MASTER

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Time-Continuous Modelling of the Influence of the Dominant Modulating Factor on Heart Rate Variability

by R.F.H. Kock

Master of Science thesis

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Preface

Before you lies my master’s thesis, which is the culmination of the final year project and is the last step on the road to becoming a master of science of electrical engineering at the Technical University of Eindhoven.

During my well-spent years at the university, I have grown both scientifically and socially. Scientifically, the education of the university has bestowed me with significant knowledge in the fields of electrical engineering and information technology. More importantly, I have learned abstract and structured reasoning, which should allow me to tackle any of challenges that the future will doubtlessly bring.

Socially, I have learned a lot from my time spent as a project manager at the so-called electro-technical science shop, an organisation that grants the general public access to advanced knowledge. I was in the fortunate position to coach students and control electrotechnical projects, enabling me to learn about both team interaction and management, and the relationship between a team and its client. Furthermore, I have been intensively involved with the student life and student associations of the university, partaking in many social, cultural and education events.

I have spent a scientific trainee ship in Singapore, where I was given the opportunity to learn the points of view of people of various nationalities. I have also visited the countries of Indonesia, Malaysia, Poland, South-Africa and Thailand; in each of these countries I met interesting people, who helped to broaden my perspective on the events that transpire in the world. I learnt that while many different people differ fundamentally of opinion on a variety of subjects, rational discussion is possible under the condition of respect for each other. Intercultural business relations have consequently become an area of interest for me, and I will certainly pursue a career in that field.

The primary lesson that I have learnt during this final project, is that one can be too meticulous: I have spent far too much time on small details, which in the end resulted in just a single sentence in this report. Controlling time
is an ability that I have just learned. Furthermore, I discovered that during projects which span a more significant amount of time, careful planning and documentation is required.

Finally, I have come to the part that is written in reminiscence, and which is probably the most fun to read. First of all, I would like to thank my parents for supporting me all this time; their help was simply invaluable. By brother Ad and sister Leontine provided invaluable support and have always stood up for me.

Next, I would like to thank Herman Ossevoort, who has been my mentor and has helped and guided me for the past years. Furthermore, I would like to thank dr. Blom for the time invested in me. I also thank dr. Cluitmans and dr. de Beer, who were my supervisors, for their comments and for their assistance. A final thanks is extended to my professor, prof. Bergmans.

Last but not least, I would like to thank my friends from home, the ‘Tap­persgilde’, ‘Thor’ and from Singapore. I would also like to thank the various interesting people that I have met during my travels. I will not mention any names here, since the list would be overly long.
Abstract

The Technical University Eindhoven and the Máxima Medical Centre cooperate on several areas including perinatal monitoring. Two systems, vital to foetal and neonatal health, are the cardiovascular system and the autonomic nervous system. The cardiovascular system, consisting of the heart and of blood vessels, provides the rest of the body with oxygen and nutrition. The autonomic nervous system controls the function of the body ranging from level cognition to the cellular level. The most important component of the autonomic nervous system is the brain: the seat of human intellect.

Both the cardiovascular system and the autonomic nervous system influence the heart rate. Consequently, foetal and neonatal heart rates (partly) reflect both the cardiovascular and the autonomic state. Several factors modulate, i.e. influence, the heart rate through the cardiovascular system or the autonomic nervous system; these factors include thorax movements, pressure and stress.

Because of the ready availability of the electrocardiogram, and especially of the inter-beat-intervals—the time intervals between successive heart beats—we hope to be able to extract modulating factors from the inter-beat-intervals. These modulating factors may be used as an indicator of cardiovascular or autonomic state, and as a means to remove the influence of such a factor from the heart rate in order to be able to better estimate other factors.

Analysis of heart rate variability is carried out using inter-beat-intervals. Traditional methods treat inter-beat-intervals as a series of numbers, without taking into account that the underlying process is time-continuous and that the inter-beat-intervals represent a non-equidistant sampled signal. Unfortunately, modulating factors of the heart rate of foetuses and neonates may exceed the Shannon frequency, i.e. half the heart rate, which results in aliasing problems. An example of such a modulating factor is the respiration rate in neonates. Therefore, a time-continuous approach is required.

In this project, a model is discussed that describes the influence of the dominant modulating factor on the instantaneous heart rate, i.e. a time-continuous
notion of the heart rate. Based on this model, an extraction procedure for determining the characteristics of the dominant modulating factor from the electrocardiogram is developed.

The model and extraction procedure have been tested for a variety of parameters and signals, in order to validate their operation. The simulations revealed that the instantaneous heart rate can be recovered above the apparent Shannon frequency, if the heart rate variability is sufficiently large. In that case, the non-equidistant sampling allows for 'super-Shannon' reconstruction. A mathematical description and quantification of this phenomenon is still required.

Finally, the extraction procedure has been tested on a measured electrocardiogram signal. This proved that the algorithm has potential, but cannot be applied to any measured signal since real-life electrocardiogram signals often consist of multiple components. Measured electrocardiogram signals with only a single modulating factor commonly correspond to brain-dead patients.
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Chapter 1

Introduction

The Technical University Eindhoven and the Máxima Medical Centre cooperate on several areas including perinatal monitoring, i.e. the observation of foetal and neonatal health. The current M.Sc. project was carried out within the context of this cooperation. Prior to describing the project at hand, the general research area is sketched.

During the course of some pregnancies foetal growth retardation, foetal oxygen deficiency, or maternal rejection can occur. In many cases, it is difficult to treat these conditions while the foetus is still in the uterus; such a situation requires premature delivery. The uterus is a far more desirable environment for a foetus than an incubator, except when the detrimental effects of the condition at hand outweigh the benefit of remaining in utero. Thus, when such a condition is discovered, one has to decide the exact moment of delivery.

For example, Andriessen\(^1\) is investigating the consequences of intra/extra uterine growth retardation on the cardiovascular autonomic function in neonates and children in [And01]. A possible explanation for this relationship is offered by the foetal origins hypothesis from Barker in [Bar95], which states that intra-uterine growth retardation causes hypertension at later age. A systematic review of 34 studies[And01], including a total of 66 thousand subjects, supports the theory that low birth weight is a precursor for hypertension of children and adults. In summary, it can be concluded that a trade-off has to be made between foetal gestation and reducing perinatal health risk. In order to make the decision for the suitable moment of delivery, a tool is needed that is able to either predict when or measure whether the foetal health state is about to deteriorate. To avoid unnecessary discomfort for mother and foetus, a non-invasive, easily available and accurately measurable quantity has to be

\(^1\)Máxima Medical Centre, location Veldhoven, the Netherlands
Monitoring neonatal health is as important as monitoring foetal health, and the method developed in this text is developed for neonates because of the more readily available measurement data. In the future, this project is to be extended to included foetuses. In this text the particularities of the foetal electrocardiogram are not discussed any further; only the inter-beat-intervals (IBIs) are considered. In the remainder of this chapter, the problem at hand is introduced.

Two vital systems of a human being—and of the foetus—are the cardiovascular system and the autonomic nervous system. The cardiovascular system is responsible for the transportation of nutrition, and the paramount distribution of oxygen. As long as the heart is beating, the brain usually survives. The autonomic nervous system controls the body, and exerts its control on each level from cognition and motion to peristaltic reflex, and the beating of the heart. Because the heart is controlled by the autonomic nervous system, its behaviour also reflects part of the state of that autonomic nervous system. In conclusion, the condition of both the cardiovascular system and the autonomic nervous system are reflected in the beating of the heart. Because of the low signal-to-noise ratios (SNRs) of the foetal electrocardiogram when measured non-invasively, and because of the possibility of extracting IBIs from alternative sources, such as Doppler-ultrasound measurements, this project is limited to using only IBIs, i.e. the series of time intervals between successive heart beats.

The autonomic nervous system, which controls the heart rate, exerts its control based on many variables. Consequently, the heart rate partially reflects all of these variables, such as workload, oxygen requirement, respiration, pressure and stress. Each of these variables has an influence on the heart rate, i.e. it modulates the heart rate. The time-continuous result of the regulating mechanism of the heart rate is denominated the instantaneous heart rate (IHR). This situation, leads to the schematic representation of heart rate regulation as depicted in Figure 1.1.
Both the modulating factors and the regulation mechanism of the heart (rate) are time-continuous, i.e. they function in parallel and do not adhere to any concept of a 'system clock'. The beating of the heart represents a non-equidistant sampling of the IHR. The heart rate can be too low to accommodate lossless reconstruction of either the IHR or of a modulating factor. That is, the Shannon frequency of the IHR or of a modulating factor, may be higher than half the heart rate.\(^2\)

The current project deals with the characterisation of the dominant time-continuous modulating factor from a series of discrete IBIs.

Time constraints on this project, have lead to the following restrictions:

- The link between the concept of the IHR and any physiological mechanism has not been researched. It is expected that the IHR is associated with the permeability of the cells of the Sino-Atrial node.

- No model of the influence of any modulating factor was created, but only basic signals are used for evaluation. Consequently, the value of the method in 'real world situations' remains uncertain.

Traditionally, when analysing the heart rate or linking the heart rate to a physiological parameter, IBIs are modelled as a time discrete process, i.e. the IBIs themselves are described and not the underlying time-continuous processes. This approach is suitable for determining intra-beat relations and frequency spectra, but can only be used for demonstrating statistical relations.

In the current report, a time-continuous approach is applied:

1. A simple time-continuous model is designed, which can be adapted to describe the influence of any single modulating factor on the heart rate. This model uses an intermediate stage to describe the IHR.

2. Based on the resulting IBIs, the IHR is recovered.

3. Based on the IHR, the dominant modulating factor is recovered. Hilbert transform based instantaneous frequency analysis is used to recover the dominant modulating factor from a frequency-modulated signal.

\(^2\)The Shannon frequency of a signal, also known as the Nyquist frequency, is the minimal sampling frequency that is required to perfectly reconstruct an equidistant sampled signal from its sampled version. For baseband signals, this corresponds to twice the cut-off frequency.
In this project, the following goals have been achieved:

1. The model presented in [Koc03], which describes a model that is capable of reproducing the statistical relations between respiration and the heart rate, has been generalised to describe the influence of any heart rate modulating factor on the heart rate. This model uses a time-continuous concept for the modulating factors and the IHR.

2. The need for a time-continuous approach, at least when the modulating factors may have frequency content near, or even exceeding, the Shannon frequency has been demonstrated.

3. The feasibility of recovering the IHR, even when its frequency content exceeds the Shannon frequency of the heart rate has been demonstrated.

4. The feasibility of recovering the a single modulating factor, even when its frequency content exceeds the Shannon frequency of the heart rate has been demonstrated.

5. The limitations and applicability of Hilbert transform based instantaneous frequency analysis within medical context, particularly for heart rate variability analysis, have been elucidated.

6. The procedure outlined in this text can only be applied to IBIs that have but a single dominant modulating factor. This is mainly caused by the fact that when then Hilbert transform based instantaneous frequency analysis is applied to multi-component signals, an averaged frequency is returned. However, in this project we are interested in extracting the components of the heart rate. For application to real-life subjects, physiological based models for the modulating factors is required to enable pre-selection of the factor that is to be extracted.

The main body of this text is organised using the following structure.

In Chapter 2, the physiological background of the processes underlying the regulation of the heart rate is explored. The traditional approach of describing IBIs and their link with this project is also discussed. The problem at hand is thus described in detail.

In Chapter 3, a model of the beating of the heart and the regulation of the heart rate is presented. This model is based on linear superposition of modulating factors. An individual modulating factor reflects the influence of a process that influences the heart rate.

\[^3\text{signals with spectrally separated components}\]
In Chapter 4, the extraction procedure for first determining the IHR from the IBIs, and subsequently for determining the dynamics of the dominant modulating factor from the IHR is described.

In Chapter 5, the results of several simulations using basic signals as modulating factors are presented in order to gain a better understanding of the signals that can be recovered from the IBIs, and which conditions need to be met for a successful extraction.

In Chapter 6, the procedure is applied to six real-life neonatal electrocardiogram (ECG) signals in order to see whether the IBIs can be described using simple mathematical models for the modulating factor.

In Chapter 7, the work is discussed, conclusions are drawn and a list of recommendations for further work is presented.

As a final note: this is an interdisciplinary project, in which mathematical modelling is applied to a medical problem. Because readers from either discipline be interested in this report, more detailed background information is included than usual.
Chapter 2

Heart Rate Analysis: a Survey

2.1 Introduction

In this chapter, various possibilities for analysing the heart rate are discussed. Before analysis of the heart rate is carried out, a general understanding of the origins of the heart rate is advantageous. The physiology of the heart and the mechanics of a cardiac cycle (the heart beat), as discussed in Section 2.2, provide the foundation to understanding the processes underlying the heart rate fluctuations. An isolated heart beats regularly at a constant rate. Generally, a heart is subject to control by the nervous system and to influences by hormones. Furthermore, the heart can also be subjected to various drugs and environmental conditions. The fundamentals of the heart rate regulation are discussed in Section 2.3.

