of the finger. The circuit diagram and the program listings are included in the appendix.
The pinch valve is a solenoid operated pinch valve and as a result, produced a lot of noise when it switched between configurations. The noise level was not acceptable as the instrument was designed to be used in a clinical environment. It was not feasible to encase the pinch valve in an acoustic absorber like the micro air pump as the heat built up in the pinch valve would cause it to stop working altogether.

To resolve this problem, the pinch valve was modified internally such that a thin layer of rubber was inserted between the piston and the base of the pinch valve. The thin layer of rubber serves as a cushion for the piston when the pinch valve is energised. This modification completely eliminates the noise produced without compromising the pinch valve’s efficiency.

The whole design of the artificial pulse generating mechanism is encased in a metal box, with only an outlet for the tubing (Figure 3.6). The metal case is fitted with its own power supply, such that the artificial pulse generator can be powered from the mains.

Figure 3.6 - The PPG system and the artificial pulse generator
3.1.2 Recording of the Artificial Venous Pulsatile Signal

The artificial venous pulsatile signal was recorded using a PPG system via a standard pulse oximeter transmission mode finger probe. The finger probe was first mounted onto the subject’s index finger and the digit cuff was wrapped around the base of the same finger. When the artificial pulse generator was turned on, the digit cuff wrapped around the base of the finger will inflate and deflate at a given frequency. This would cause a venous blood volume change in the vascular tissue. The blood volume changes were then recorded along with the PPG signal by the PPG system via the finger probe.

The PPG system used incorporates most features found in the standard PPG system such as the subtraction of ambient light through time multiplexing of the signals. It is also able to support six analogue channel inputs although only five are used currently. The PPG system is interfaced to the computer by a PLD card via a parallel link. Both the PPG signals and the artificial venous pulsatile signal are sampled at a rate of 300Hz, then digitised and fed into the computer for analysis and signal processing.

The artificial pulse generator and the PPG system are to be used in conjunction with a computer during operation. The operations of the PPG system and artificial pulse generator can be controlled through a computer program interface.

3.1.3 Software for Artificial Pulse Generator and PPG System

The PPG system and the artificial pulse generator can be controlled through the PLD control software. The intensity of the light sources, the sampling rate and the gain of the PPG signal and other parameters can be specified and tuned within the software environment. The software used to control the PPG system and the artificial pulse generator was further interfaced to Matlab using Dynamic Data Exchange (DDE). In this way, the various parameters can be set by writing Matlab programming codes within the Matlab programming environment. Moreover, the data can also be imported directly into Matlab, ready to be analysed during operation.
The figure below shows the output control of the PLD software.

![Output control of the PLD control software](image)

**Figure 3.6 - Output control of the PLD control software**

At present the first four latching outputs labelled, 1 to 4 were used for controlling the two intensities of the finger probe light sources and the two gains of the PPG signals. Non-latching output 5 was used for controlling the air pressure of the micro air pump.

The enabling of the interrupt that would start data logging, the sampling rate of the analogue data and the size of the buffer were set in the input settings of the PLD control software as shown in the figure on the following page.
During operation, the output and input settings were set before the Interrupt was enabled. The enabling of the interrupt would start the data logging process. The data was first stored on a memory buffer before being imported into Matlab.

The decimation level will determine the combined sampling rate of all the channels. A combined sampling rate of 2000Hz was used resulting in a sampling rate of 330 Hz per channel.

The different settings of the PLD control software that can be configured using Matlab programming codes are shown in the figure on the following page.
This method of setting the inputs and outputs is extremely convenient since the same configuration can be used repeatedly without having the need to reset them manually each time.

The program listings of the Matlab program used to record the artificial venous pulsatile signal along with the PPG signal will be included in the appendix.

### 3.2 SUMMARY

The design of an artificial pulse generator has been outlined in this chapter, with a description of the different components in the design and the different electronic control circuitry controlling them. The use of a digit cuff in generating the pulsatile signal was the best method available to us. The implementation was rather straightforward. The use of the micro air pump and pinch valve has eliminated the use of an expensive system available in the market.
With the artificial pulse generator implemented and everything automated through computer control, we are now ready to conduct experiments to assess the feasibility of the new method in venous oximetry. In the next chapter we will look at the various experiments conducted to investigate this novel method of measuring venous oxygen saturation through venous blood volume modulation.
Various experiments involving the application of an artificial pulsation to the vascular tissue will be outlined in this chapter. In these experiments, both the arterial pulsatile signal and the artificial venous pulsatile signal were recorded. The objectives of these experiments were as follows:

- The appearance and characteristic of certain terms as predicted in the heuristic model developed in chapter 2 will be verified against experimental results.
- To explore and identify the effects of increased modulation depth on arterial oxygen saturation measurement.
- Experiments were carried out to show how optimisation of the design could be achieved.
- To explore and identify the effects of prolonged application of artificial pulse to the vascular tissue.
- The relationship of arterial oxygen saturation and venous oxygen saturation was explored in the simple “hold-the-breath” experiment.
- An occlusion method was used to induce a decrease in peripheral venous oxygen saturation whilst leaving the arterial oxygen saturation relatively unchanged. The experiments were conducted to verify the validity of peripheral venous oxygen saturation measurement by the new oximetry technique.
4.1 COMFIRMATION OF THEORETICAL RESULTS

In chapter 2, a heuristic model of applying an artificial pulse to the venous system of the vascular tissue has been developed. The model separates the received intensity into all the possible optical paths and accounts for the DC and AC PPG signals as well as the artificial venous pulsatile signal,

\[ I(t, \lambda) = \sum_{j=1}^{n} I_j(t) \left[ \beta_j^T(\lambda) + \beta_j^{T+V}(\lambda) - \beta_j^V(\lambda) \nu_m(t) + \ldots \right] \]

As mentioned in chapter 2, the first two terms in the model represent the DC signal, the next term represents the artificial venous pulse. The next two terms are the PPG signal. The last term is called the multiplicative term and is the measure of the degree of coupling between the PPG signal and the artificial pulse; the degree at which the arterial system is being disturbed by the artificial pulse. The heuristic model of introducing an artificial venous pulse in the context of PPG signal assumes that the effect is both additive and multiplicative.

The multiplicative term will be small and insignificant if the magnitude of the artificial pulse remains small. It is also predicted that the multiplicative term will appear at the frequencies of the sum and difference of the fundamental PPG signal frequency and the artificial pulsatile signal frequency.

The experiments that will be outlined in this section will seek to verify the various predictions and assumptions made by the heuristic model against experimental data. In this way, the applicability of the heuristic model can be assessed. The experiment also acts as another way of interpreting the heuristic model.
4.1.1 The Artificial Pulsatile Signal has an Additive Effect

Although the heuristic model predicted that the artificial pulse is both an additive and multiplicative effect, the effect is mostly additive as the multiplicative term is small and insignificant as long as the magnitude of the artificial pulse remains small. An experiment was conducted to verify this prediction of the heuristic model. With an application of artificial pulsation to the venous system of the vascular tissue under test, the two signals (artificial pulsatile signal and the PPG signal), were recorded and then a Fast Fourier Transform (FFT) was operated on the recorded signals to transform the signals from a time domain spectrum to a frequency domain spectrum. This will serve to identify the different frequency components therein. If the artificial pulse was mostly additive, then filtering techniques should be able to separate the two signals. However, if the effect was mostly multiplicative, simple digital filtering will have a minimum effect on separating the two signals.

The experiment was set up with the subject sitting on a chair with his left arm rested on a cushion at heart level. The subject was male, 28 years of age, healthy and had no known history of vascular diseases. The subject was asked to relax and breathe normally, whilst trying to keep his arm still as much as possible. A finger probe was mounted onto the left hand, index finger of the subject and the digit cuff was wrapped gently around the base (proximal phalanx) of the index finger. The PPG system was turned on for a period of 2 minutes without any application of artificial pulse to the venous system. The signals were sampled at a rate of around 330 samples per second and then stored for post-processing. The PPG system was turned off at the end of 2 minutes. The second part of the experiment was conducted with the artificial pulse generator turned on whilst maintaining the exact settings as before. The artificial pulse generator modulation frequency and the peak modulation depth pressure were set at 6.5Hz and 100 mm Hg respectively. A 2-minute sample of the signals sampled at the same rate as before, and recorded for post processing. The diagram on the following page shows the set up of the experiment.
The first set of signals recorded with the artificial pulse generator turned off were plotted and shown on the figure below. Without any venous blood volume modulation, the signals recorded were just the PPG signals alone.