Acquisition of the heart rate can be done in several ways. The most common possibilities for determining the instances at which the heart beats are explored in Section 2.4. Equipped with insight of the underlying principles governing the heart rate, a study of the traditional approaches to analyse the IBIs is undertaken in Section 2.5. This study revealed that these approaches are less suitable for analysing the heart rate of neonates than that of adults heart rate as a result of the following particularities: the high frequencies of the heart rate modulating factors, such as the respiration, a high heart rate, and a high variance of the heart rate.

The primary drawback of most traditional approaches is that the IBIs are considered as a discrete sequence of numbers without taking into account that the underlying heart rate regulation is time-continuous. Because of the particularities of the neonatal heart rate a time-continuous characterisation of the
CHAPTER 2. HEART RATE ANALYSIS: A SURVEY

heart rate regulating processes seems to be required. The time-continuous approach to the heart rate analysis that is explored in this project is introduced in Section 2.6.

2.2 The Physiology of the Human Heart

The circulatory system provides the body with oxygen and transports nutrients, hormones and other substances, and uses blood to do so. The blood flow is driven by the heart, which acts as a dual organic pump. The right half of the heart drives the pulmonary circulation that provides blood to the lungs for oxygenation. The left half drives the systemic circulation which supplies blood to the rest of the body. Because it has to drive blood through a much larger system, the left half of the heart is stronger and thicker than the right half, but it still pumps the same volume of blood as the right half: every amount of blood has to pass through the lungs.

To understand the functioning of the heart, its anatomy and the cardiac cycle are discussed in this section. The electrochemical processes that play an important role in the cardiac cycle, give rise to changes of the surface potential. The graphical representation of this surface potential is known as the ECG.

2.2.1 Anatomy of the Heart

The anatomy of the human heart is introduced using Figure 2.1.

The heart consists of three muscular structures. The upper half is the atrial muscle; contains two chambers, known as the atria. The lower half of the heart is the ventricular muscle; it contains two larger chambers known as the ventricles. The two halves are connected by a third muscular structure known as the Purkinje muscle fibres.

The atria collect blood when they are not pumping, and are capable of quickly filling the ventricles during contractions. This construction allows blood to flow into the heart almost continuously, and greatly increases the efficiency of the heart. The ventricles are filled by the atria, and subsequently force the blood through the circulatory system. The Purkinje system consists of muscular fibres between the atria and the ventricles. It has a special structure and serves an important role in the cardiac cycle.
2.2. THE PHYSIOLOGY OF THE HUMAN HEART

Figure 2.1: Anatomy of the human heart

2.2.2 The Cardiac Cycle

The cardiac cycle consists of a contraction and relaxation phase of the heart. The former part of the cardiac cycle is known as the systole and the latter as the diastole. During the systole, the atria contract first and fill the ventricles. Subsequently, the ventricles contract and thereby propel the blood through the body. The cardiac cycle starts when the heart is first formed, and is repeated uninterrupted until the demise of its owner. The discussion of the cardiac cycle in this section is based on [Guy00] and begins at the fundamental level of the cell. In this discussion, only the normally, healthy situation is discussed; many diseases and pathologies can perturb the heart function.

Cells are the basic structural and functional units. Inside the body they are contained in the interstitial fluid. The perimeter of the cell, a membrane, separates the interstitial fluid from the contents of the cell — the nucleolus and the cytoplasm. Most cells are polarised, i.e. a negative potential can be measured across the cell’s membrane; the potential of the interstitial fluid is defined to be zero. In rest, this potential is kept constant by the Na/K-pump.

The excitable cells of the body, such as the nerve and muscle cells, are those
cells that can transmit electrochemical impulses, known as action-potentials, along their membranes. An action-potential begins when the potential across the membrane is locally raised above a certain threshold; this is known as activation of the membrane. When the membrane is activated, the cell fires: the entire cell quickly depolarises, i.e. it loses all its electrical charge and gains a positive electrical potential. When the depolarisation is complete, the cell slowly repolarises. The sequence from passing the threshold to repolarisation is called the action-potential. The action-potential follows the so-called 'all-or-nothing' rule, i.e. there either is an action-potential or there is no action-potential. Isolated action-potentials do not carry any information, that is, other information than their occurrence.

The firing of a cell can be the result of pressure, chemical processes, temperature and other physical influences; direct electrical effects such as applying a current or a voltage have the same effect. All these influences disturb the potential balance across the membrane from the inside to the outside of the cell. When the cumulative effect of all influences raises the potential to a certain threshold, even locally, the membrane activates and the action-potential begins. In muscle cells, the action-potential causes the muscle filaments to contract.

Because of special properties of the heart muscle, the cells of the heart slowly depolarises, that is, they continuously lose their charge; a phenomenon known as (charge) leakage. When a muscle cell is sufficiently depolarised, it fires and contracts. Furthermore, because of its complete depolarisation, it also triggers the firing of its adjoining cells. When the cell is repolarised, the contraction stops. After a short delay, the cell is ready to fire again, and the cycle starts anew. A sufficient amount of heart muscle cells that contract simultaneously results in the pumping of blood.

The heart is capable of pumping blood, and thus, of keeping the body alive, through this sequence. However, various additional structures, anatomically difficult to discern, impose timing on the various parts of the heart, thereby increasing the efficiency (amount of blood displacement into the aorta versus energy consumption). Figure 2.2 elucidates this and is referred to in the remainder of this section.

A cluster of cells, known as the Sino-Atrial node, has a much higher firing rate than the other cells of the heart. In each cycle it —consequently— is the first cluster of cells to depolarise, thereby starting the systole. The depolarisation wave causes a slightly delayed contraction wave from the top to the bottom of the atria, efficiently pushing the blood from within the atria into the ventricles.

The depolarisation wave spreads across the atria until it reaches the Atrio-
2.2. THE PHYSIOLOGY OF THE HUMAN HEART

Figure 2.2: The electrophysiology of the heart: the Sino-Atrial node, the Atrio-Ventricular node, the Atrio-Ventricular bundle branches and the Purkinje system

Ventricular node. It is delayed in the Atrio-Ventricular node, and is subsequently transmitted slowly by the ventricular septum (the Atrio-Ventricular bundle) to the two parts of the Purkinje fibres. The entire system from Atrio-Ventricular node to the Purkinje fibres forms the Purkinje system. The Purkinje system is a unidirectional conductor; this prevents contraction of the ventricles to trigger contraction of the atria.

When the depolarisation wave reaches the end of the Purkinje fibres, the depolarisation of the ventricles begins, and spreads from the bottom to the top of the ventricles. Meanwhile, the repolarisation of the atria takes place. At the end of the contraction, the ventricles start to repolarise.

The heart is now in diastole, waiting for some heart muscle tissue to trigger another systole; usually this is again the Sino-Atrial node.
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2.2.3 The Electrocardiogram

The electrical phenomena associated with the de- and re-polarisation of the cells of the heart muscle can be measured at the outer surface of the body. If these measurements are taken according to common convention, the ECG becomes visible. A stylised version of the ECG is depicted in Figure 2.3. Note that the visibility, and even the polarity, of various tops of the ECG depends on the position of the electrical leads in relation to the heart.

The depolarisation wave of the atria is reflected by the P wave. The delay caused by the Purkinje system can be measured as the delay between the P and the Q tops in the ECG. The depolarisation wave of the ventricles corresponds to the QRS complex of the ECG. The expected wave reflecting the atrial repolarisation is concealed by the depolarisation of the ventricles. The electrical effects of this repolarisation are reflected by the T and U waves of the ECG. The QT interval reflects the duration of the ventricular contraction. Furthermore, the ST interval can be used to predict future cardiac infarcts.

2.3 Regulation of the Heart Rate

An isolated heart beats on a constant rate. The intrinsic rates of the various parts of the hearts vary from individual to individual. The following rates com-
monly found: the Sino-Atrial node generates 65 to 75 beats per minute (BPM), the atrial muscle generates 30 to 40 BPM. The Atrio-Ventricular node generates 50 to 60 BPM, and the ventricular muscle generates 10 to 30 BPM. Because the Sino-Atrial node generates the highest amount of BPM, the isolated heart also beats at 65 to 75 times per minute. The simple fact that each part of the heart is capable of generating heart beats, provides a certain measure of robustness: regulatory mechanisms can fail, without becoming immediately life-threatening.

The heart is subjected to environmental influences, such as hormones and temperature. It is also influenced by the autonomic nervous system and, through the autonomic nervous system, by the various needs of the body, such as workload and oxygen consumption.

The fundamental issues pertaining to the regulation of the heart rate are discussed in this section. Finally, the sympathovagal balance is addressed, which has an important modulating influence. Finally, the sympathovagal balance has to be addressed since it has an important modulating influence.

2.3.1 Biochemical and Biomechanical Influences

As already mentioned, chemical and mechanical processes influence the heart. Some of these influences are regulated by the autonomic nervous system: once a certain substance is released, the autonomic nervous system has no further influence. In this section, several important influences are discussed.

- Local temperature has a direct effect on various chemical and mechanical processes, such as the mobility of various ions. Therefore, temperature also directly influences the de- and repolarisation of the heart, and thus of the heart rate.

- Various hormones and drugs have a direct influence on the conductivity of various ionic channels in the cells of the heart; this also influences the heart rate. For example, adrenaline increases the conductivity of the ionic channels and thereby increases the heart rate.

- Pressure has a direct mechanical influence, but the influence through the baroreflex is far more important, and is therefore be discussed in the next section.

- The heart also contains a number of reflex loops (through the autonomic nervous system) that influence the functioning of the heart itself.
For example, if a heart chamber still contains blood at the end of a contraction, the stroke volume of the next beat is increased (the Frank-Starling mechanism). This control loop also creates a dependency on respiration [Hoo98].

### 2.3.2 Control by the Autonomic Nervous System

The Sino-Atrial node is innervated by the autonomic nervous system, and through this innervation subject to control by the autonomic nervous system. The autonomic nervous system has consequently a large degree of control over the firing rate of the Sino-Atrial node.

Through the control of the Sino-Atrial node, the autonomic nervous system is able to influence the functioning of the heart—specifically rate, stroke volume and contraction power—in such a manner that the needs imposed by other physiological systems can be met. The following list describes some of the particularities.

- The overall workload of the body, results in the need for a certain amount of oxygen. Dropping oxygen levels and rising carbon-dioxide levels result, amongst others, in an increased heart rate.
- The activities of several organs, such as the smooth muscles\(^1\) and the intestines, require more or less blood; this results in a changing demand for blood flow.
- The baroreflex is a control loop that is primarily used to keep the blood pressure within acceptable limits. As a result of this control loop, atmospheric pressure, respiration and body position (standing, sitting or lying down) influence the heart rate.
- The autonomic nervous system is very susceptible to stress, such as fight-or-flight reactions, and has its influence on the heart rate as well.

In neonates, the control of the autonomic nervous system over stroke volume and contraction power is more limited than in adults [Fri72], and the baroreflex is still maturing [Gou02]. The latter maturation results in a fast shift of the LF/HF ratio within a hundred days [Mro96].

\(^{1}\) the skeleton muscles
2.3. REGULATION OF THE HEART RATE

Consequently, the primary control mechanism that can be used by the autonomic nervous system over functioning of the heart is the heart rate. One may hypothesise that these facts lead to an increased need to vary the heart rate, and thus to an increased amount of 'control energy' of the heart rate.

This would result in an increased variance of the neonatal heart rate. Further research is necessary, but the increased variance is measured (relatively to the average heart rate) in [Fin95, Mas97, Pik99, Fuk99].

2.3.3 The Sympathovagal Balance

The autonomic nervous system uses the sympathetic and parasympathetic (vagal) nerves to control the heart. The vagal nerves have limited, if any, influence on the ventricles. Sympathetic excitation (1) increases the firing rate of the Sino-Atrial node, (2) strongly increases the force of contraction. Vagal excitation (1) decreases the firing rate of the Sino-Atrial node and (2) decreases the transmission speed of the Atrio-Ventricular bundle and the Purkinje system.

The sympathetic regulation is transmitted by noradrenaline, which has a relatively long duration and, consequently, the control exercised by the sympathetic regulation is relatively slow. The parasympathetic, i.e. vagal, control is mediated by acetylcholine, which acts shorter, and vagal control is therefore relatively fast. These observations might shed some light on the $\frac{LF}{HF}$ ratio that often considered to be an indicator for sympathetic versus vagal activity.