Figure 4.1 - Experimental Set up

Figure 4.2 - PPG signals recorded in the first part of the experiment
In order to display the frequency components, an FFT was operated on the signals and Figure 4.3 shows the frequency domain of the PPG signal,

![Power Spectrum for InfraRed signal](image)

![Power Spectrum for Red Signal](image)

**Figure 4.3 – PPG signals in frequency domain spectrum**

The power spectral density was estimated by taking the modulus-squared of the discrete Fourier Transform of the time series samples. It can be seen from the above frequency spectra that the PPG signals consisted of just the fundamental PPG frequency and its harmonics. The harmonics were present because PPG signal is not a perfect sinusoidal waveform. With the application of an artificial pulse, we would expect an additional frequency component to appear on the frequency spectra if the effect of applying an artificial pulse to the venous system is additive.
The figure below shows the signals that were recorded with the artificial pulse generator turned on.

![Figure 4.4 - Signals recorded with artificial pulse generator turned on](image)

It can be seen from the signals recorded above that although the signals were recorded with the artificial pulse generator turned on, the signals still retained a semblance of the PPG signals. The edges found on the pulses were caused by venous blood volume changes due to the artificially generated pulsation. An FFT transform was again operated on the time domain signals above to transform them into a frequency domain signals so as to identify the different frequency components.

Figure 4.5 shows the frequency spectra of the FFT transformed signals. The power spectral density was estimated by taking the modulus-squared of the discrete Fourier Transform of the time series samples.
The difference between these spectra and the one on Figure 4.3 is that there is an additional frequency component at 6.5Hz. This additional frequency component was attributed to the artificial venous pulsations. The appearance of the additional frequency component further reinforced the notion that the effect of applying an artificial pulse to the venous system on the underlying natural pulsatile pulsation was mostly additive.

Figure 4.5 - Frequency spectra of the recorded signals with the artificial pulse generator turned on.

The multiplicative terms that would have had appeared at frequencies 5 Hz and 8 Hz (sum and difference of modulation frequency, 6.5 Hz and PPG fundamental, 1.5 Hz) were not present or any presence would be insignificant due to the fact that the modulation depth used was small.
To further illustrate the fact that the artificial pulsatile signal is additive with respect to the underlying PPG signal, the recorded signals were made to pass through a 10th order digital low-pass filter with a cut-off frequency, $f_c$, at 5Hz. The figure below shows the time domain plot of the low-pass filtered signals. The PPG signals recovered markedly resemble the PPG signals in Figure 4.2.

![Recovered PPG (IR source)](image)

![Recovered PPG (Red source)](image)

Figure 4.6 - Low-pass filtered signals of the recorded signals in Figure 4.4

The successful recovery of the PPG signal has shown that the effect of the artificial generated pulsatile signal on the underlying PPG signal is indeed mostly additive. Similarly, by passing the signal through a narrow band-pass filter centred at 6.5Hz, the artificial pulsatile signal could be recovered.
The figure below shows the artificial pulsatile signal recovered by passing the recorded signals through a narrow 4th order digital band-pass filter with cut-off frequencies, $f_{cl}$ and $f_{c2}$, at 5.5Hz and 7.5Hz respectively. Although the modulation waveform was a square wave, due to the frequency response of the vascular tissue and the band-limited data acquisition system used, the artificial pulsatile signal resembled more of a sinusoid, as shown in the Figure 4.7.

![Figure 4.7 - Artificial venous pulsatile signal](image)

The applicability of the heuristic model is further substantiated by this experiment, which proves that the effect of the artificial pulse to the arterial system is mostly additive. This is an important result which shows that the application of an artificial pulsation to the venous system will have a minimal or no effect on the arterial system as long as the modulation depth remains small.
4.1.2 The Appearance of the Multiplicative Term

The heuristic model predicted that although the artificial pulse is mostly an additive effect, there is a multiplicative term which is caused by the coupling of the artificial pulsatile signal with the arterial PPG signal. This is deemed an undesirable effect in the context of venous oximetry. As explained in chapter 2, if the arterial system is affected, it would affect the flow of the arterial blood to the vascular tissue under test and thus the measurement of venous oxygen saturation would be erroneous. The multiplicative term in the heuristic model,

\[ T + A + V + \gamma_j^T + \gamma_j^V (\lambda) p_j(t)v_m(t) \] .........................................................4.2

has both the artificial pulsatile signal component and the arterial pulsatile signal component. Since both the two signals are small in comparison to the DC signal level, the multiplicative term will remain insignificant. Problems will start to arise if the artificial pulsatile signal component is increased, which will result in a multiplicative term of significant amplitude. In chapter 2, the multiplicative term was expanded by trigonometric identity to,

\[ p_j(t)v_m(t) = \frac{1}{2} p_j v_o \left[ \cos(\omega_m t - \omega_{HR} t + \phi_m - \phi_{HR}) - \cos(\omega_m t + \omega_{HR} t + \phi_m + \phi_{HR}) \right] \] ....4.3

therefore the model also predicted that the cross product or the multiplicative term would appear at both the sum and difference of the PPG fundamental frequency, and the artificial pulsatile signal frequency as in classic Amplitude Modulation theory.

An experiment was therefore carried out to investigate the appearance of the multiplicative term and the frequencies that would appear as predicted by the heuristic model. This is important information regarding the multiplicative term, which will influence the design of venous oximeter based on the new technique.
The experimental set up was similar to the previous experiment with the same subject. The modulation depth was increased to 160 mm Hg. At this high modulation depth, the magnitude of the multiplicative term would become significant as a result, almost comparable to the 1st or 2nd harmonic of the PPG signal.

In the experiment the peak modulation depth pressure and modulation frequency were set to 160 mm Hg and 6.5Hz respectively. The various signals were sampled simultaneously, recorded and stored in 2-minutes length duration for post analysis.

An FFT transform was performed on the recorded signals and the frequency spectra are shown in Figure 4.8,
It can be seen that the artificial modulation peak was larger than the PPG fundamental peak as opposed to the previous frequency spectra in Figure 4.5. Other than the PPG harmonics, there were two other peaks are on each side of the modulation peak. This is the multiplicative term which is the measure of the degree at which the arterial system is disturbed by the artificial pulsation. The zoom-in view of Figure 4.8 is shown in Figure 4.9. It shows that the multiplicative term appeared at the sum and difference of the PPG fundamental frequency and the modulation frequency, i.e. classic amplitude modulation.

![Power Spectrum for InfraRed signal](image1)

![Power Spectrum for Red Signal](image2)

**Figure 4.9 – Zoom-in figure of the multiplicative term**

The fundamental PPG frequency (which is also the heart rate) was around 1Hz and the modulation frequency was at 6.5Hz. The sum and difference of the two frequencies are 7.5Hz and 5.5Hz respectively and the multiplicative term was found at these frequencies.
The same experiment was repeated on a different subject and the frequency spectra of the recorded signals are shown in Figure 4.10 below,

![Power Spectrum for InfraRed signal and Power Spectrum for Red Signal](image)

**Figure 4.10 - Multiplicative term was also found to be present using a different subject**

The experiments conducted have ascertained the applicability of the heuristic model and that the assumptions made in the development of the heuristic model were indeed valid. The mostly additive effect of the artificial pulse to the arterial system shows that it is possible to induce a mild perturbation to the venous system without affecting the arterial system.
This is an important conclusion as venous oximetry utilises a differential measurement of the absorption of light intensity (similar to that used in pulse oximetry), which will not be possible if the effect has been anything otherwise. The multiplicative term magnitude reflects the extent to which the arterial system is being disturbed by the artificial pulsation, thus it provides us with a means of optimising the modulation depth with respect to the distance away from the measurement site. The frequencies at which the term appears also give us a means of optimising the modulation frequency. The effect of the multiplicative term on the measurement of the arterial oxygen saturation ($SaO_2$) will be examined in the next section.

4.2 Effect of Multiplicative Term on $SaO_2$ Measurement

The question at this stage of the research was to what extent the effect of the multiplicative term had on $SaO_2$ measurement? Was the effect small and insignificant such that it could be ignored? An experiment was therefore carried out to study the effect of the multiplicative term on $SaO_2$ measurement. According to the heuristic model developed in the last chapter, it can be seen that the magnitude of the multiplicative term is dependent on the size of the PPG signal and the modulation depth of the artificial venous pulsation. Hence, an increase in the modulation depth (modulation pressure) would cause the multiplicative term to increase in magnitude as well.

Five healthy subjects were used in this experiment. The subjects were between 22 and 42 years of age with no known history of any vascular disease. The experimental setup was similar to the previous experiment. In the first part of the experiment, 3 minutes of PPG signal and the artificial venous pulsatile signal using a low pressure modulation depth at 103 mm Hg were recorded simultaneously. In the second part of the experiment which was carried out immediately following the completion of the first, another 3 minutes of the signals were recorded but this time, with an increase in the modulation pressure to 113 mm Hg.
After a 5 minutes recovery time, the two sets of experiment were repeated again, with the first set using the normal low-pressure modulation pressure of 103 mm Hg and the second set with a further increase of 10 mm Hg in the modulation depth to 123 mm Hg.

Altogether, the procedure was repeated 8 times. On each occasion, the modulation depth of the first set was kept constant at 103 mm Hg whilst the second set’s modulation depth was increased in steps of 10 mm Hg.

Each two sets of experiment was analysed spectrally by performing an FFT on the recorded signals. The signals that were recorded were the two DC PPG signals and the two AC PPG signals, plus the artificial pulsatile signals. The absolute peaks of the fundamental PPG components in the red and infra red frequency spectra, together with the average DC PPG signal were used to calculate the ratio of ratios of the PPG signal according to the equation 1.10 as outlined in the first chapter of this thesis.

The two ratios of ratios for the two sets of recorded signals were then used to calculate the percentage error according to the equations below:

\[ \frac{R_1 - R_2}{R_1} \times 100\% \quad \text{or} \quad \frac{R_2 - R_1}{R_1} \times 100\% \]

Depending on the magnitudes of \( R_1 \) (ratio of ratios of the first set of data) and \( R_2 \) (ratio of ratios of the second set of data), the percentage errors were then plotted against the modulation pressure (this is a reflection of the magnitude of the multiplicative term) and is shown on the graph in the following page.
It can be seen from Figure 4.11 that the percentage error increased with an increase in the magnitude of the multiplicative term. Due to the fact that we were modulating the venous system, the effective modulation pressure will be around half of the applied pressure. There was a sharp increase from 143 mm Hg to 153 mm Hg as the effective pressure used was closer to the diastolic pressure. At higher pressures, the percentage error was quite severe as the effective pressures were at the diastolic pressure or above it.
The experimental results illustrate the point that the effect of the multiplicative term should not be ignored and should be taken into consideration when designing the instrument. Next, we will look at the ways we could optimise the design of the instrument by taking the magnitude of the multiplicative term and its effect into consideration.

4.3 Optimization Of The Design

As mentioned earlier, due to the effect of the multiplicative term at high modulation depth, the modulation depth must be kept low in order to render the term insignificant. On the other hand, the magnitude of the modulation depth cannot be too small either as this would affect the signal-to-noise ratio of the system and thus the sensitivity and the effective venous oxygen saturation range of measurement. Similarly, too low a modulation frequency would cause the artificial pulsatile signal to fall within the PPG frequency band and too high a modulation frequency might cause it to fall out of the venous system frequency response range.

In this section, we will describe the experiments conducted to optimise the new venous oximetry method in terms of the modulation frequency and the modulation depth with respect to the distance away from the measurement site. The multiplicative term becomes important in the optimisation process as it is the single, most useful information in determining the degree of coupling between the artificial venous pulsatile signal with the arterial PPG signal.

4.3.1 Modulation Depth Optimisation

The experimental set up was similar to the previous experiment and was conducted with five subjects, age ranging from 22 to 42. Both the transmission-mode finger probe and the digit cuff were mounted on the index finger. The distance of the digital cuff away from the measurement site was measured as the distance from the receiver of the finger probe to the centre of the digit cuff.
The artificial pulse generator was set at a particular modulation depth and signals of 2 minutes length were recorded. After the 2 minutes interval, the experiment was repeated again with a small increase in the modulation depth. In total, 15 sets of data were recorded with the modulation depth ranging from 55mm Hg to 165mm Hg. The whole procedure was repeated with the distance from the measurement site to the digit cuff shortened. Altogether 3 different distances were used, each with 15 sets of data recorded.

4.3.1a Data Analysis of the Recorded Data

To analyse the signal, an FFT was operated on each data set. The magnitude of both the modulation peak and multiplicative term were then plotted against the modulation depth. The figure on the following page shows the modulation peaks plotted against the modulation depths for three different distances away from the measurement site.

The two vertical markers on the left and right represent the normal average diastolic pressure at 80 mm Hg and the normal average systolic pressure at 120 mm Hg. Modulation depth above the average diastolic pressure is more likely to affect the arterial system. If this happens, the overall blood flow to the underlying vascular tissue would be affected. The horizontal marker at 0.1% is known as the digital precision. Modulation peaks below this horizontal marker would have a poor signal-to-noise ratio and will be less sensitive to small changes in venous oxygen saturation.
From the above figure, it can be seen that the modulation peaks increased with an increase in modulation depth. There appears to be a relatively flat region between the two vertical markers and then a sharp rise at modulation depths above 120 mm Hg (right vertical marker). Similarly, as the distance of the modulation site and the measurement site got closer, the modulation peaks increased accordingly.

Now let us look at the multiplicative term magnitude plot on Figure 4.13 on the following page. The plot shows that with an increase in modulation depth, there followed a parallel increase in the magnitude of the multiplicative term, as was predicted by the heuristic model.
Once again the horizontal marker, 0.01% is the digital precision at which the multiplicative term becomes measurable and significant in a 16-bit digital system.

From Figure 4.13, it can be seen that at 47mm away from the measurement site, the multiplicative term peaks were below the 0.01% horizontal marker at the modulation depths between the two vertical markers. Therefore, the upper limit of the modulation depth is at the pressure where the multiplicative term magnitude was at or below, the 0.01% horizontal marker.
The lower limit of the modulation depth is the pressure at which the modulation peak magnitude in Figure 4.12 was at or above the 0.1% horizontal marker. By combining the two plots, a sketch can be made to highlight the ideal design window as on the figure below,

**Figure 4.14 - A sketch to highlight the ideal design window for venous oximetry**
By combining the two graphs, the ideal design window lies within the boundaries of the digital precision of the digital system. It highlights how the diastolic and systolic pressure markers, together with the pressure at each distance range where the multiplicative term is located, becomes significant.

The optimisation of the new venous oximetry design pertaining to the modulation depth is made easier with the multiplicative term. It acts as the upper limit indicator to which the modulation depth could be set. The optimisation also depends on the digital precision that could be afforded by the digital system and the minimum sensitivity required of the instrument. Now we shall look at the optimisation of the modulation frequency. Again, we shall see that the frequencies at which the multiplicative term is found are important in the optimisation process.

4.3.2 Modulation Frequency Optimisation

The modulation frequency or the cyclic inducement of a mild perturbation to the venous system should be set preferably away from the PPG fundamental frequency and its harmonics such as to aid spectral separation through digital filtering techniques. The commercial pulse oximeter used a low-pass filter with a cut-off frequency at about 4 to 5Hz. Therefore, the pass band usually encompasses the fundamental PPG and the first 2 harmonics. In order to optimise the modulation frequency, both the modulation fundamental frequency and the multiplicative term (if any) should be set away from the second harmonic of the PPG signal. The frequencies of the multiplicative term not only depend on the modulation frequency but also on the PPG fundamental frequency, that is, the heart rate.

There are two conditions which need to be satisfied during modulation frequency optimisation. In order to illustrate these two conditions, it helps to use a mathematical model for each condition to represent the PPG signal and the modulating signal.
The PPG signal could be modelled after a summation of sinusoidal waves,

\[ f_{HR}(t) = \sum_{n=1}^{\infty} f_n \sin(n\omega_{HR} t + \phi_{HR}^n) \] \hspace{1cm} 4.5

Where \( f_n \) is the coefficient, \( \omega_{HR} \) is the PPG fundamental frequency, \( n \) represents the harmonics (\( n=1 \) is the fundamental frequency), and \( \phi_{HR}^n \) is the phase involved.

The modulating signal could be modelled in a similar fashion by the equation:

\[ f_m(t) = g_0 \sin(\omega_m t + \phi_m) \] \hspace{1cm} 4.6

Where \( g_0 \) is the coefficient \( \omega_m \) is the modulation frequency and \( \phi_m \) is the phase in the model.

The two conditions that need to be met for optimisation of the measurement are:

\[ \omega_m \neq n(\omega_{HR} \pm \Delta\omega_{HR}) \] \hspace{1cm} 4.7

and

\[ \omega_m \pm (\omega_{HR} \pm \Delta\omega_{HR}) \neq n(\omega_{HR} \pm \Delta\omega_{HR}) \] \hspace{1cm} 4.8

where \( n > 1 \)

In this way, a table can be constructed to identify the forbidden frequencies. Let us assume the average heart rate to be 70 and the variability is ± 10

<table>
<thead>
<tr>
<th>( n )</th>
<th>Forbidden frequency bands</th>
<th>( \omega_m ) for condition at (4.7)</th>
<th>( \omega_m ) for condition at (4.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2Hz to 2.7Hz</td>
<td>1Hz to 4Hz</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3Hz to 4.05Hz</td>
<td>2Hz to 2.7Hz</td>
<td></td>
</tr>
</tbody>
</table>

Therefore \( \omega_m \) must be at least greater than 4.05Hz but less than the digital system’s filter upper cut-off frequency for signal detection (typically 3Hz to 6Hz).
Most commercial SpO₂ devices use low cut-off frequencies. Thus, \( \omega_m \) must be set in a narrow range of optimised band.