However, it should be noted that the fact that the vagal control is slow, does not negate the possibility of sympathetic control in the LF region. For example, the parasympathetic control of the HF is well established [Gra97], but blocking the sympathetic nervous system does not suppress the LF oscillations of the heart. However, sympathetic control over the LF part of the bloodpressure is also undisputed. This might explain why a certain sympathetic influence on the LF part of heart rate variability is observed, i.e. through mediation of the baroreflex.

\footnote{\textsuperscript{2}Low Frequency (0.04-0.15Hz) component of the power spectral density of the heart rate}
\footnote{\textsuperscript{3}High Frequency (0.15-0.4Hz) or 9-24 beats per minute}
2.4 Acquiring Inter-Beat-Intervals

Although the framework of the current project focuses on perinatal monitoring, here this project is limited to neonatal ECG analysis, leaving foetal ECG for future work.

For this project, the developed method is only allowed to use IBIs. These IBIs can be acquired from a large number of sources. If the ECG is available, it provides a readily available source through determining the QRS complexes. In that case, the IBIs are known as RR-intervals. However, any method that is able to determine the durations of successive heart beats can be used. Thus, methods such as Doppler-ultrasound, MRI scans, and even acoustic measurements may be used. In the near future, extraction of a foetal electrocardiogram may become possible as well.

2.5 Traditional Inter-Beat-Interval Analysis

In this section, various inter-beat-interval (IBI) analysis methods are discussed, as well as their shortcomings with regard to our particular subject. Note that IBI analysis is usually denominated by heart rate variability analysis, since one is really interested in the variations of the heart rate, as opposed to its long-term average. Note also that many of the methods introduced in this section were designed to operate on RR-intervals. That is irrelevant since the RR-intervals are a specific method for determining an IBI series.

The heart rate, is usually determined as the number of BPM. The estimate of the heart rate based on a single IBI, is defined as the single beat heart rate:

\[
SBHR = \frac{60 [\text{seconds per minute}]}{\text{inter-beat-interval [seconds]}}
\]

The IBIs are not equal, as the R-peaks are not equidistant. Thus, the single beat heart rate varies; this fact is called heart rate variability.

The clinical significance of heart rate variability was not known, until the discovery of, amongst others, increased mortality rates for patients with decreased heart rate variability. After this discovery, and because of the easy derivation of heart rate variability, one obtained a seemingly simple tool for analysis. This resulted in extensive research, albeit with a lot of myriad of different definitions and interpretations, which made it difficult to compare the results of different papers. A task force was created to rectify the problem.
This task force from the European Society of Cardiology and the North American Society of Pacing and Electrophysiology was instituted to standardise measurements and methods. This culminated in the creation of a set of guidelines on heart rate variability, standardising measurements and a review of the contemporary physiological interpretation, described in [Tas96]. This document divided the methods into two approaches: time-domain based measurements and frequency based measurements.

The time-domain based methods either consider all intervals, or the differences of the intervals:

- **NN-intervals** (= IBIs): the standard deviation (SDNN), its average over time (SDANN), and the mean of 5-minute SDANN over 24 hours (SDNN index).

- The differences of NN intervals: RMSSD (root mean squared differences), NN50 the number of subsequent intervals differing more than 50 ms, pNN50 NNN50/#NN, the heart rate variability triangular index (geometrical distribution fit), and the TINN (triangular interpolation).

The frequency methods are defined as the power spectral density of the RR-interval series, i.e. the sequence of IBIs. They defined ULF, VLF LF and HF spectral regions as well as the LF/HF ratio. [Tas96] notes that this analysis may be conducted on an interpolated IBI series for better result; this is an attempt to cope with some of the problems introduced by the non-equidistant sampling. All methods defined in [Tas96] consider IBIs as a series of numbers, i.e. without regard to the time-continuous process that underlies their generation, and the irregular sampling that is imposed by the heart rate.

Inspired by the success of heart rate variability, and sometimes frustrated by unexplained phenomena, more advanced measures for heart rate variability, still based on IBIs, have been introduced. Most of these methods are discussed in [Tei00].

The first extension to [Tas96], is to use general point processes, that is to assume that the next IBI depends on the last IBI. This is subsequently generalised to an auto-regressive process [Ama99, Mai93]. Furthermore, Poisson point processes were studied; these processes are memoryless and rely on a notion of the chance that a beat occurs in a next time-interval delta; however the heart rate is not. Further more the Allan-factor, wavelet-transform variance analysis [New02, Wik98], neural networks [Mae98, Nag98], detrended function analysis [Abs99, Ech03] and fractal processes [Coc98, Gou95], deterministic chaos [Wag98, Bor94, Sig92], and approximate entropy [Pin00] were studied.
All traditional IBI analysis methods consider the heart rate to be based on a time-discrete process. Many even consider the IBI to be the dominant process. This assumption is inferred out of the fact that they use time-discrete domain based analysis methods, and a fixed number of beats for IBI analysis.

2.6 A Time-Continuous Approach to Inter-Beat-Interval Analysis

In [Bar01], the new concept of heart instantaneous frequency was introduced. It was observed that in heart rate variability research, where one is interested in an event that occurs no more than four times per second, one samples with 500Hz. In order to reduce the sampling frequency, the ECG is filtered to obtain exclusively the fundamental frequency. Since this signal fluctuates a good deal slower than the heart rate, it is possible to even further reduce the sampling rate. By estimating the frequency of the resulting sinusoid, an estimate of the heart instantaneous frequency is obtained. The traditional heart rate variability statistics can be determined from this signal as well as from the original high frequency sampled IBIs series.

This paper led to the consideration whether it is possible to use a time-continuous approach to modelling the heart rate, and to subsequently extract the model parameters from the heart rate by using instantaneous frequency analysis as well.

In this project, an existing time-continuous model by [Koc03] is generalised to describe any modulating factor, as described in Section 2.3. The model parameters have subsequently been extracted. Both due to time constraints, the influence of the modulating factors has not been modelled. However, this method is still applied to real-life data in order to evaluate potential pitfalls.
Chapter 3

Time-Continuous Modelling of Heart Rate Variability in the Electrocardiogram

3.1 Introduction

In this chapter, the model that is used for describing the influence of the dominant modulating factor on the heart rate is developed. The model is based on a time-continuous model for the influence of respiration on heart rate variability that is described in [Koc03]. Two modifications to the original model have been made:

1. Instead of modelling the influence of respiration on the heart rate, the model is adapted to describe the influence of an arbitrary heart rate modulating factor.

2. The model is adapted to describe the influence of more than one simultaneous modulating factor.

These generalisations were possible because the original model did not describe the influence of the respiration based on the underlying physiology. Note that only two modulating factors have been described in this project due to time-constraints.

The model is based on assumptions about the underlying physiology, and these assumptions have led to the following considerations:
1. The heart rate is determined by heart rate regulating mechanisms, such as the baroreflex. Each mechanism has an effect on the heart rate in order to keep a variable, such as the end-diastolic blood pressure, or set of variables, within a certain range\(^1\). In order to do so, the heart rate regulating mechanism 'measures' at least one input signal, such as the blood pressure. Based on its set of input signals, the mechanism exerts an influence on the IHR, and thus modulates the heart rate as well.

In the model, the effect of any modulating factor depends on at least one input signal. Input signals may be used by more than one modulating factor. The function between a set of input signals and the effect of a modulating factor may be non-linear and time-dependent.

2. Heart rate regulating mechanisms directly influence the physiology of the Sino-Atrial node, and thus directly influence the heart rate.

Modulating factors do not influence one another. This does not exclude the possibility of modulating factors sharing an input signal, and thus of an input signal influencing more than one modulating factor. This structure should enable future modelling of interdependent heart rate regulating mechanisms.

3. The effects of individual heart rate regulating mechanisms on the Sino-Atrial node are combined by linear superposition. The influences of the modulating factors are added to obtain the IHR.

4. The Sino-Atrial node regulates the heart rate; this does probably not depend linearly on the combined effects of the heart rate regulating mechanisms. That is, the function that transforms the IHR into a series of trigger pulses does not have to be linear in the IHR.

The IHR is integrated, and whenever a threshold is reached, the integration is reset, and a trigger pulse is given; this is a linear function. In future work, it may be interesting to explore non-linear functions.

5. The beating of the heart, and the resulting ECG, depends only on the trigger pulses. The trigger pulses are transformed into an ECG by convolving the trigger pulses with a template-ECG of a single heart beat.

This assumption is clearly false, however as only IBIs are used, the differences are not taken into account anyway.

Even though the physiological reality is more complex than sketched by the preceding assumptions, the model provides a solid foundation for further research.

\(^1\)this range can be dynamic, i.e. time-dependent
3.2 THE INFLUENCE OF MODULATING FACTORS ON THE IHR

Because of time constraints, only two modulating factors are considered: the base heart rate (the average heart rate), and the dominant modulating factor to be characterised. Both modulating factors continually change and the underlying physical processes are not sufficiently known to establish a deterministic model. Therefore, the parameters of these modulating factors are described by using (coloured) noise, allowing the spectral information that is known about these modulating factors to be used.

The remainder of this chapter has the following structure: in Section 3.2, the influence of the modulating factors on the IHR is modelled. In Section 3.3, the linear superposition is described. In Section 3.4, the train of trigger pulses is transformed into a series of triggers. In Section 3.5 the train of trigger pulses is transformed into an ECG. In Section 3.6, the final signal model is shown. Finally, in Section 3.7, an initial model validation is carried out of generated statistics with measured data.

### 3.2 The Influence of Modulating Factors on the Instantaneous Heart Rate

Because of the limited time available for this project, modelling the influence of modulating factors on the IHR was not done based on the physiology. Therefore, only a set of elementary signals is explored. These signals are: a constant value, a block waveform, a triangle waveform, an exponential waveform and a sinusoid. Note that, in order to better reflect the dynamics of real-life, the amplitude and frequency of these signals can be perturbed by coloured noise. This method was used for the simulations in Chapter 4.

Each of these models is explored for the following five cases:

1. Very slow modulation: a transition every four seconds (approximately every eight heart beats).
2. Slow modulation: a transition every two seconds (approximately every four heart beats).
3. Average modulation: a transition every 1.5 seconds (approximately every three heart beats).
4. Fast modulation: a transition every second (approximately every two heart beats).
5. Extremely fast modulation: a transition every 0.5 seconds (approximately every heart beat).
3.2.1 A Constant Value

A constant value, or more specifically, a constant value with added coloured noise, can be used to describe the average heart rate, denoted the base heart rate, during quasi steady-state period. Such a period is characterised by nearly constant statistics of selected variables. In Figure 3.1 the characteristics of a constant heart rate, perturbed with $1/f$ noise, are displayed. $1/f$ noise is an important noise profile for many natural processes.

![Figure 3.1: Base heart rate with $1/f$ spectrum.](image)

Top-Left: the designed, and the realised spectrum.
Top-Right: a ‘smoothed’ spectrum which allows for better comparison.
Note that the produced spectrum matches the desired spectrum.

Bottom-Left: sample of the generated base heart rate, entire signal.
Bottom-Right: sample of the generated base heart rate, short segment.
Note that not withstanding the low noise power, large variations of the base heart rate are possible over large periods of time.
3.2. THE INFLUENCE OF MODULATING FACTORS ON THE IHR

3.2.2 A Block Wave

Probably the easiest to model, is a block wave shaped influence by the modulating factor: alternating positive (+15 BPM) and negative modulation (−15 BPM). The characteristics of the modulation, and the resulting IHR are elucidated by Figure 3.2.

![Figure 3.2: Block wave modulation](image)

Top-Left: block wave shaped excitation.
Top-Right: spectrum of the excitation.
Bottom-Left: block wave modulated IHR.
Bottom-Right: spectrum of the resulting IHR.

Note that notwithstanding the large impact of the noise on the generated signal, the spectrum is almost unperturbed.
3.2.3 Triangular Excitation

A triangular excitation is obtained by integrating the block wave. The result is scaled to yield the same energy as the generating block wave. The characteristics of the modulation, and the resulting IHR are elucidated by Figure 3.3.

![Figure 3.3: Triangular modulation](image)

Top-Left: triangular excitation.
Top-Right: spectrum of the excitation.
Bottom-Left: triangular modulated IHR.
Bottom-Right: spectrum of the resulting IHR.

Note that notwithstanding the large impact of the noise on the generated signal, the spectrum is almost unperturbed.
3.2. THE INFLUENCE OF MODULATING FACTORS ON THE IHR

3.2.4 Exponential Excitation

When some set point varies, and the heart rate is controlled to match this set point using some feedback controller, a possible model is that of a capacitor that is connected to the set point by a resistor. This model is associated with the exponential function. The characteristics of the modulation, and the resulting IHR are elucidated by Figure 3.4.