Experiments were carried out to illustrate that the modulation frequencies within these forbidden bands will cause the multiplicative term frequency or the modulation frequency itself, to overlap with the first two harmonics of the PPG signal. The experimental set up was similar to the previous experiment.

A modulation depth of 160 mm Hg was chosen so as to induce a multiplicative term that was of significant magnitude, and which was also comparable to the first two harmonics of the PPG signal. The PPG system and the artificial pulse generator were switched on for 2 minutes and the modulation frequency was set at 4Hz. During these 2 minutes, the PPG signal and the artificial venous pulsatile signal were recorded. The systems were then turned off for 2 minutes before the whole experiment was repeated again; this time, however, with the modulation frequency increased to 4.5Hz.

The experiment was repeated with an increase of modulation frequency in steps of 0.5 Hz until 6.5Hz. The plots on the following pages are the power spectrums of the PPG signal with venous modulation at various frequencies.
In Figure 4.15, the first harmonic \((n=2)\) of the PPG signal overlaps with the multiplicative term and the modulation fundamental frequency overlaps with the 2nd harmonic. A 4Hz modulation frequency fails both the conditions set out earlier. This would pose a problem should the signals be spectrally separated between two signals. Furthermore, in optimising the modulation depth, the magnitude of the multiplicative term is important in determining the degree of coupling between the two signals. The overlapping of the multiplicative term with PPG harmonics would cause erroneous measurements of the magnitude.

Figure 4.15 - Frequency spectrum of signals with modulation frequency at 4Hz
Figure 4.16 - Frequency spectrum of signals with modulation frequency at 4.5Hz

In Figure 4.16, at 4.5Hz, the multiplicative term starts to move away from the first harmonic but the modulation frequency remains dangerously close to the 2nd harmonic.
Figure 4.17 - Frequency spectrum of signals with modulation frequency at 5Hz

Figure 4.17 illustrates the situation when the heart rate is increased. Although the modulation frequency has increased to 5Hz, the multiplicative term and modulation fundamental frequencies still overlap the 1st and 2nd harmonics respectively. This result shows that the optimisation process also depends on the heart rate variability.

Although we could still increase the frequency further, it should be noted that the venous compliance of an elderly person will be less than that of a young adult and therefore higher frequencies might cause the venous blood volume modulation to fail to register completely.
In such cases, the optimisation will be solely on the modulation depth alone so as to ensure that the multiplicative term is small and relatively insignificant as compared to the harmonics of the PPG signal.

![Diagram](image)

**Figure 4.18 - Frequency spectrum of signals with modulation frequency at 5.5Hz**

When the modulation frequency was increased to 5.5Hz, the multiplicative term was too close to the 2nd harmonic of the PPG signal to facilitate separation of the two signals through filtering. Figure 4.19 on the following page shows the frequency spectrum of the signals recorded when the modulation frequency was at 6Hz. It can be seen that both the multiplicative term and the modulation frequency have moved out beyond the 2nd harmonic region of the PPG signal.
Due to the variability of the heart rate, it is essential to maintain an isolating band between the second harmonic and the multiplicative term. The frequency spectrum of the signals recorded with the modulation frequency set at 6.5Hz in Figure 4.20 shows that the multiplicative term has moved away from the 3rd harmonic of the PPG signal. This creates an isolating band between the 2nd harmonics and the multiplicative term. In cases where the heart rate of the patient does not fluctuate greatly, a narrower isolating band can be used instead.
EXPERIMENTAL INVESTIGATION

Figure 4.20 - Frequency spectrum of signals with modulation frequency at 6.5Hz

The optimisation of the modulation frequency once again depends on the multiplicative term as well as the heart rate of the subject. Due to the proximity of the multiplicative term with the harmonics and the variability of the heart rate, the optimisation process will result in a fairly narrow frequency band.

Using a lower frequency other than the optimized frequency might be possible if the modulation depth applied is such that the multiplicative term remains small and insignificant compared to both the PPG signal and artificial pulsatile signal. With both the modulation depth and frequency optimised, it is time to look at the physiological effect, if any, of prolonged application of artificial pulsatile signals on the vascular tissue under test conditions.
4.4 PROLONGED APPLICATION of ARTIFICIAL PULSE

The application of artificial pulsatile signal to the venous system (so as to induce a mild perturbation in the venous blood) in order to measure the oxygen saturation of the venous blood through differential measurement, is intended to be a continuous method. The prolonged application of the artificial pulse will be inevitable if the measurement is continuous. There is the potential risk that with prolonged application of the artificial pulse, venous pooling might occur and this will affect the venous oxygen saturation\(^{[71,72]}\). This is important as pressure-induced ischemia might lead to localized necrosis\(^{[73]}\).

In normal conditions, prolonged applications of artificial pulsation in the venous system cause venous pooling and affect normal tissue oxygenation. An experiment was conducted to access this risk and to throw some light into this issue. The experimental set up was similar to the previous experiment; the subject was 28 years of age, with no known history of any vascular disease. He was placed in a sitting position with his left arm rested on a cushion at heart level. The PPG probe was mounted on the index finger of the left hand and the digit cuff was wrapped around the proximal phalanx of the same finger. The artificial pulse generator was turned on for 30 minutes and the signals via the finger probe were recorded. The modulation frequency and the modulation depth were set at 6.5Hz and 100 mm Hg respectively.

The recorded signal was analysed by breaking the recorded signal into 30 sets of data, each one minute in length. An FFT was performed on each set of data, and the absolute power of the PPG fundamental frequency peak, the modulation frequency peak and the mean value of the mean DC value for each source were used to compute the ratio of ratios which is related to the oxygen saturation. The ratio of ratios was calculated each for the PPG signal and the artificial venous pulsatile signal using the formula,

\[
R = \frac{AC_{\lambda_i} / DC_{\lambda_i}}{AC_{\lambda_o} / DC_{\lambda_o}}
\]

\[4.9\]
where $\lambda_1$ and $\lambda_2$ were the red and infra red light sources respectively. For the arterial PPG signal, 28 sets of ratio of ratios were calculated as two sets of data were discarded due to movement artefacts. The mean value of the ratio of ratios was 0.3768 (SD ± 5.6%).

Similarly, for the ratio of ratios of the artificial venous pulsatile signal, 28 sets were included in calculating the mean and standard deviation. The mean value of the ratios of ratios was 0.5127 (SD ± 4.7%). Figure 4.21 shows the plot of the ratio of ratios of the two signals and the mean value for each.

The mean value of the artificial pulsatile signal’s ratio of ratios was greater than that of the PPG signal due to the fact that the oxygen saturation in the venous blood was less than the arterial oxygen saturation.
The result was in-line with our expectation; after the tissue has extracted the oxygen it needs from the arterial blood, this will cause a reduction in the oxygen saturation in the venous blood as discussed in chapter 1, section 1.3.1. The small variance shows that the prolonged application of a mild perturbation to the vascular tissues has little or no significant effect on tissue oxygen extraction. The modulation frequency used was far below the average time (15 seconds) required by the haemoglobin concentration to respond to the venous occlusion\textsuperscript{[74]}. A separate experiment conducted by T.Rooke \textit{et al}. involving the use of a pneumatic cuff on the lower limbs had concluded that skin blood flow was augmented in ischemic limbs by intermittent venous occlusion method\textsuperscript{[75]}.

The experiment has shown that the risk of venous pooling in prolonged applications of mild perturbation to vascular tissue is small. It does not have a significant effect on tissue oxygen extraction.

Next, we shall look at the relationship between arterial oxygen saturation and venous oxygen saturation. The hypothesis was that if we were truly measuring venous oxygen saturation, then we would expect the measured venous oxygen saturation to reduce if arterial oxygen saturation was reduced. The next experiment to be outlined was set out to prove this hypothesis.

4.5 \textbf{RELATIONSHIP BETWEEN S_{\text{aO}_2} AND S_{\text{vO}_2}}

The relationship between arterial oxygen saturation and venous oxygen saturation is intimately linked. As discussed in chapter 1, a reduction in arterial oxygen saturation will cause venous oxygen saturation to be reduced if tissue oxygen extraction remained relatively unchanged.

The experimental set up was again, similar to the previous experiment and 3 different subjects were used with an average age of 25. Each subject was asked to hold his breath for as long as he possibly could.
The experiment was repeated with a 5 minute interval for each subject. Altogether 3 sets of the same experiment were conducted for each subject. The length of each recorded signal was about 1 to 1.5 minutes in length. Each set of recorded data was then broken up into data sets of about 20 seconds in length. An FFT transform was operated on each 20 seconds length of data set. The absolute power peaks of the PPG fundamental frequency, modulation frequency and the mean DC value for each light source were used to calculate the ratio of ratios. Two ratio of ratios were calculated; one for the PPG signal and the other for the artificial venous pulsatile signal. Figure 4.22 shows the artificial pulsatile signal’s ratio of ratios plotted against the ratio of ratios for the PPG signal.

![Desaturation Experiment](image)

**Figure 4.22 - Uncalibrated SaO2 versus uncalibrated SvO2**
The simple hold-the-breath experiment was not a proper desaturation test but the result did establish a relationship between arterial oxygen saturation and venous oxygen saturation. In the plot in Figure 4.22, as the arterial saturation decreased, venous oxygen saturation also decreased. With the reduction in arterial oxygen saturation and with an unchanged demand for oxygen by the tissues, the venous oxygen saturation was reduced since there was less oxygen in the blood to begin with.

A different experiment (which will be discussed with more details in the next section), was conducted to induce a reduction in the peripheral venous oxygen saturation without affecting the arterial oxygen saturation. The objective of this experiment was to prove that what we were measuring was indeed venous oxygen saturation.

4.6 \textbf{SvO}_2 \textbf{REDUCTION INDUCED BY VENOUS OCLUSION}

An experiment was conducted to verify that the measurements we made were indeed venous oxygen saturation. Although a change in the venous oxygen saturation can be brought about by a change in the arterial oxygen saturation, there is always the potential danger that we might be just measuring a secondary measurement of the arterial oxygen saturation. Therefore, an experimental protocol was devised to induce a change in the venous oxygen saturation whilst leaving the arterial oxygen saturation relatively unchanged. One way of doing this was described in an experiment by Nitzan \textit{et al}. Although the experiment detailed a method to measure the oxygen saturation by applying a relatively low external pressure of about 25 mm Hg to the forearm, it also concluded that venous occlusion also reduced venous oxygen saturation because of the ongoing de-oxygenation of the blood due to lower blood flow\cite{76}. A separate study by Casavola \textit{C et al}. on the effect of time of inflation and pressure on tissues oxygen consumption\cite{74} arrived at the same conclusion, namely that different levels of oxygen consumption at the calf muscle could be induced through venous occlusion.
The subject was a healthy 28 year-old male, with no known history of any venous disease. A pneumatic pressure cuff attached to an aneroid sphygmomanometer was wrapped around the upper arm (brachialis muscle) of the subject, just above the elbow. The digit cuff was wrapped around the base of the index finger (proximal phalanx) of the same arm. A transmission-mode PPG finger probe was also attached to the fingertip of the same index finger. At the start of the experiment, the pulse generator (set at 6.5Hz) was switched on at the same time the PPG system started to acquire data. The pressure cuff on the upper arm remained deflated until 30 seconds into the experiment where it started to inflate until it exerted a pressure of 30 mm Hg at the upper arm. It took approximately 10 to 15 seconds to inflate the cuff to the required pressure of 30 mm Hg. The cuff was then made to deflate 30 seconds after the cuff had started to inflate. A timeline for the protocol is shown in the figure below.

Figure 4.23 - Timeline of the protocol for the experiment
In this experiment, a pressure of 30 mm Hg would cause venous pooling in the arm but the low pressure would not obstruct arterial inflow. Due to lower blood flow, the venous blood would be subjected to ongoing de-oxygenation, whereas the arterial oxygen saturation would remain relatively unchanged. With this protocol, we would expect the venous oxygen saturation within the time when the pressure cuff at the upper arm was inflated, to reduce and then return to its normal level after the pressure cuff was released.

The experiment was 120 seconds long. The data analysis consisted of separating the PPG signal and the venous modulation signal spectrally. The data collected was filtered using a bandpass filter to extract the low frequency PPG signal. The artificial venous pulsatile signal was extracted using a narrow bandpass filter centred on the modulation frequency of the artificial pulse generator. The DC signals for both sources (namely, red and Infrared) were also extracted using lowpass filter.

Both the extracted AC PPG signal and the AC venous modulation signal were made to pass through an envelope detection algorithm which will trace the envelope of the waveform. The envelope detection algorithm was used to calculate the peak-to-peak values of the AC signals. The algorithm would first trace the peaks of the waveform and then the troughs; the difference of which would yield the peak-to-peak values.

The values of the DC signals and the peak-to-peak values of the AC signals were then used to formulate the ratio of ratios which is related to the oxygen saturation of the blood. Figure 4.24 shows the AC artificial venous pulsatile signal from the Infrared source that was extracted by filtering the recorded signal with a narrow bandpass filter centred at the modulation frequency. Figure 4.25 shows the envelope detected by the envelope detection algorithm.
Figure 4.24 - AC venous modulation signal from the Infrared source

Figure 4.25 - Envelope of the AC venous modulation signal from the infrared source
The AC peak-to-peak values were calculated by subtracting the troughs (bottom waveform in Figure 4.25) from the peaks (upper waveform in Figure 4.25). With these peak-to-peak values, the ratios of ratios of both the PPG signal and the artificial venous pulsatile signal were then formulated according to equation 4.9.

In the experiment, the PPG signal ratio of ratios remained fairly constant with a mean of 0.6729 (SD ± 2%, variance $1.8965 \times 10^{-4}$). This value was higher than previously measured in other experiments because an envelope detection peak-to-peak measurement method was used here as opposed to an FFT method. The absolute value of the ratio of ratios was not important at this stage as the instrument was not calibrated yet. The important observations in this experiment are that the ratio of ratios of the PPG signal remained relatively unchanged, whilst there was a significant change in the ratio of ratios of the artificial venous pulsatile signal during the time when venous occlusion pressure was applied to the upper arm. The ratio of ratios of the artificial pulsatile signal which was related to the venous oxygen saturation was plotted against time as shown in the figure below,

![Figure 4.26 - Ratio of ratios of the artificial venous pulsatile signal](image)

It can be seen from Figure 4.26 that there was a big change in the ratio of ratios within the 30 to 60 sec time window when the cuff was exerting a pressure of 30 mm Hg on the upper arm.
This shows that the reduction in venous oxygen saturation induced by venous pooling was correctly detected by the artificial venous pulsatile signal. The fluctuations in the values were greater after the cuff had been released than before the cuff was inflated. This could be due to sloshing of the venous blood when the cuff was suddenly released.

Figure 4.27 shows the decrease in the venous oxygen saturation from the perspective of the raw data and the Infrared spectrum of the artificial venous pulsatile signal.
During the event when the cuff was inflated and exerted a low pressure of 30 mm Hg on the veins, it can be seen from Figure 4.27 that this event coincided with the narrowing of the artificial venous pulsatile signal AC peak-to-peak value in the Infrared source. The significant change in the AC peak-to-peak values provided us with some level of confidence that the significant change in the ratio of ratios was not created due to complex analysis of the raw data.

The experiment was repeated twice, each with a slight change to the initial protocol used; the time when the pressure cuff started to inflate was changed to the 40th second and then to the 50th second. In both cases, the period of reduction in venous oxygen saturation coincided with the time when the venous occlusion was applied to the upper arm. Figure 4.28 shows the artificial venous pulsatile signal’s ratio of ratios at three different periods of venous occlusion.

In this experiment, the new venous oximetry technique was able to correctly detect the reduction in venous oxygen saturation in those periods where venous occlusion was applied to the upper arm. Since the inducement only affected the venous oxygen saturation and not the arterial oxygen saturation, the increase in the ratio of ratios derived from the artificial pulsatile signals could only be a reflection of the level of venous oxygen saturation and not a secondary arterial oxygen saturation measurement.

The reduction in venous oxygen saturation only appeared as a peak within the narrow time window. This was due to the fact that the average time required for the haemoglobin to react to venous occlusion is about 15 seconds[74]. The double peaks at the third set was purely due to experimental errors since when the cuff was inflated to 30 mm Hg, it would then start to reduce a little. The second peak might be due to the effect of pumping the cuff back to 30 mm Hg in the course of the experiment.
Figure 4.28 - Artificial venous pulsatile signal’s ratio of ratios at three different periods of venous occlusion
4.6.1 *SvO₂* reduction induced by different venous occlusion pressures

In the previous experiment, the time the pressure cuff on the upper arm started to inflate was varied in order to induce a reduction in peripheral venous oxygen saturation at different points in time and the new venous oximetry technique was then used to detect these changes at those points in time. In this experiment, the venous occlusion pressure was varied so as to induce different levels of reduction in peripheral venous oxygen saturation. The experimental setup was similar to the previous experiment. The pressure cuff was wrapped around the upper arm of the subject and the PPG probe and digit cuff were mounted on the index finger of the same arm. Initially, the PPG signal and artificial pulsatile signals were recorded for a period of 3 minutes with the pressure cuff at the upper arm remaining deflated. This initial period of recording was to establish the baseline of the *SvO₂* before any venous occlusion was applied to the upper arm. After the initial period of recording, the pressure cuff was inflated to 20 mm Hg. After a minute had elapsed whereby the cuff remained inflated at 20 mm Hg, the PPG signal and the artificial pulsatile signals were recorded for a period of 3 minutes.