Figure 3.4: Exponential modulation

Top-Left: exponentially shaped excitation.
Top-Right: spectrum of the excitation.
Bottom-Left: exponentially modulated IHR.
Bottom-Right: spectrum of the resulting IHR.

Note that notwithstanding the large impact of the noise on the generated signal, the spectrum is almost unperturbed.
3.2.5 Sinusoidal Excitation

Another important wave form to test is the sinusoid. The characteristics of the modulation, and the resulting IHR are elucidated by Figure 3.5.

![Figure 3.5: Sinusoidal modulation](image)

Top-Left: sinusoidal excitation.
Top-Right: spectrum of the excitation.
Bottom-Left: sinusoidal IHR.
Bottom-Right: spectrum of the resulting IHR.

Note that not withstanding the large impact of the noise on the generated signal, the spectrum is almost unperturbed. However, it cannot be clearly distinguished from the exponentially modulated IHR.
3.3 Modelling the Instantaneous Heart Rate

The IHR is the heart rate that would correspond to the combined effect of all heart rate regulating mechanisms, at a certain moment in time. The IHR is determined primarily by the oxygen requirement of the body and is modulated by a tremendous variety of factors as discussed earlier. Except for a single dominant modulating factor that is to be characterised, the influences of all remaining modulating factors are lumped together, and this combined influence is called the base heart rate.

Stationarity is assumed for the base heart rate; this can be modelled with a constant and some coloured noise. The base heart rate $\beta$ is the mean base heart rate $\langle \beta \rangle$ and noise component $\nu_{\beta}$:

$$\beta(t) = \langle \beta \rangle + \nu_{\beta}(t)$$  \hspace{1cm} (3.1)

In this section, a sinusoidal influence of the modulating factor is described; the other elementary models, described in the previous section, are explored in Chapter 5. The instantaneous frequency $\alpha$ of the dominant modulating factor is the linear superposition of the mean frequency $\langle \alpha \rangle$ of the dominant modulating factor and a noise component $\nu_{\alpha}$:

$$\alpha(t) = \langle \alpha \rangle + \nu_{\alpha}(t)$$  \hspace{1cm} (3.2)

This instantaneous frequency is integrated, used as the angle of a sinusoid and scaled with a modulation index $\lambda$ to obtain the influence of the dominant modulating factor $m$:

$$m(t) \triangleq \lambda \cdot \Re \left\{ \exp \left[ j \int_0^t \alpha(\tau) \, d\tau \right] \right\}$$  \hspace{1cm} (3.3)

Note that $\Re \left\{ \exp \left[ j \int_0^t \alpha(\tau) \, d\tau \right] \right\}$ denotes frequency modulation, i.e.

$$\Re \left\{ \exp \left[ j \int_0^t \alpha(\tau) \, d\tau \right] \right\} = \sin \left[ \int_0^t \alpha(\tau) \, d\tau \right]$$

The complex notation is used because this notation elucidates the usage of the Hilbert transform based instantaneous frequency analysis, as described in [Coh95]; the Hilbert transform based instantaneous frequency analysis is used in Section 4.2.3, Section 4.4 and Section 5.4.3.
The base heart rate $\beta$ and the influence of the dominant modulating factor $m$ are now summed to obtain the IHR $h$.

$$h(t) = \beta(t) + m(t) \quad (3.4)$$

These equations can be combined to:

$$h(t) = \langle \beta \rangle + v_{\beta}(t) + \lambda \cdot \mathbb{R} \left\{ \exp \left[ j \int_{0}^{t} \langle \alpha \rangle + v_{\alpha}(\tau) \, d\tau \right] \right\}$$

A diagram with the mathematical model is displayed in Figure 3.6.

### 3.4 Generating a Series of Trigger Pulses from Instantaneous Heart Rate

Given the IHR, the train of trigger pulses to the heart (i.e. the action-potentials of the Sino-Atrial node), has to be determined. In this section, two alternatives are discussed.
3.4. GENERATING A SERIES OF TRIGGER PULSES

The heart rate modulating mechanisms influence the effective permeability of the membrane of the Sino-Atrial node. This influences the rate of spontaneous charge leakage.

Such a process can be described by integrating the IHR, and is called integrate-and-fire. The most straightforward approach is to integrate until a threshold is reached, and then fire.

The integration of the IHR, yields an instantaneous phase, and is transformed into a sinusoid, which is dubbed the heart wave \( f \). Thus, the heart wave is the frequency modulated version of the IHR:

\[
f(t) \triangleq \Re \left\{ \exp \left[ j \int_0^t h(\tau) \, 2 \, d\tau \right] \right\}
\]  

(3.5)

The relation between the IHR and the heart wave are displayed in Figure 3.7. The modulation on the heart rate is exaggerated to reveal its effect on the heart wave.

The trigger is given on the negative-to-positive zero-crossings of this heart wave.

\(^2\)effective in the sense of permeability and ion channel effects
wave, thus the heart-trigger sequence $\Delta$ is determined by:

$$\Delta(t) = \sum_{n=0}^{\infty} \delta(t - t[n]), \quad f(t[n]) = 0 \land f'(t[n]) > 0 \quad (3.6)$$

This is elucidated by Figure 3.8.

This method yields exactly the same trigger instances as the straightforward approach, i.e. triggering when the integration of the IHR is equal to 1. However, instantaneous frequency analysis is the natural reverse of frequency modulation. This fact elucidates why the extraction process uses instantaneous frequency analysis.

### 3.4.2 Single Heart Beat Based Triggering

In order to study the possible effects of the choice of the IHR to trigger pulses transformation, another approach was designed. The IHR at the instance when a heart beat starts, determines the duration of that heart beat. This is achieved by

\[
t_0 = 0 \\
HR[n] = \frac{60}{2\pi} \cdot h(t[n]) \\
t[n] = t[n-1] + \frac{60}{HR[n]} = t[n-1] + \frac{2\pi}{h(t[n-1])} \\
\Delta(t) = \sum_{n=0}^{\infty} \delta(t - t[n])
\]

### 3.4.3 Comparison

Triggering based on the heart wave is expected to be a better triggering method than the triggering based on solely the IHR, even though in [Koc03] is proven that the generated statistics did not differ significantly.
In order to compare both triggering methods, an IBI series was simulated using a base heart rate of 90 BPM, a modulation index of 40 BPM, and a sampling frequency of 500 Hz. First a 30-second sample of the IHR is generated. Based on this sample a trigger signal is determined. The initial estimate of the heart rate is based on the duration to the next interval. By using a low-pass FIR-filter, with a cut-off frequency slightly higher than the maximum single-beat heart rate, an interpolated heart rate signal is determined. The middle 3 seconds of the signals are displayed in the figures.

Two triggering methods are used, one based on the IHR and the other based on the heart wave. For both triggering methods, a 20 oscillations per minute and a 30 oscillations per minute modulating factor is explored. This results in a total of four examples, displayed in Figure 3.9. The top line shows the two examples of triggering based on the IHR. On the right axis, the duration (fixed on the trigger instance) is displayed. The bottom line shows two examples of triggering based on the heart wave, which is shown on the right axis.

These figures show that the IHR is best approached by determining the triggering based on the heart wave. The interpolation based on a trigger signal using the IHR seems to be 'phase-shifted', as can be expected since the heart rate is allocated to the entire heart beat. Furthermore, the estimates degrade more rapidly at higher modulation frequencies than the estimates based on triggering on the heart wave. It is clear that, using the IHR, the estimates are far more sensitive to aliasing.

An investigation of the differences between the two approaches revealed that the produced average heart rate was identical. This is explained by the fact that a random sampling of the IHR, on average produces the averaged IHR. However, the second approach resulted in far more heart rate variability, because more extremely slow and fast heart beats are not averaged out as when using the first approach.

In conclusion, only triggering based on the heart wave is used in this text.

3.5 Generating the Electrocardiogram

The Sino-Atrial node triggers each heartbeat based upon the notion of IHR. This heartbeat and its corresponding electrical wave form are assumed to be invariant: the only input of the ‘heart’ in the model is the trigger. This is not true in reality, yet since data other than the IBIs is discarded, the differences in the ECG morphology are irrelevant.
Figure 3.9: Comparing heart wave and single heart beat triggering

Top: single heart beat based triggering.
Bottom: heart wave based triggering.
Left: low modulation frequency.
Right: high modulation frequency.

In these figures, it can be seen clearly that the heart wave based triggering method is far less susceptible to aliasing effects.
3.5. GENERATING THE ELECTROCARDIOGRAM

The electrical phenomena associated with this process can be described using a dipole model\cite{Win77}, which provides a stylised ECG wave. Noise is added to simulate the inaccuracies that occur in determining the QRS complexes.

Mathematically, the model simply concatenates a template generated by a dipole based model. This is the same as convolution with the single heart beat template (the impulse response) $\ell$. First the noise-free ECG $L$ is determined by convolving the trigger signal heart-trigger sequence $\Delta$ with the single heart beat template (the impulse response) $\ell$:

$$L^*(t) = \{\Delta * \ell\}(t)$$  \hspace{1cm} (3.7)

Then, noise component $v_L$ is superimposed on the output data, in order to model interference by other sources and measurement errors; this results in the ECG $L$:

$$L(t) = L^*(t) + v_L(t) = \{\Delta * \ell\}(t) + v_L(t)$$  \hspace{1cm} (3.8)

For clarification, see Figure 3.10.
3.6 The Entire Signal Model

An overview of the entire model is given in Figure 3.11. The modulation of the heart rate is exaggerated to reveal its effect on the heart wave. The plot with the heart wave shows the trigger based on the IHR. The triggering based on the heart wave would occur at the negative-to-positive zero crossings. No noise is present in this model, thus the instantaneous modulation frequency and the base heart rate are constants.
Figure 3.11: The entire model
3.7 Model Validation

The resulting model was validated in [Koc03]; this section presents a summary of the original validation. It was repeated to verify that the modifications of the model did not introduce errors.

In short, the followed procedure consisted of deriving the model parameters values (all constants and spectra) from available literature, and subsequently running a number of simulations. Comparing the results to data available from the literature yielded that the model is able to reproduce the statistics that were available in the literature.

In the original paper, simulations were run for all possible permutations of the following input signals:

- Respiration rate profiles: low, medium and high respiration rate.
- The base heart rate spectra: a flat spectrum and a spectrum containing two peaks.
- Both triggering methods (directly from the IHR and from the heart wave).
- Convolution and peak detectors for detecting the start of each heart beat.

Furthermore, the modulation index was selected.

The noise on the ECG was exaggerated in order to test the procedure.

First, it was verified that the spectra generated by the modulating factor, the base heart rate and the noise on the ECG matched the designed spectra.

Subsequently, the following statistics of the resulting ECG were compared to data found in the available literature[Me02].

- The mean heart rate.
- The power in the ultra low, very low, low, high spectrum components of the heart rate variability.
- The total power of the heart rate variability.
- The HF/LF ratio.
3.7. **MODEL VALIDATION**

<table>
<thead>
<tr>
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<td>332 739 731</td>
<td>655 570</td>
</tr>
</tbody>
</table>

Table 3.1: Model validation: subset of the resulting statistics.

- The heart rate variability triangular index.

These statistics were determined from only the IBIs, estimated using two different detector methods: a threshold detector and a convolution based detector. Table 3.1 contains a subset of the results. Using the results, the following conclusions were drawn:

- Since neither detection method (threshold or convolution based) resulted in any significant detection error, they had no influence whatsoever in the resulting statistics.

- Neither triggering model, i.e. triggering based on the IHR or on the heart wave, resulted in any significant difference in the resulting statistics.

- The mean heart rate (130 BPM) showed no significant fluctuation.

- Except for the power found in the low frequency range for a peak base heart rate profile in combination with a medium to high respiration rate, all resulting statistics remain within the statistics presented in the available literature.

The anomaly found in the last case can be explained since:

1. The modulation index is not decreased for the higher respiration rates, even though this is logical: if one breathes rapidly, the individual breaths become shallower.
2. The available literature only presents long-term measurements, which results in averaging, and thus smoother spectra.

The results showed clearly that the statistics available in literature were reproduced by the model. This leads to the conclusion that the presented model is suitable to describe at least the statistics found in the literature [Meh02].
Chapter 4

Determining the Characteristics of the Dominant Heart Rate Modulating Factor from the Electrocardiogram

4.1 Introduction

The time-continuous model of heart rate variability in the ECG, which is used in this project, is described in Chapter 3. In this chapter, an extraction procedure to determine the IHR and the characteristics of the (dominant) modulating factor from the ECG, based on that model, is developed.

In order to do so, the 'data flow' from the model is reversed. The IHR is extracted first (Section 4.2). Subsequently the influence of the dominant modulating factor is determined (Section 4.3). Finally, the characteristics of that modulating factor can be determined (Section 4.4). Figure 4.1 depicts this approach.

In Section 4.5 two error estimates are introduced. This chapter concludes with

Figure 4.1: Basic structure for the extraction of the modulation rate
an overview of the entire processing chain in Section 4.6.

Note that the procedure described in this chapter focuses on the model, and on simulated data. The intricacies of recovery IBIs from real-life electrocardiograms (ECGs) are discussed in Chapter 6. For example, there is no (single) template for the ECG corresponding to a single heart beat; using convolution detectors is consequently not trivial.

4.2 Estimating the Instantaneous Heart Rate from the Electrocardiogram

The measured ECG signal is perturbed by noise. This influence of the noise on the signal needs to be suppressed before any further processing is attempted; this pre-processing is described in Section 4.2.1. Subsequently, the IBIs are detected and transformed into a train of trigger pulses (Section 4.2.2). The IHR is reconstructed from this train of trigger in Section 4.2.3. This section ends with an overview of the extraction of the IHR from the ECG in Section 4.2.4.

4.2.1 Pre-Processing the Electrocardiogram

Generally, little or no attention is paid to noise suppression in ECG analysis, because the SNRs are excellent. However, for perinatal monitoring, the available ECG signals have more noise as well as a greater amount of artefacts. As stated before, processing simulated results is the main focus of this chapter; consequently the general methods developed by communication theory can be used.

General communication theory learns that an optimal (maximum a-posteriori probability) detector for a template signal, which is embedded in noise, first employs a process called noise whitening on the input signal. Subsequently, the resulting signal is convolved with the template of the signal that is to be detected. Finally, the final signal is compared with a threshold in order to establish whether the template to be detected is present or not.

Noise whitening consists of emphasising those parts of the signal spectrum that contain little or no noise, and attenuating those parts of the spectrum that contain a lot of noise. The subsequent convolution emphasises the parts of the signal spectrum that are present in the signal template whilst attenuating the parts of the signal spectrum that are not present in the signal template.
4.2. **ESTIMATING THE INSTANTANEOUS HEART RATE**

![Diagram](image)

**Figure 4.2: Preprocessing the ECG to remove the noise**

Note that the known part of the noise spectrum, should be larger than the ‘unknown’ part, i.e. inaccuracies in the noise spectrum should not result in a reversal of the larger and the smaller parts of the noise; otherwise the noise whitening may have a detrimental effect.

Mathematically, this can be described as: the noise component $v_{\mathcal{L}}$ on the ECG $\mathcal{L}$ needs to be whitened, which is accomplished by using the inverted spectrum of the known part of the noise. This corresponds to a convolution with the time-reversed impulse response, the whitening filter whitening filter $v_{\mathcal{L}}^{-1}$. The result is the pre-processed ECG $\hat{\mathcal{L}}$:

$$\hat{\mathcal{L}}(t) = \left\{ \mathcal{L} * v_{\mathcal{L}}^{-1} \right\}(t) \quad \text{[inverts 3.8]}$$

(4.1)

As stated before, this approach is followed for the simulations only. In real-life ECG measurements, the noise spectrum is not known accurately enough, the template that is to be detected is subject to change, and transient artefacts can occur. A transient artefact is an undesired signal component that occurs within the input signal. Examples are 50/60 Hz interference of the mains, DC drift, and electrical interference from other devices.

Consequently, the optimal detector approach cannot be used in real-life situations. In Chapter 6, where the real-life measurements are discussed, the relevant noise filtering and artefact rejection is discussed; Figure 4.2 elucidates the general situation: noise whitening and artefact rejection are required.

### 4.2.2 Determining the Trigger Sequence

Based on the pre-processed ECG, the trigger sequence needs to be determined. The detection of the template of the ECG corresponding to a single heart beat, corresponds to recovering the train of delta pulses. This is accomplished by deconvolving the pre-processed ECG and then using a detector as shown in Figure 4.3. The preprocessed ECG is deconvolved using the template for the ECG. This is accomplished by convolving with the time reversed template. The final signal is passed through a peak detector, which selects the instances
that have maximum likelihood to be the trigger events.

Mathematically, the recovered heart-trigger sequence $\hat{\Delta}$ is determined using a peak detector (PD) on the convolution of the ECG with the time-reversed impulse response $\ell^{-1}$:

$$\hat{\Delta}(t) = \text{PD} \left\{ \hat{\mathcal{L}} \ast \ell^{-1} \right\} \quad \text{[inverts 3.7]}
\tag{4.2}$$

This procedure leads to a time shift, for which the algorithms compensate.

Note that since in vivo no exact single beat ECG is known, a threshold detector, or some more advanced method needs to be done: deconvolving is not possible. In Chapter 6, the pre-processing for real-life data is discussed.

### 4.2.3 Determining the Instantaneous Heart Rate from the Train of Delta Pulses

If one assumes that the triggering is based on the heart wave instead of the IHR, the estimation sequence changes as well. The trigger sequence is interpolated to obtain an estimate of the heart wave. This estimate will have a phase shift since the trigger has delta-pulses on each QRS-complex, whereas the heart wave has a negative-to-positive zero-crossing on the start of a heart beat. Since the heart wave is the a sinusoid with an instantaneous frequency equal to the IHR, the Hilbert transform can be used to obtain an estimate for the IHR. This is shown in Figure 4.4.

The interpolation filter is necessary because of the (almost) white spectrum introduced by the delta-pulses. Through filtering with a small band near the heart rate, the Hilbert transform can be used to obtain the IHR.
4.2. ESTIMATING THE INSTANTANEOUS HEART RATE

Mathematically, the above is formulated as: the recovered heart-trigger sequence $\hat{\Delta}$ is interpolated to obtain the recovered heart wave $\hat{f}$. Subsequently, the noise polluted estimate of the instantaneous heart rate $\hat{h}^*$ is determined by using the Hilbert transform:

$$\hat{f}(t) = \left\{ \hat{\Delta} \ast \text{[interpolation filter]} \right\}(t) \quad \text{[inverts 3.6]} \quad (4.3)$$

$$\hat{h}^*(t) = \mathcal{H}[\hat{f}](t) \quad \text{[inverts 3.5]} \quad (4.4)$$

4.2.4 Signal Processing Chain

The processing chain to estimate the IHR from the ECG is displayed in Figure 4.5.

$$\hat{\Delta}(t) \xrightarrow{\text{interpolation}} \hat{h}^*(t)$$

Figure 4.5: Estimating the instantaneous heart rate
4.3 Determining the Influence of the Dominant Modulating Factor from the Instantaneous Heart Rate

In the previous section, various approaches to determine the IHR from the ECG have been explored. In this section, the influence of the dominant modulating factor on the IHR is determined.

In Chapter 3, the IHR was modelled as the linear superposition of the dominant modulating factor and the base heart rate, i.e. all other influences on the heart rate lumped together. In a 'steady state' situation, the base heart rate is almost constant. Consequently, the base heart rate can be determined, and thus the influence of the dominant modulating factor as well. The influence of a modulating factor is modelled as a modulation index multiplied by a sinusoid with unit amplitude but a varying instantaneous frequency. Inverting this model is possible, and results in an estimate of the instantaneous modulation frequency; from which the mean modulation frequency can be estimated. Figure 4.6 clarifies the situation.

4.3.1 Estimating the Base Heart Rate

As described in Chapter 3, the base heart rate captures all influences on the heart rate except the influence from the dominant modulating factor. This base heart rate is modelled as a constant rate perturbed with coloured noise that describes the heart rate variability spectrum without the influence of the dominant modulating factor. The IHR is also modelled as a linear superposition, namely of the base heart rate and the dominant modulating factor.
4.3. THE INFLUENCE OF THE DOMINANT MODULATION

Consequently, the IHR can be modelled as the linear superposition of three terms: the constant representing the base heart rate, the dominant modulating factor and the noise on the base heart rate.

Inverting this model is simple: an estimate for the base heart rate can be obtained by averaging the noise-whitened version of the IHR; this is displayed in Figure 4.7.

Mathematically, this can be described using the following system of equations. The noise is removed from the noise polluted estimate of the instantaneous heart rate $h^*$ using a whitening filter $v_{\beta}^{-1}$, which has the inverted power spectral density from the noise component $v_\beta$. This results in the IHR-estimate $\hat{h}$:

\[
\hat{h}^*(t) \rightarrow v_{\beta}^{-1} \rightarrow \hat{h}(t) = \{\hat{h}^* * v_{\beta}^{-1}\}(t) \quad \text{[inverts 3.1]} \tag{4.5}
\]

The IHR-estimate $\hat{h}$ is passed through an averaging (low-pass) filter; this results in the estimated base heart rate $(\hat{\beta})$, thus:

\[
\hat{h}(t) \rightarrow \text{AVG} \rightarrow (\hat{\beta})(t) = \{\hat{h} * \text{averaging filter}\}(t) \tag{4.6}
\]

4.3.2 Estimating the Influence of the Modulating Factor

As described earlier, the IHR is the linear superposition of noise, base heart rate and the influence of the dominant modulating factor. The obvious solution to recovering the influence of the dominant modulating factor consists of removing the first two terms from the IHR. The base heart rate has already been determined. However, it is not possible to exactly determine the noise term. Since the estimated influence of the dominant modulating factor is going to be processed, the estimate of the influence of the dominant modulating factor should preferably not contain coloured noise from the base heart rate.
Thus the noise needs to be whitened; this was already done in the previous section. The approach is depicted in Figure 4.8.

Mathematically, this is trivial: simply deducting the estimated base heart rate \( \langle \beta \rangle \) from the IHR-estimate \( \hat{h} \) results in an estimated influence of the dominant modulating factor \( \hat{m} \):

\[
\hat{m}(t) = \hat{h}(t) - \langle \beta \rangle(t) \quad \text{[inverts 3.4]}
\]

\[
(4.7)
\]

### 4.3.3 Overview

Combining the chunks from this section results in Figure 4.9.

Figure 4.9: Estimating the influence of the dominant modulating factor
4.4 THE CHARACTERISTICS OF THE MODULATING FACTOR

Influence by Modulation \[\xrightarrow{\text{Hilbert Transform}}\] Noise Whitening \[\xrightarrow{\text{Average}}\] Modulation Frequency

Figure 4.10: Estimating the mean modulation frequency

4.4 Determining the Characteristics of the Dominant Heart Rate Modulating Factor

The modulating factor is modelled as a modulation index multiplied by a frequency modulated sinusoid. The Hilbert transform essentially inverts frequency modulation, and does not depend on the amplitude of the signal; thus the modulation index does not have to be known. Application of the Hilbert transform to the influence by the dominant modulating factor, results in a continuous estimate of the frequency of the influence of the dominant modulating factor. This signal is modelled as a constant perturbed by noise. The constant can be recovered by first whitening the noise and subsequently averaging the whitened signal. The situation is clarified by Figure 4.10. Mathematically, the following system of equations describes the situation:

Using the Hilbert transform on the estimated influence of the dominant modulating factor \( \hat{m} \) results in the initial estimate of the instantaneous frequency of the dominant modulating factor \( \hat{\alpha}^* \):

\[
\hat{m}(t) \xrightarrow{\mathcal{H}} \hat{\alpha}^*(t)
\]

\[
\hat{\alpha}^*(t) = \mathcal{H}\{\hat{m}\}(t) \quad \text{[inverts 3.3]} \quad (4.8)
\]

Using the whitening filter \( v^{-1}_\alpha \) results in the estimate of the instantaneous frequency of the dominant modulating factor \( \hat{\alpha}^* \):

\[
\hat{\alpha}^*(t) \xrightarrow{v^{-1}_\alpha} \hat{\alpha}(t)
\]

\[
\hat{\alpha}(t) = \left\{ \hat{\alpha}^* * v^{-1}_\alpha \right\}(t) \quad \text{[inverts 3.2]}
\]

\[
(4.9)
\]

After which, short-term averaging (tenth of a heart beat) leads to the estimate of the mean frequency \( \langle \hat{\alpha} \rangle \) of the dominant modulating factor:

\[
\hat{\alpha}(t) \xrightarrow{\text{AVG}} \langle \hat{\alpha} \rangle(t)
\]

\[
\langle \hat{\alpha} \rangle(t) = \{ \hat{\alpha} * \text{averaging} \}(t) \quad \text{[inverts 3.2]}
\]

\[
(4.10)
\]
4.5 Error Estimates

Since the application is crucial, as it involves living beings, it is vital to obtain a measure of reliability. Accurate determination of the influence of the dominant modulating factor, as well as determining the characteristics of that influence, is only possible in a (relatively) steady state of the heart rate. In this section, a concise description of steady state is given first, and subsequently two measures of steady state, and thus of the accuracy of the estimates of the remaining model parameters, are described.