The whole procedure was repeated with an increase in venous occlusion pressure of 5 mm Hg to 25 mm Hg after a 5 minutes recovery time. Altogether, the procedure was repeated 7 times with different venous occlusion pressures applied to the upper arm ranging from 20 mm Hg to 50 mm Hg in steps of 5 mm Hg each time.

For every venous occlusion pressure two sets of signals were recorded; one when the pressure cuff remained deflated and the other when the occlusion pressure of the pressure cuff on the upper arm was set at a desired level. An FFT was operated on these two sets of recorded signals in order to measure the absolute power peaks of the PPG fundamental frequency, modulation frequency and the mean DC value for each light source. These values were then used to calculate the ratio of ratios.
By comparing the two SvO₂ ratio of ratios in these two sets of recorded signals, we would be able to determine the level of SvO₂ reduction that was caused by the venous occlusion pressure applied to the upper arm indirectly by calculating the percentage increase in the SvO₂ ratio of ratios,

\[ \frac{R_2 - R_1}{R_1} \times 100\% \]

where \( R_1 \) is the SvO₂ ratio of ratios baseline and \( R_2 \) is the SvO₂ ratio of ratios measured with venous occlusion pressure applied to the upper arm. Figure 4.29 shows the percentage increase in SvO₂ ratio of ratios at different venous occlusion pressures.

![Figure 4.29 - (Subject A): different levels of venous oxygen saturation reduction induced by different venous occlusion pressures.](image-url)
Following informed full consent, the experiment was repeated on another subject. The results of the experiment are shown in Figure 4.30.

**Figure 4.30** - (Subject B): different levels of venous oxygen saturation reduction induced by different venous occlusion pressures

From Figures 4.29 and 4.30, it can be seen that the venous oxygen saturation at the index finger gradually decreased with an increase in venous occlusion pressure. In both cases, the PPG signal’s ratio of ratios or the indirect measurements of arterial oxygen saturation level remained fairly constant throughout with a standard deviation below ±6%.
The arterial system was not affected as the venous occlusion pressures used were well below normal diastolic pressure; Casavola C et al. had also arrived at the same conclusion when performing venous occlusion at the human calf muscle\textsuperscript{[74]}.

In their experiment it was also found that oxygen consumption of the muscles increased (i.e. a decrease in peripheral venous oxygen saturation) with an increase in venous occlusion pressure, but this relationship broke down when the venous occlusion pressure was above a certain critical pressure. Although the percentage increase in SvO\textsubscript{2} ratio of ratios was much less in subject B - probably due to a higher mean blood pressure, both graphs have a rather similar bell-shaped curve. In our experiment we found that venous oxygen saturation did not decrease further but actually increased when the pressure applied was between 40 to 45 mm Hg for subject A and 50 to 55 mm Hg for subject B. The results are similar to the findings of Casavola C et al.

The experiment has demonstrated that the new method of venous oximetry can detect changes in the venous oxygen saturation that was induced by different venous occlusion pressures. It has proved that the measurement we were making was indeed the venous oxygen saturation and not some kind of secondary arterial oxygen saturation measurement.

4.7 CONCLUSION

Altogether, six different experiments with different objectives were conducted in this research. Each experiment was designed to answer some of the questions regarding the feasibility of the new method of venous oximetry. The verification of the heuristic model as developed in chapter 2 was adequately proven in the first experiment in regards to the additive nature of the artificial venous pulsatile signal to the underlying PPG signal and the appearance and the frequency location of the multiplicative term at high modulation pressure. All these features that were predicted in the heuristic model were shown to be true and proven adequately in the experiment.
The effect of the multiplicative term had on \( \text{SaO}_2 \) measurement was assessed in the next experiment and the results shown that the effect was quite significant when the magnitude of the multiplicative term was increased. The experiment concluded that it is essential that the multiplicative term and its effects are taken into consideration when designing the new venous oximeter.

By exploiting the multiplicative term, it is possible to optimise the design of the new method of venous oximetry. The next experiment was conducted to optimise the modulation frequency and the modulation depth.

One part of the experiment was conducted to optimise the modulation frequency with respect to the PPG signal, its harmonics and the multiplicative term frequency. The second part of the experiment was conducted to optimise the modulation depth with respect to the magnitude of the multiplicative term. The combination of the two yielded an ideal design window in terms of modulation frequency and depth. The optimisation would ensure the best possible accuracy and sensitivity to venous oxygen saturation measurement.

The next experiment was conducted to explore the effects of prolonged application of the artificial pulse to the venous system on the measurement of venous oxygen saturation.

The experiment was conducted over a significantly long period of time to establish the fact that prolonged application of the artificial pulse would not cause venous pooling and thus affect the venous oxygen saturation measurement. This is important as the new method of venous oximetry is designed to monitor venous oxygen saturation in real time. The experiment concluded that prolonged application of artificial pulse to the venous system would not have an effect on venous oxygen saturation measurement.
The next three experiments were conducted to verify that the measurements taken were indeed related to the venous oxygen saturation and not just perhaps a secondary measurement of the arterial oxygen saturation. There exists a relationship between the arterial oxygen saturation and venous oxygen saturation. If the tissue metabolism remains unchanged, a reduction of arterial oxygen saturation would lead to a reduction in the venous oxygen saturation too. This is simply because there is less oxygen in the blood to begin with. A simple experiment was conducted to reduce the oxygen supply to the arterial blood by holding one’s breath. The reduction in arterial oxygen saturation reduced the venous oxygen saturation globally and this was reflected in the measurement taken.

The experimental results have shown that there exists a relationship between the arterial oxygen saturation and the venous oxygen saturation measured using the new venous oximetry technique.

The second experiment was conducted to induce a reduction in the venous oxygen saturation locally without affecting the arterial oxygen saturation. The pressure cuff occlusion method on the upper arm was used to induce a reduction in venous oxygen saturation locally.

The experimental results have shown that the period where the venous oxygen saturation was reduced coincided with the time the cuff was inflated during which, the arterial oxygen saturation remained fairly constant.

The third experiment was an extension to the last experiment whereby the pressure of venous occlusion was varied instead of the time of cuff inflation. By varying the venous occlusion pressure, different levels of venous oxygen saturation reduction could be induced. This was to test whether our instrument could faithfully detect those changes in the level of venous oxygen saturation. Once again, our instrument proved to be up to the task.
The experiments conducted and outlined in this chapter have proved that it is feasible to measure the peripheral venous oxygen saturation by introducing an artificial pulsatile signal to the venous system.

A venous oximetry instrument that is designed based on this new method could be calibrated in the same way as conventional pulse oximeter.

In conclusion, the new method of measuring venous oxygen saturation is based on a sound heuristic mathematical model that can be interpreted through experimental data. The experimental results of various experiments conducted have that artificial pulse based venous oximetry is a promising new technology poised to replace invasive monitoring of venous oxygen saturation in the near future.
The primary objective of this thesis has been to investigate the possibility of measuring peripheral venous oxygen saturation by introducing an artificial pulsatile signal to the venous system such that a differential measurement, similar to the one used in pulse oximetry, could be used to derive venous blood oxygen saturation. A heuristic mathematical model with respect to the artificial pulsatile signal was developed and experimentally justified. The side bands or the multiplicative term within the model played an important role in the optimisation of the design with respect to the distance of modulation from the measurement site, the modulation frequency and the modulation depth. The non-invasiveness of the measurement could be used to replace the existing invasive method which involves catheterisation. In this chapter we will discuss the applications of this technique, future improvements and developments to the new venous oximetry technique.
5.1 **Conclusion**

Clinical monitoring of venous oxygen saturation has been impeded by its invasive method involving catheterisation and as such it comes with the complications that might arise with catheterisation. Venous oxygen saturation monitoring provides vital information on assessing a patient’s oxygenation. Its use in clinical environments would have a greater impact on medical care if it is more widely adopted. The main obstacle standing in the way for venous oximetry in achieving its full potential is its invasive nature. The aim of this thesis has been to devise a new non-invasive method of venous oximetry that we hope, in the future, could replace the existing invasive method, without compromising the accuracy and sensitivity to real time changes in venous oxygen saturation.

Pulse oximetry uses the natural arterial pulsations to separate the absorption due to arterial blood from other static or quasi-static components in the finger such as the tissues, bone and venous blood. Hypothetically, if there is a pulsation that is associated with the venous blood and its characteristic is different from the natural arterial pulsation, then it would be possible to separate the absorption due to the venous blood from all other components in the finger. With this hypothesis, we further developed the means to induce an artificial pulsation in the venous system.