4.5.1 Steady State

In this text, steady state is defined as the condition that the values of the model parameters are constant. In a transitional state, for example during stress or exercise, the changes in the model parameters are too fast for the extraction procedure discussed in this chapter.

Therefore, testing for steady state is possible: the estimation procedure provides continuous estimates of the values of various model parameters. When the variance of these values is below a certain threshold, the measured heart rate is considered to be steady state. The values of the thresholds need to be determined empirically.
4.5. ERROR ESTIMATES

4.5.2 Variance of the Modulation Frequency

The frequency of the dominant modulating factor should be constant, and an upper limit to the superimposed noise power can be assumed. Consequently, the variance of the instantaneous modulation frequency should be related to the power of the superimposed noise. The situation is elucidated by Figure 4.12.

Mathematically, this is expressed as follows: the error estimate $\hat{e}_\alpha$ is the variance of estimate of the instantaneous frequency of the dominant modulating factor $\hat{\alpha}^*$:

$$\hat{e}_\alpha = \text{var}\{\hat{\alpha}(t)\} \quad (4.11)$$

4.5.3 Variance of Influence by the Modulating Factor

The extraction process does not reveal any other possible measures for the error in the estimations. Because the estimate for the base heart rate is directly linked to the estimate of the influence of the dominant modulating factor, the former cannot be used as an independent measure for detection of steady state.

However, careful inspection of the model shows that another constant occurs in the model: the modulation index. This constant has not yet been estimated. It is possible to estimate the influence by the dominant modulating factor excluding the noise factor by creating a frequency modulated sinusoid of the instantaneous modulation frequency. Comparing the power of both signals enables estimating the modulation index. This situation is clarified in Figure 4.13.

Mathematically, the reconstructed influence by the dominant modulating factor $\hat{m}$ is determined from estimate of the instantaneous frequency of the dom-
The estimated modulation index $\hat{\lambda}$ is the ratio between the power in of the influence of the dominant modulating factor and the estimate thereof during a limited time-interval:

$$\hat{\lambda}(t) = \mathcal{A} \sqrt{\frac{\|\hat{m}\|^2(t)}{\|\tilde{m}\|^2(t)}}(t)$$

where $\mathcal{A}$ is an averaging filter [inverts 3.3] (4.13)

By integrating over a smaller interval, this estimate can be made time-dependent. Then, the second error estimate $\hat{e}_\lambda$ is the variance of this estimate:

$$\hat{e}_\lambda(t) = \text{var} \hat{\lambda}(t)$$ (4.14)

4.6 The Entire Processing Chain

An overview of the entire processing chain is presented in Figure 4.14.
Figure 4.14: Overview of the entire extraction chain
THE CHARACTERISTICS OF THE MODULATING FACTOR
Chapter 5

Evaluation with Simulated Data

5.1 Introduction

In Chapter 3, a time-continuous model of the influence of the dominant modulating factor on the heart rate is described. In Chapter 4, a procedure to determine the characteristics of the dominant modulating factor is developed. In this chapter, simulations are run in order to determine whether the extraction procedure is indeed capable of recovering the model parameters from the generated ECG.

The chosen values of the model parameters are discussed in Section 5.2. The details of the (software) implementation are discussed in Section 5.3. In Section 5.4, the various parts of the extraction procedure are evaluated by determining whether or not they are able to recover the parameters or signals of the corresponding model blocks. The following evaluations are carried out:

1. Implementation details: for a limited set of experiments, the required changes in the implementation are verified (evaluating Section 5.3).
2. Recovery of the trigger sequence (evaluating Section 3.5 and 4.2.2).
3. Recovery of the IHR (evaluating Section 3.4 and 4.2.3).
4. Recovery of the base heart rate (evaluating Section 3.3 and 4.3.1).
5. Recovery of the influence of the dominant modulating factor (evaluating Section 3.3 and 4.3.2).
CHAPTER 5. EVALUATION WITH SIMULATED DATA

6. Recovery of the parameters of the dominant modulating factor (evaluating Section 3.3 and 4.4).

Finally, in Section 5.5 the rationale for continuing with real-life data is discussed.

5.2 Parameter Values

In order to evaluate the extraction procedure, a set of model parameters has to be designed that describes important features of real-life data. The following parameters have to be determined:

- The base heart rate.
- The shape and power of the noise on the base heart rate.
- The wave form of the dominant modulating factor.
- The frequency of the dominant modulating factor.
- The shape and power of the noise on the frequency of the dominant modulating factor.
- The modulation index.
- The template for the ECG.

Because the results have to be compared, input SNRs have to be equal for all experiments. Since the value of all heart rate related parameters are scalable by the base heart rate, the base heart rate can be constant as well. The following parameters are fixed for all experiments:

- The base heart rate is 120 BPM.
- The noise on the base heart rate has a power (variance) of 200 BPM$^2$.
- The influence of the dominant modulating factor has a power of 225 BPM$^2$, (and thus determines the modulation index).
- The wave form of the dominant modulating factor is one of the basic five: a constant, a block wave, a triangular wave, an exponential, or a sinusoid. The modulating factor frequency is 15, 30, 40, 60 or 120 BPM.
- The noise on the frequency of the modulating factor has a $1/f$ noise spectrum, and has a total power of $-20$ dB of that frequency.
5.2. PARAMETER VALUES

Four different shapes for the noise on the base heart rate are explored:

1. A $1/f$ noise spectrum that stretches over the entire frequency domain as demonstrated in Figure 5.1\(^1\).

2. A $1/f$ noise spectrum that is limited to 0.05 Hz, as demonstrated in Figure 5.2.

3. A $1/f$ noise spectrum that stretches over the entire frequency domain with a total power of 100 BPM\(^2\) with additive coloured noise. This coloured noise also has a total power of 100 BPM\(^2\), but is limited to 12 BPM. This yields again a total power of 200 BPM\(^2\). The resulting signal and spectrum is demonstrated in Figure 5.3.

4. A $1/f$ noise spectrum that stretches over the entire frequency domain with a total power of 100 BPM\(^2\) with additive white noise, that has a total power of 100 BPM\(^2\) as well. This yields again a total power of 200 BPM\(^2\). The resulting signal and spectrum is demonstrated in Figure 5.4.

As a template for the ECG, the signal depicted in Figure 3.10 is compressed using a 1 : 2 ratio, in order to obtain a valid ECG for the increased heart rates. The noise on the ECG is modelled as a $1/f$ noise (−10 dB) with superimposed white noise (−20 dB). Figure 5.5 displays the spectrum, resulting noise, template and the template with noise.

\(^1\)This figure was already displayed as Figure 3.1, but is repeated to allow for easy comparison.
Figure 5.1: Base heart rate with $1/f$ spectrum.
Top: left the designed, and the realised spectrum; right a 'smoothed' spectrum which allows for better comparison. Bottom: left a sample of the generated signal, right a short segment. This layout is used for the subsequent figures.

The produced spectrum matches the desired spectrum; not withstanding the low noise power, large variations are possible over large periods of time.

Figure 5.2: Base heart rate with limited $1/f$ spectrum.
5.2. PARAMETER VALUES

Figure 5.3: Base heart rate with limited $1/f$ and colour noise spectrum.

Figure 5.4: Base heart rate with limited $1/f$ and white noise spectrum.
Figure 5.5: Noise on the ECG: spectrum, sample and resulting impulse response
5.3 Implementation Details

5.3.1 Coping with Memory and Runtime Limitations

In order to cut down the running time of the different simulations, as well as to cope with memory limitations, the sampling frequency of various time series has been reduced. This is allowed since these series do not have any energy in the higher frequency ranges, i.e. ranges with frequencies larger than 16 Hz or 960 BPM. The sampling frequency of the ECG, 512 or even 1024 Hz is not necessary for these signals.

The sampling frequency of the following signals is only 16 Hz:

- The base heart rate $\beta$.
- The noise component $v_3$.
- The influence of the dominant modulating factor on the heart rate $m$.
- The IHR $h$.
- The estimate of the instantaneous heart rate $\hat{h}$.

The sampling frequency of the following signals is 512 or 1024 Hz, depending on the measured data:

- The heart wave $f$.
- The action-potentials of the Sino-Atrial node $\Delta$.
- The waveform corresponding to a single heart beat $\ell$.
- The electrocardiogram without noise $L^*$.
- The noise component $v_L$.
- The electrocardiogram $L$.
- The noise-whitening filter $v_L^{-1}$.
- Pre-processed electrocardiogram $\hat{L}$.
- The time-reversed electric waveform $\ell^{-1}$.
- The recovered action-potential sequence of the $\hat{\Delta}$.
- The recovered heart wave $\hat{f}$. 
5.3.2 Processing the Signal in Blocks

The noise related signals are generated for $2^{17}$ seconds ($\approx 36$ hours). The derived signals, such as the IHR, are processed in blocks of $2^{10}$ seconds ($\approx 15$ minutes). The analysis of these signals is done using overlapping blocks of $2^7$ seconds; this last number is based on getting at least 200 heart beats. If the algorithm would be applied to adults, using analysis blocks with a length of $2^8$ second is recommended.

All these figures are a power of two for computational purposes: the Fourier transform, which is extensively used, functions optimally when its input signal has a number of samples that is a power of two, in which case the fast Fourier transform is automatically used. For this reason, the sampling frequencies also have to be a power of two.

5.3.3 Pre-processing

The pre-processing, described in Section 4.2.1, has been implemented somewhat differently than described in the original procedure. Instead of an optimal filter, a high pass filter with a cut-off frequency of $\frac{f}{\text{length}(f)}$ has been used. This removes any influences of frequencies that are not used by the detector, but disregards any noise on the relevant frequencies. However, because of the good signal-to-noise ratio (SNR) in this part of the signal, no adverse effects resulted from this simplification. The frequency response of the filter has been included in Figure 5.6.

5.3.4 The Convolution Detector

Because the preprocessing results in a DC free signal, the detector signal (a time-reversed impulse response $\ell^{-1}$), has been corrected for DC as well. A noise free signal, that has been pre-processed, and detected by the convolution detector, results in the signals displayed in Figure 5.7.
5.3. IMPLEMENTATION DETAILS

Figure 5.6: Frequency response of the noise-whitening filter

Figure 5.7: The signals of the convolution detector
On the left, the time-reversed template, used by the convolution detector is displayed. On the right, the ideal output with the threshold value is displayed.
5.3.5 The Interpolation Filters for the Heart Wave

The filter that needs to transform the recovered heart-trigger sequence $\hat{A}(t)$ into IHR-estimate $\hat{h}(t)$ is described in Section 4.2.3. This filter has to limit the pulse train to its base frequencies. This is achieved by the design displayed in Figure 5.8. In this filter, the parameters on the right side depend on the difference between the maximum and the mean heart rate, and the parameters on the left side depend on the difference between the minimum and the mean heart rate. Several filters with varying cut-off filters, slopes and windows, are explored using the following ranges for the design parameters:

- $\alpha$: 0.8 to 4 times the difference between the maximum heart rate and the mean heart rate,
- $\beta$: 0 to 0.5 times the difference between the maximum and the mean heart rate, and
- $\gamma$: 0 to 9 times $\beta$
- Different filter lengths: 1 second to the analysis block size.
- All pre-programmed Matlab windows: Bartlett, Bartlett-Hann, Blackman, Blackman-Harris, Bohman, Chebwin, Flat Top, Gaussian, Hamming, Hann, Kaiser, Nutall, Parzen de la Valle-Poussin, rectangular, triangular and Tucky, and no window. Some of these windows need an additional parameter that also has been varied.
5.4 **Experiments and Results**

5.4.1 **Consequences of the Implementation Details**

The following observations were made:

1. The reduction of the sampling frequency for a limited set of signals, as described in Section 5.3.1, did not result in significant differences in the resulting total error. The experiment to verify this fact was run after all other simulations because the other simulations were necessary to determine various parameters, such as the bandwidth of the interpolation filters. This verification was only conducted for two data sets: the best and the worst result in terms of total error, and varied from 0.6% to 2.3% respectively. Even though only two simulations are used, it is not expected that the reduction of the sampling frequency can have a significant impact on the results. On real-life (i.e. measured) data, this reduction is not necessary since a lower quantity of data is processed.

2. The effects of processing the signal in blocks (the $2^7$ second analysis blocks) were more difficult to evaluate. Experimenting with this block size, showed that when the block size became $2^5$ seconds or less the results deteriorated rapidly. However, increases above $2^7$ seconds results in deterioration as well when the signal contained a lot of power in the higher frequency regions, or when the noise on the base heart rate was high. The algorithm that is used on measured data tries different analysis block sizes and select the size that has the smallest estimated error.