In order to investigate the physiological effects that the artificial pulse has on the underlying tissues, especially on the underlying arterial pulsations, we developed a heuristic model that is based on a model of photoplethysmography that was interpreted previously by using both the Beer-Lambert law and the diffusion theory. In the model, the multiplicative term is a function of both the PPG signal term and the modulation signal term. It will therefore remain small if the modulation depth is small. The heuristic model was then interpreted using the Beer-Lambert law and later justified through experimental results.
The frequency and the magnitude of the multiplicative term were also used to optimise the design of the new venous oximetry method. Experiments were conducted to optimise the modulation frequency and the modulation depth with respect to the distance from the measurement site. Although the multiplicative term is an undesirable effect which should be minimised as much as possible, it does provide us with a means to optimise the design.

The results from the various experiments conducted have clearly shown that the new method of venous oximetry was indeed feasible and has the potential to be developed into a non-invasive method of monitoring venous oxygen saturation in a clinical environment.

5.2 Future Applications

In this section, we shall look at a few applications of this artificial pulse-based venous oximetry method. Applications of injecting an artificial pulse into the venous system as well as the new method of venous oximetry will be discussed.

5.2.1 Venous Diagnosis

Venous Occlusion Plethysmography (VOP) is the measurement of changes in tissue volume in response to the temporary obstruction of venous return. It is used clinically to measure certain physiological conditions of blood vessels such as venous capacitance. VOP relies on the principle that the occlusion of venous return causes a slight swelling of distal portion of the tissue under test due to continued arterial inflow. The changes of venous blood volume over time during VOP is illustrated in Figure 5.1.
The slope of the volume change ($\alpha$) following occlusion, is used to measure arterial blood flow. $\Delta V$ can be used to measure the venous capacitance. Other parameters that can be measured using VOP are venous outflow and venous compliance.

The current VOP methodology involves an examination of the step response of the venous system. The new method described in this thesis offers a different methodology in which the frequency response of the venous system is examined. Generally, we would expect healthy veins to have a higher frequency response as in having a higher cut-off frequency than unhealthy, calcified veins.

The implications of using this methodology in VOP are yet to be established. Further research would need to be carried out in this area in order to ascertain the viability of this new methodology in diagnosing the venous system.
5.2.2 Physiological Control of a Totally Artificial Heart

Mixed venous oxygen saturation has been proposed as one of the suitable parameters for the physiological control of a totally artificial heart. In a study by Nakamura et al., by monitoring mixed venous oxygen saturation (SvO₂) and cardiac output (CO) of a calf during a three-stage step treadmill exercise test, it was found that there existed a linear correlation between the magnitude of changes in CO and SvO₂. CO and SvO₂ exhibited a similar course of change, expressing an inverted exponential curve.

In order to develop a practical artificial heart that could give the user mobility, it is essential to be able to monitor SvO₂ in a ready and prompt manner. This would be made easier if SvO₂ could be monitored non-invasively. The new method of venous oximetry proposed in this thesis could be further developed and miniaturised in order to monitor SvO₂ “on-the-go”, thereby controlling CO of the artificial heart in real time and affording the user mobility. The development of a totally artificial heart is still in its infancy; much research and development would need to be done in this area to determine the best way to control it. If SvO₂ proved to be the best way, then the development of SvO₂ monitoring would move in the direction of being non-invasive and portable.

5.3 SUGGESTION FOR FUTURE WORK

This section outlines the author’s suggestions on future work in this area. Some of the possible applications of the method will be discussed in detail. Trials that could be conducted to further verify the feasibility of the method to be used in clinical environments, experiments and hardware designs that could improve the usability of the instrument will also be described in this section.
5.3.1 Calibration

The new method described in this thesis concerns the measurement of peripheral venous oxygen saturation in the finger. The existing method of measuring venous oxygen globally is through the catheterisation of the pulmonary artery. More recently, the central venous catheter has been used instead as central venous oxygen saturation (ScvO₂), is obtained in a less risky and costly manner\cite{78}, and can offer an attractive alternative to SvO₂ monitoring. Although the oxygen saturation values for these two cases would be different, in one study, SvO₂ could be estimated with great accuracy through ScvO₂ by using a power model\cite{16}.

In a similar way, it is hoped that SvO₂ could be estimated through peripheral venous oxygen saturation at the finger. In order to do this, an investigation would need to be carried out that would calibrate the new method to SvO₂. It would also be interesting to find out what is the relationship between SvO₂ and peripheral venous oxygen saturation in the finger. The calibration process would involve subjects breathing through a spirometer; a calibration method similar to that used for the pulse oximeter. Periodic blood sampling and analysis would also be carried out. This new method of venous oximetry can be calibrated due to the fact that it uses differential measurement similar to that used in pulse oximetry.

If the calibration process proved to be successful and clinical trials proved that SvO₂ could be estimated accurately through peripheral oxygen saturation measured at the finger tip, then this new method could replace the existing invasive method and reduce the risk and complication involved with continuous invasive SvO₂ monitoring. Controversial issues surrounding SvO₂ monitoring include the cost effectiveness of using the special SvO₂ catheter over the normal pulmonary catheter\cite{79,80} as the fibre optic SvO₂ catheter costs much more than a normal catheter. With the introduction of this new method of venous oximetry, the cost of continuous monitoring of SvO₂ could be significantly reduced as the new method eliminates the use of special catheters.
5.3.2 Clinical Trial

A clinical trial would need to be conducted on real patients, especially patients undergoing SvO₂ monitoring through pulmonary artery catheterisation. In this way we could compare the measurement between using the new method of artificial pulse-based venous oximetry and the invasive method of pulmonary artery catheterisation. The measurements should also be compared to samples of blood taken from the pulmonary artery. During the clinical trial, the performance of the new method of venous oximetry could be assessed and improvements in areas like signal processing or mechanical designs of the instrument could be fine-tuned accordingly. Feedback from the patients and clinicians regarding the instrument could also help in designing the instrument to be more user-friendly.

Clinical assessment of the new instrument is valuable in determining the accuracy and sensitivity of the instrument to changes in the venous blood oxygen saturation. The instrument would need to be able to reflect a change in the venous blood saturation within a relative short period of time so as to allow clinicians enough time to direct therapies accordingly.

Clinical trials would also provide us with a means to find out under what circumstances would the instrument fail. Although adequate experiments have been conducted to assess the instrument's feasibility in measuring peripheral venous oxygen saturation, real patients were never used as subjects. Therefore there might arise conditions during the trial that could affect the performance of the instrument.

In order for the instrument to be adopted in clinical environments, the application of clinical trials is a vital step for reaching that goal. The trials will lead to modification and fine-tuning of the instrument, thereby making it more suitable for use in a clinical environment. It is also hoped that clinical trials will lead to the endorsement of the new instrument by clinicians.
5.3.2a Preliminary Clinical Trial I

A preliminary clinical trial was conducted at the cardiothoracic surgical department in Glenfield hospital. With the approval from the ethics committee and full consent from the patient, a clinical trial was carried out to compare the patient’s Cardiac Output (CO) measured using the traditional Swan-Ganz thermodilution method with the new venous oximetry measurement.

A 66 year-old woman was undergoing a mitral and tricuspic valves repair operation. Due to her low CO, an Intra-Aortic Balloon Pump (IABP) was inserted into the aorta to improve the CO of the patient. Figure 5.2 shows the SvO₂ ratio of ratios waveform that was recorded before and after the IABP was inserted.

Before insertion of the IABP, the patient’s CO was 2.4 l/min as measured by Swan-Ganz thermodilution method. When the IABP was first inserted, it caused a transient decline in SvO₂ as shown in the sharp rise in SvO₂ ratio of ratios at the 2nd minute on Figure 5.2. When the pump was turned on and the IABP was fully operational, the CO of the patient was increased to 4.42 l/min and this improvement in CO was reflected in the SvO₂ ratio of ratios waveform that was recorded by the new venous oximetry technique.
The results in this preliminary clinical trial were quite promising as it shows that the new venous oximetry technique was able to trace the improvement in CO by reflecting an increase in SvO₂ peripherally.

5.3.2b Preliminary Clinical Trial II

A 74 year-old man was being weaned off the IABP after a mitral valve repair operation. The IABP augmentation was reduced in steps of 20% approximately every 15 minutes and the CO was then measured using Swan-Ganz thermodilution method. At 100% augmentation, the patient’s CO was 6.01 l/min and when the augmentation was turned down to 20%, the CO reduced to 5.5 l/min. The figure below shows the patient’s SvO₂ ratio of ratios recorded using the new venous oximetry method at different stages of the weaning-off period.