5.4.2 **Recovery of the Trigger Sequence**

Detecting the trigger instances was accomplished by detecting the QRS complexes. Whether the simple peak detector, or the (ideal) convolution detector was used, did not seem to matter: the maximum error was 4 samples / 1024 Hz sampling, which occurs approximately every million wave forms. This small error does not influence the rest of the extraction process, because they are 'smoothed' over by the interpolation process.

Note that the IBI series of the simulated and the recovered signal were compared. For the simulation this does not result in differences, but in reality the time between the QRS complex and the triggering can vary: when the IHR is
recovered, this phase errors occur. This demonstrates that the procedure in Section 4.2.2 is able to invert the model of Section 3.5.

5.4.3 Recovery of the Instantaneous Heart Rate

In Section 5.3.5 the interpolation filter to determine the IHR from the detected trigger sequence was designed. The parameters for this filter were extensively explored (4 base heart rate models, $1 + 6 \cdot 4 = 25$ test signals, 6 filter lengths ($2^3$ to $2^8$, and signal length), and 41 window/parameter combinations, 16 runs each, totalling 393600 experiments), no significant differences in the resulting IHR occurred. That is, except for very wide filters that included too much noise. Finally, this resulted in using a very narrow filter. In some cases the combination seemed to work better, but other runs (with a different random input signal), revealed that this were just good combinations for certain inputs. Furthermore, very odd filters (widths, window parameters) resulted in deterioration.

The best results, resulting in less than 5\% distortion, are documented in Table 5.1. The values show the total amount of distortion power, normalised to the best case scenario, i.e. lower is better. The undisplayed parameters had the following values:

- Base heart rate model: limited $1/f$ spectrum; 120 BPM.
- Test signal: sinusoid. 40 BPM generated 225 BPM² variance on the base heart rate.
- Filter length equal to signal length, i.e. filtering in the frequency domain.
- Window: none.
- Beta: 0.5; note that $\beta$ results in a smoothing of the edges of the filter, an effect comparable to various windowing techniques.

From the table, it is observed that decreasing the total width of the filter ($\alpha + \beta + \gamma$) leads to discarding data of the modulating factor, whereas too wide a filter leads to the inclusion of too much noise.

It should be noted, that if one insists on using a limited filter length, the window type and parameter are almost irrelevant, under the condition that the parameters of the window have reasonable values. The filter length should be at least 64 seconds.
5.4. EXPERIMENTS AND RESULTS

5.4.4 Recovery of the Base Heart Rate

The next step in the extraction process estimated the base heart rate. The lower frequency ranges of this base heart rate were correctly assigned, but the higher frequencies were identified as the dominant modulating factor; this result was expected. The impact of these frequencies is negligible considering their low total power.

5.4.5 Recovery of the Influence of the Dominant Modulating Factor

The difference between the input signal and the estimated base heart rate is filtered to obtain the dominant modulating factor. The recovered instantaneous heart rates (IHRs) deteriorated for the higher frequency regions. The IHR had a SNR of 23 dB for a 45 BPM modulating factor frequency, but this decreased to 16 dB for 60 BPM, and 13 dB for 75 BPM and 10 dB for 90 BPM.

In some cases, when the base heart rate was particularly low, but the modulation was very high, aliasing occurred. Since this aliasing is a result of the sampling of the IHR by the beating of the heart, no solution can be found. What is possible, however, is to expand the spectrum and select only the correct band. This is only possible when the frequency of the original signal is known.

Given a number of conditions on frequency content of the modulation factor (in relation to the base heart rate), the procedure of Section 4.3 was able to invert the model of Section 3.3. These conditions are all related to limiting the maximum frequency of the dominant modulating factor.

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<thead>
<tr>
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Table 5.1: Determining the parameters $\alpha$ and $\beta$ of the interpolation filter
5.4.6 Recovery of the Parameters of the Dominant Modulating Factor

If the IHR was consistent with the original, the parameters of the modulating factor were correctly identified. Unfortunately, it is very simple to differentiate between the test signals, and by forcing the recovered influence of the dominant modulating factor to match one of the available models, parameter identification was accurate. In real-life situations, less strict underlying processes are probable.

The following observations were made:

- The block wave deteriorated most, since it has a lot of power in the high frequency part of the spectrum.
- For high frequencies of the influence of the dominant modulating factor, the dominant modulating factor was often identified as a sinusoid, because of the loss of the higher order harmonics.
- Proper identification of the exponential shape versus the block wave was not always possible.
- Determining the frequency of the dominant modulating factor without taking the detected shapes of the dominant modulating factor into account resulted in errors of up to 5–25%, depending on the frequency content.
- Detection of the frequency of the dominant modulating factor when correctly identifying the shape of the dominant modulating factor resulted in inaccuracies of 3–10%.

5.5 Conclusion

In conclusion, the results of the simulation are sufficiently encouraging to proceed with real data. When the IHR is recovered, the signals lose some of their high frequency components. However, as a result of the varying sampling frequency, the Shannon frequency is no longer an insurmountable limit. The higher the heart rate variability becomes, the higher the frequency that can be recovered (up to a degree) in relation to the Shannon frequency becomes. This effect has to be researched further, but is beyond the scope of this project.
Chapter 6

Evaluating the Algorithm with Measured Data

6.1 Introduction

The results of the simulations, carried out in Chapter 5, are sufficiently promising to start with real-life data. In this chapter, the initial attempt is made at applying the procedure to real-life data that has been collected from neonates.

As a result of the fundamental differences between the simulated and the measured data, some modifications were required for the algorithm; these modifications are discussed in Section 6.2.

As a first validation, it is investigated whether the detected IBIs can be reconstructed from the results of the extraction (Section 6.3). Subsequently, various results of the extraction are described using simple models, usually constants, and the reconstructed IBIs are again compared with the measured data Section 6.4.

Finally, the results of applying the procedure to the ECG are correlated with various signals that were recorded simultaneously. The measured data, i.e. the measured signals and their physical relevance, is discussed in Section 6.5. These signals are correlated with the results of the method in Section 6.6.
6.2 Adapting the Algorithm to Real-Life Data

Several differences exist between the simulated (ideal) data, and the data that can be measured in real subjects. As a result of these differences, the implementation of the algorithm must be modified. In this section, the differences, and their consequences for the implementation, are discussed.

6.2.1 Artefact Rejection

In real-life data, a signal may display patterns that cannot be explained by the underlying physical processes that is measured; these aberrations are known as artefacts. Artefacts can occur as a result of movement, electrical interference, calibration and a number of internal and external influences. These artefacts need to be detected in all three signals; this results in regions that are free of artefacts, and are suitable for analysis.

Several types of artefacts need to be detected, though it is not necessary to identify them:

- Drift: very low frequency noise, which can be removed by cutting of a the very low frequencies of the spectrum (< 2 Hz).
- Movement: can result in displacement of the ECG sensors and in electrical signals that do not correspond to the heart, but are measured nonetheless. Movement can result in electrode disconnect or malfunction, or in the measurement of muscle activity; respiration is often the source of the latter.
- Electrical interference, such as noise resulting from the mains, electrical instruments and particularly from mobile phones.

Artefact detection and rejection has been kept straightforward, with an emphasis on artefact detection, rather than on keeping as much of the data as possible.

This has been implemented by verifying the following criteria:

- The maximum time difference between two QRS complexes, in order to detect the complete loss of a signal.
6.2. ADAPTING THE ALGORITHM TO REAL-LIFE DATA

The minimum time difference between two QRS complexes, in order to detect special circumstances or erroneous data.

The maximum difference between successive IBIs, in order to detect dubious or non-stationary data.

The minimum and maximum width of the QRS complexes, in order to detect whether a real QRS complex or a glitch has been detected.

Note that the actual values for these parameters are determined in the next section.

The period around each detected artefact is removed; human operators have the possibility to review the detected artefacts. The reason for which an artefact has been marked is displayed for visual verification; an example can be found in Figure 6.1.
6.2.2 Inter-Beat-Interval Detector

The IBI detector has been implemented as a QRS complex detector. Because measured data has more parameters than the simulations, a more careful method for detecting the QRS complexes is needed. The following procedure, depicted in Figure 6.2, is used:

1. The low-frequency components (< 2 Hz) are removed to compensate for drift and low-frequency effects.

2. Then a first-order estimate of the QRS complexes is generated by the following algorithm:

   (a) A threshold detector determines possible QRS complexes.
   (b) Initial artefacts rejection using the preceding criteria (Section 6.2.1). A strict selection is necessary because the templates for the convolution detectors have to be of the best achievable quality. The parameters used for the artefact detection are listed in Table 6.1.
   (c) The viable QRS complexes are grouped based on their time difference between the previous and the next detected QRS complex. Subsequently, the groups are averaged to obtain a template for each length of the heart beat, in steps of 10 ms and having least 50 QRS complexes. Half of the heart beat length is used, 1/3 of that length is allocated after the QRS top.

3. Multiple convolution detectors are used to detect the candidate QRS complexes. The resulting IBI series are combined to a single series (using the result of the detector that has a template length that best matches the length of each individual heart beat).
6.2. ADAPTING THE ALGORITHM TO REAL-LIFE DATA

<table>
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<tr>
<td>QRS-width</td>
<td>ms</td>
<td>10</td>
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</table>

Table 6.1: Artefact rejection

Convolution detector templates for different lengths of a heart beat

Figure 6.3: Templates for the convolution detector

Note: numbers represent signal indices

4. On the resulting IBIs the second artefact detection is used to reject the real artefacts, now again using the criteria of Section 6.2.1. Thus, the artefact detection is somewhat less strict; the parameters are again listed in Table 6.1.

The use of multiple templates (for the different lengths of heart beats) is necessary because real ECGs do not have a constant template that is repeated over and over again: an important parameter that seems to determine the shape (especially length) of the signal is the heart rate

These estimates are used to create several templates, as demonstrated by Figure 6.3 that are used by the multiple convolution detectors in order to detect the QRS complex. This has resulted in a significant improvement (in comparison with a simple peak detector or with a single convolution detector), especially during episodes of signal drift, expanding the useable data area.
6.2.3 Instantaneous Heart Rate Estimation

From the series of IBIs, the IHR has to be recovered. The cut-off frequencies of the interpolation filter is related to the minimum and maximum IBI of the series. The procedure is depicted in Figure 6.4.

A bandfilter with cut-off frequency at twice the difference between the minimum and median IBI, and thrice the difference between the maximum and median IBI, and a Blackman-Harris window, sliced over 128 seconds, using the middle 4 seconds was used to calculate to estimate the heart wave. The latter signal was fed into the Hilbert transform in 256 second chunks. If insufficient data was available for the latter, the first and last IBIs are repeated.

6.2.4 Determining the Length of an Analysis Block

The Hilbert transform, that is required for determining the instantaneous frequency, becomes more accurate given a longer length of the input signal. However, the IHR, that is used as input signal, is non-stationary when measured over longer periods of time. To cope with these conflicting interests, the algorithm has been modified to test which length suits each section of the ECG signal best. As a measurement for optimisation, the error estimate based on the variance of the instantaneous frequency of the dominant modulating factor is used. This situation is depicted in Figure 6.5.

6.3 Reproducing the Inter-Beat-Intervals

The first verification of the algorithm consists of trying to reproduce the initial IBIs. This is accomplished by feeding the results of the algorithm into the model, and subsequently comparing the generated and the measured IBIs.
6.3. REPRODUCING THE INTER-BEAT-INTERVALS

Two implementations of this verification are feasible:

1. Reproduction based on the estimated influence of the dominant modulating factor $\hat{m}$. In this verification, the estimated base heart rate $\langle \hat{\beta} \rangle$ and the estimated influence of the dominant modulating factor $\hat{m}$ are added to reconstruct the IHR-estimate $\hat{h}$. Figure 6.6 demonstrates the setup.

Figure 6.5: Adaptive control of the length of an analysis block

Figure 6.6: First reconstruction of the instantaneous heart rate
2. Reproduction based on the estimate of the instantaneous frequency of the dominant modulating factor $\hat{\alpha}$ and the estimated modulation index $\hat{\lambda}$. In this verification, $\hat{\alpha}(t)$ and $\hat{\lambda}(t)$ are used to reconstruct estimated influence of the dominant modulating factor $\hat{m}$. Subsequently, $(\hat{\beta})(t)$ and $\hat{m}(t)$ are added to reconstruct $\hat{h}(t)$. Figure 6.7 clarifies the setup.

Both reconstructions are able to regenerate the measured data almost perfectly, since no data is discarded. A time-shift was introduced but this could be manually corrected by discarding the first few samples of the reconstructed signal.