![Figure 5.3 - SvO₂ ratio of ratios at various levels of augmentation during weaning off period.](image)

It can be seen that there was a gradual upward drift of the ratio of ratios as the IABP augmentation was gradually reduced. This indicates that there was a decrease in the patient’s SvO₂ peripherally when the CO was reduced. Although the CO was only reduced slightly, from 6.01 l/min to 5.5 l/min, the new venous oximetry technique was still able to detect the slight changes. This shows that the new venous oximetry technology is sufficiently sensitive to reflect these changes.
5.3.3 Design of the Finger Probe

In the present system, a separate digit cuff is used to modulate the venous system. A future design of the instrument would encompass combining the digit cuff with the transmission mode finger probe. This would reduce the set up time for the instrument. The digit cuff would be made adjustable, both in the circumference and the distance from the measurement site so as to cater for fingers of different lengths and sizes. Furthermore, the digit cuff would need to be replaceable as the pneumatic cuff will be subjected to wear and tear during inflations and deflations. The tube leading to the cuff would also need to be combined with the finger probe. All these design requirements would pose quite a challenge in designing the new probe. The new finger probe could be designed according to the sketch in the figure below. The careful design and construction of the probe would lead to a more integrated instrument and a shorter set up time for the instrument.

![Figure 5.4 - Sketch of the new finger probe](image)
5.3.4 Natural Venous Pulsations

The new method of venous oximetry proposed in this thesis is based on inducing a mild perturbation in the venous system by artificially injecting a pulsatile signal into it. However there is strong evidence that a natural peripheral venous pulsation of central venous origin is present\(^{[81]}\). In a study\(^{[82]}\) by Shelley et al., venous pulsations were being recorded using a pulse oximeter as a plethysmographer. The detection of a venous pulse with a standard pulse oximeter opens up an intriguing avenue of investigation. It should be theoretically possible to determine the peripheral venous oxygen saturation by using the plethysmographic information. The feasibility of this method of monitoring venous oxygen saturation has never been explored before.

One of the difficulties in this method would lie in the area of extracting the central venous pulsations from other waveforms in the plethysmograph, which is the product of a complex interaction between a number of factors, such as the presence of competent venous valves, vascular tone, right heart function, hand position, and relative blood volume. Advanced signal processing techniques would need to be implemented to extract the signal. The use of the natural venous pulsations to monitor venous oxygen saturation would eliminate the use of any artificial pulse generator.

This natural pulse-based venous oximetry method, if proven to be feasible, would expand the functionality of the existing pulse oximeter without any significant change in the hardware. This is definitely an area worth looking into in the future.
REFERENCES


REFERENCES


REFERENCES


REFERENCES


This appendix will include the design and implementation of the electronic circuitry of the artificial pulse generator. The circuit consists of the air pump circuitry and the pinch valve driving circuitry. This section will also include the program listings for the micro-controller used to generate the modulation frequency for driving the pinch valve as well as the Matlab program listing used to conduct the experiments.
I.1 Artificial Pulse Generator Circuitry & Pinch Valve Controlling Circuitry

Figure I.1 - Schematic for the artificial pulse generator and pinch valve controlling circuitry.
This section describes the design and operation of the artificial pulse generator circuitry. The circuitry can be divided into two sections, the air pump circuitry and the pinch valve driving circuitry. We shall take a closer look at the air pump controlling circuitry first.

I.1.1 Air Pump Controlling Circuitry

A Digital to Analogue Converter (DAC), MX7224, U1 in the circuit diagram is used to interface the air pump to the computer via the PLD card. There are 8 data lines from the PLD card with an extra line for chip enable. The outputs of these data lines are not latched, the DAC register is latched when the chip enable line goes from a low to a high. An inverter (74HCT04), U3A in the diagram is used to invert the chip enable line such that it could be used for latching the data onto the DAC register. The input data has a range from 00 hex to FF hex, 255 steps in total. The DAC is referenced with a 10V voltage regulator (MX584), U4 in the diagram. The output of the DAC is connected to an amplifier (U6) implemented using a non-inverting Opamp with a gain of 1.68. The gain is chosen such as to match the maximum voltage that could be applied to the air pump at the DAC’s full range. The output from the Opamp is then applied across the air pump through a transistor, TIP31C, Q1 in the diagram. Using this simple DAC controlling circuitry, the air pump pressure could be controlled according to the data at the input data lines.

I.1.2 Pinch Valve Driving Circuitry

The pinch valve circuitry is implemented using a microcontroller from Microchip (PIC12C509), U8 in the diagram, it is programmed to output a square wave in a frequency of 6.5Hz. This frequency is the modulation frequency of the artificial pulse generator. The output from the micro-controller is connected to a buffer (U9) and then to a transistor (Q2) which acts as a switch to switch on and off the pinch valve according to the square wave frequency.
The pinch valve controlling circuitry is interfaced to the PC via the air pump circuitry, the voltage applied across the air pump is connected to a transistor switch (Q3) which will switch off the pinch valve when the voltage across the pump is 0V.

The program listing is shown below.

```
; Title: Venous Modulation
; File Name: veinmod.asm
; Date: Aug 9, 2000
; Processor: PIC12C509
; Clock Frequency: Internal 4MHz
; Description: simple program to output a square wave for driving the pinch valve

#include "pl2c509.inc" ; include standard assembler routines

BOOTC509 equ 0x0000 ; the 12C509 boots up at address 0x0000

CounterA equ H'0007'
CounterB equ H'0008'
CounterC equ H'0009'

ORG 0000
Goto LOAD_OPTIONS

; PIC Time Delay = 0.0769230s with osc = 4 MHz

DELAY_ROUTINE movlw D'100'
movwf CounterB
movlw D'228'
movwf CounterA
loop decfsz CounterA,1
goto loop
decfsz CounterB,1
goto loop
retlw D'0'

LOAD_OPTIONS movlw 0x0F ; zero bit 5 of option register to disable timer 0 clock source
option

LOAD_TRIS movlw 0x08 ; define GPIO 0-2, 4 & 5 as outputs, 3 as input
TRIS

DO_AGAIN bsf GPIO,0
CALL DELAY_ROUTINE
bcf GPIO,0
CALL DELAY_ROUTINE
GOTO DO_AGAIN
END

Figure 1.2 - PIC program listing for generating 6.5Hz square wave
```
The PIC microcontroller program is a rather simple program which uses a delay subroutine to calculate how long a state ‘HIGH’ or state ‘LOW’ should be maintained. The program starts by outputting a ‘HIGH’ state at one of the output pins and then it calls the delay subroutine which will count down to the required time delay. The program then changes the state at the output pin and calls the delay subroutine again. By looping this program indefinitely, the output pin will produce a square wave which frequency depends on the delay subroutine.

1.2 MATLAB CONTROL PROGRAM

As mentioned in Chapter 3, the artificial pulse generator is controlled by the computer. The pressure of the air pump, the intensity of the LEDs in the finger probe can be all controlled by the computer. A program can be written to control these settings, including the sampling rate and the duration of the data acquisition. The Matlab program controls the different settings through Dynamic Data Exchange (DDE). All the experiments conducted in this research used a variation of the program.

The program starts by initialising the different settings of the artificial pulse generator. The air pressure for the pump, the intensity of the LEDs in the finger probe, the gain at the input channels, sampling rate and the duration of data acquisition.

The data acquisition is activated by enabling the interrupt of the parallel port. The duration of the data acquisition is determined by the sampling rate and the number of data samples required.

The program listing can be found on the following page.
clear;
'variables used for saving data (used by the matrix data_name)
x=1;
y=6;

ch=openplddde;
start_voltage=173; %set air pump pressure at 100 psig.
postmessage(ch,1025,1,147); %set RED LED to mid range.
postmessage(ch,1025,2,147); %set Infra RED LED to mid range.
postmessage(ch,1025,3,10); %set gain on receiver for RED signal at mid range.
postmessage(ch,1025,4,10); %set gain on receiver for Infra Red signal at mid range.
postmessage(ch,1041,1); %set destination level to 1.
postmessage(ch,1040,1); %enable hardware interrupt.
for i=1:1
    total_sample=0;
    postmessage(ch,1025,5,start_voltage); %set air pressure.
    postmessage(ch,1040,1); %enable hardware interrupt
    postmessage(ch,1044); %clear buffer.
    while total_sample<270000 %collect 270000 samples for every air pressure setting.
        [d,n]=getdata(ch,5000);
        if (n>0),
            if (exist('data')),
                data=adddata(data,d);
            else
                total_sample=total_sample+n;
                data=d;
                total_sample=n;
            end;
        end;
    end;
    postmessage(ch,1025,5,0); %stop air pump.
    postmessage(ch,1044); %clear buffer.
    postmessage(ch,1040,0); %disable hardware interrupt.
    if (i==1),
        save data01,data;
    end;
    clear data;
end;

clear d;
postmessage(ch,1040,1);
postmessage(ch,1025,5,0); %turn off the air pump.
postmessage(ch,1040,0);

Figure 1.3 - Matlab program listing for controlling the Artificial Pulse Generator