The differences could be easily explained by calculation errors, less than a 0.1% of the original signal for the $\hat{m}(t)$ and less than 0.01% of the IBIs. This proves that the algorithm works and is capable of splitting the input data without losing any information. The next section will contain a figure displaying visual confirmation of these results.
6.4 Reproducing Measured Inter-Beat-Intervals from Limited Data

In the previous section, it was determined that the results of the algorithm are sufficient to reconstruct the measured IBIs. By gradually decreasing the amount of information that is used to reconstruct the IBIs, the applicability of the method developed in this text is further evaluated.

First, various parameters derived from the ECG signal are replaced by their averages (either long-term or of shorter periods); subsequently these parameters are described using simple wave forms.

6.4.1 Reproduction using Averaged Data

This leads to the following experiments and results:

1. Reconstruction using \( \langle \beta \rangle(t) \) and \( \hat{m}(t) \). This reconstruction is the first reconstruction (as discussed in the previous section) and is perfect.

2. Reconstruction using \( \langle \hat{\beta} \rangle \) and \( \hat{m}(t) \). This reconstruction was not useful as expected: the strong low-frequency components have been removed from the signal, and were averaged.

3. Reconstruction using \( \langle \hat{\beta} \rangle(t) \) and \( \bar{m}(t) \) is meaningless since the modulating factor is averaged. In Section 6.4.2, the modulating factor is described by using simple template functions.

4. Reconstruction using \( \langle \hat{\beta} \rangle(t) \), \( \hat{h}(t) \) and \( \hat{\lambda}(t) \). This reconstruction is the second reconstruction discussed in the previous section, and is perfect.

5. Reconstruction using \( \langle \hat{\beta} \rangle \), \( \hat{h}(t) \) and \( \hat{\lambda}(t) \). This reconstruction is unable to produce meaningful results, for the same reason as for case 2.

6. Reconstruction using \( \langle \hat{\beta} \rangle(t) \), \( \bar{h} \) and \( \bar{\lambda} \). This reconstruction proved to be somewhat better than for case 5. The better part of the information is discarded though; in Section 6.4.2 this factor is described using templates.

7. Reconstruction using \( \langle \hat{\beta} \rangle(t) \), \( \hat{h}(t) \) and \( \bar{\lambda} \). This reconstruction is again an improvement, but discarding the amplitude information still discards some relevant information. Fortunately, in more stationary data, the relevance of this information is limited.
8. Reconstruction using $(\beta(t), \bar{h}(t))$ and $\bar{\lambda}$. This reconstruction is meaningless, since the modulating factor is averaged. Again, in Section 6.4.2 these parameters are described using templates.

In conclusion, it is not possible to replace any of the immediate outputs of the procedure by a simple average. An exception to the rule is $\bar{\lambda}$ in the case of very stationary signals.

Figure 6.8 illustrates the preceding findings. From top to bottom, the graphs contain:

- The instantaneous heart rate. From the IHR, the original trigger sequences are reconstructed without any error.

- The base heart rate. As can be seen, the base heart rate has a large amount of power. In the left part of the signal, it seems that a simple sinusoid would be able to capture its behaviour. The right side shows that this is not the case. For a more stable heart rate it might be possible to use a simple model.

- The influence of the modulating index, has a lesser amount of power but contains many more frequencies, and consequently is even less predictable.

- The error with the reconstructed IHR, is displayed in the bottom graph. It is almost identical to zero.

The signal used in the figure was selected because it is more or less a typical situation. In some instances, during short periods, under two minutes, patterns that could be replaced by a simple model were displayed. It should be noted that whenever the influence by the dominant modulating factor could be described by a simple model, the same was true for the base heart rate.

6.4.2 Reproduction using Descriptive Templates

In this section, it is investigated whether it is possible to describe the influence by the modulation factor using one of the following elementary test signals: a block, triangular, exponential or sinusoidal wave.

Each of these wave forms is characterised using only two parameters: period [seconds] and amplitude. Each test was made both for a fixed and for a varying
Figure 6.8: Reconstructed instantaneous heart rate
Figure 6.9: Correlation between the sinusoidal model and the measured IHR base heart rate. However, as expected from the results of the previous section the tests with a fixed base heart rate proved useless because of the rather large variance of the base heart rate.

Simultaneous description of \( \dot{\lambda} \) and \( \dot{h} \) produced meager results, possibly as a result of their interaction when they are generated.

In all cases, reconstructions based on either the block or triangular wave were inferior to reconstructions based on the exponential and the sinusoidal wave.

The best result was obtained using a sinusoidal phase, in a stationary patient, resulting in the differences depicted in Figure 6.9. Note the scale, the maximum aberration is 6 ms in the instantaneous rate, which is compensated for by the two adjacent peaks that are below zero; the nominal rate is about 450 ms for this patient; thus the maximum error is 1%. Unfortunately this is not a typical result: errors of up to 20% can occur.

### 6.5 Interpreting the Measured Data

The measured data has been made available by Andriessen from the Máxima Medical Centre. The data consists out of the following signals:
6.5. INTERPRETING THE MEASURED DATA

A single lead of the ECG which serves as the input for the algorithm.

The blood pressure which results primarily from the beating of the heart. However, it also influences the heart rate through the baroreflex. Therefore, it contains information about the beating of the heart.

The thorax impedance is the electrical resistance across the thorax, and is related to the volume of the thorax, and thus through the lung volume to the amount of air in the lungs. Therefore, airflow, frequency and other information about the respiratory system can be derived from this signal.

Based on these signals, the following derived signals have been constructed:

Averages of the blood pressure over various amounts of time might reflect part of the time-delay and influence of the baroreflex.

The first derivative of the blood pressure might reflect some response of the overall system to various factors, and is included just for testing.

The first derivative of the thorax impedance reflects the changes in thorax (and lung) volume, and thus, reflects breathing movements. Unfortunately, this signal is related to breathing in a non-linear fashion, and its linearising is beyond the scope of this document.

The second derivative of the thorax impedance reflects when a subject starts to reverse the airflows (stops or starts inhaling or exhaling), and may still be correlated to the results of the procedure.

The integral of the positive edges of the first derivative of the thorax impedance is related to the inflow of fresh air, and may also be correlated to the results.

If a sufficient correlation between the results of the method, i.e. the Hilbert transform based instantaneous frequency transform of the IHR with any of the above signals is found, the algorithm is demonstrated to be capable of extracting the dominant modulating factor of the heart rate. Unfortunately, such a definite result seems unlikely. Figure 6.10 contains some of the measured signals. Note that the heart rate and the thorax impedance are related, and that the blood pressure peaks shortly after the trigger pulses.
CHAPTER 6. EVALUATION WITH MEASURED DATA

Figure 6.10: The measured signals
6.6 Correlation with Auxiliary Signals

In this section, the signals generated by the algorithm are correlated with the auxiliary signals described in the previous section. In order to eliminate unknown time delays, all correlations will be calculated for time shift ranging from minus to plus 5 seconds.

Unfortunately, these correlations proved only useful for samples of up to 1 minute. Figure 6.11 is an example of such a good period.
CHAPTER 6. EVALUATION WITH MEASURED DATA
Chapter 7

Discussion, Conclusions and Recommendations

7.1 Discussion

7.1.1 Extracting Modulating Factors from Inter-Beat-Intervals

As described in Chapter 1, it is expected that neonatal cardiovascular and autonomic state is reflected in the IBIs. These IBIs represent a sampled version of what is called the IHR. The latter signal is the superposition of all factors that influence (i.e. modulate) the heart rate. These factors partially reflect the autonomic state, and to a larger degree the cardiovascular state. The state of various (sub)systems that comprise the cardiovascular and autonomic nervous systems will be reflected in their correlating modulating factors. An example of a system that often is the dominant modulating factor of the heart rate is the respiration system.

7.1.2 Traditional Approaches

The traditional approaches, described in Chapter 2, for extracting information from the IBIs—and from the ECG—are discrete, regularly sampled series based methods. Most of these approaches have been designed and/or tested only for adults, even when this has not been explicitly stated. Many approaches even ignore the fact that the signal is a sequence of durations, and try to
determine a relation between one beat and the next, regardless of the time that elapses. It is unlikely that a time-continuous system can be described by a highly irregular sampled time series without taking its time-dependency into account. Having made this observation, it is necessary to note that these approaches often yield good results when applied to adults, because in most cases the heart rate will be stable enough to make these assumptions.

In strong contrast with adults, the respiratory rates of neonates often exceed the Shannon frequency determined by the heart rate, i.e. the respiration rate is often of the same order as the heart rate, instead of only at about a quarter of the heart rate as is common for adults.

7.1.3 Time-continuous Approach

The traditional approaches often are inadequate or produce inaccurate results. Therefore a novel approach is explored, using a so-called IHR. This approach was developed using a model (see Chapter 3) for the ECG based on this IHR. The original model was designed for a heart rate modulated by the respiratory system; it was generalised to model to use any single dominant modulating factor, and any number of less influential modulating factors, lumped together in the so-called base heart rate.

In Chapter 4, the IHR is reconstructed from the IBIs by using a Hilbert transform based instantaneous frequency analysis. Subsequently, the dominant modulating factor is reconstructed using this Hilbert transform based instantaneous frequency analysis again. It is important to note that the Hilbert transform can only be used to extract a meaningful instantaneous frequency if it is used on a single component signal. Otherwise it results in a geometric averaged frequency\cite{Coh95, Boa92a, Boa92b, Boa92c}. It is possible to generate simulation signals that fit this constraint, but in measured signals this is often not the case. The ECG and the IHR are multi-component signals, therefore a pre-selection is required in the future.

The approach yields the base heart rate, the influence of the dominant modulating factor and the frequency and amplitude components of the the dominant modulating factor. The latter components are often more easily described than the influence itself. Furthermore, the approach returns two performance measures: the variance of the frequency of the influence of the dominant modulating factor and the variance of the modulation index. The first measure is only meaningful when the dominant modulating factor consists of a single component.
7.2. CONCLUSIONS

The results of applying the extraction procedure to simulated or measured data (Section 5 and 6, respectively) already have been discussed in their respective chapters.

An evaluation of the results of these chapters shows that as long as the IHR is a single-component signal, the procedure is applicable. However, in vivo this is often not the case.

7.2 Conclusions

Based on the research and the obtained results, the following conclusions are drawn:

1. The state of the cardiovascular and autonomic nervous systems is reflected in their modulating influence on the heart rate. The IBIs of this heart rate can therefore be used as an input signal for an algorithm that tries to extract this information.

2. A time-continuous description needs to be used as a result of the greater steady-state variations of the heart rate in foetuses and neonates than in adults.

3. A time-continuous description of the heart rate is required. This IHR can be reconstructed by determining the so-called trigger sequences, filtering that sequence and determine its instantaneous frequency. The intermediate frequency always meets the requirements of the Hilbert transform.

4. Simulation has demonstrated that when signals meet the requirements of the Hilbert transform based instantaneous frequency analysis, they can be reconstructed. When they have a sufficient amount of variability, it is even possible to exceed the Shannon frequency as indicated by the heart rate.

5. The IHR can be reconstructed from the IBIs, even when its frequency content exceeds the bounds indicated by the Shannon frequency of the heart rate, as a result of the irregular sampling of the IBIs. With an increasing heart rate variability, i.e. total variance of the heart rate, the IHR can be reconstructed up to a higher frequency than the Shannon frequency of the heart rate would suggest.

6. As already noted in the discussion, when the Hilbert transform is applied to multi-component signals, an averaged frequency is returned, obscuring the differences between different modulating factors. This results in
a decreased applicability to in vivo signals, since they often consist of multiple dominantly modulating factors.

7.3 Recommendations

Based on the research and the results that were obtained, the following recommendations are made:

1. A time-continuous description might yield increased performance of the traditional approaches for adults as well. The applicability and performance increase of using the approach for adults needs to be explored.

2. The IHR that was defined as the superposition of all modulating factors, might correspond to some physical entity. A possible candidate might be the net permeability of the Sino-Atrial node. Finding a correlation between the theoretical signal and a physical phenomenon will:

   (a) increase the acceptance of to the method, boosting research in this area.

   (b) will provide a better model for the superposition of modulating factors than the current (linear) one, and

   (c) will indicate possible modulating factors and possible models for these factors.

3. The IHR can be reconstructed to frequencies above the Shannon frequency of the IBIs, because the IBIs are an inherently irregular sampled process. A mathematically sound description of the influence of this irregular sampling still needs to be established. This description is necessary in order to gain a better understanding of when and within what limits this reconstruction above the Shannon frequency is possible.

4. Since the Hilbert transform based instantaneous frequency analysis is only suitable for signals that have a single dominant modulating factor—at least when one wants to extract the frequency of a dominant modulating factor— the approach is limited to extracting single modulating factor that have a limited frequency component. Better methods for determining when a heart rate does not meet this requirement need to be found:
7.3. RECOMMENDATIONS

(a) An instantaneous frequency analysis method needs to be developed that is able to cope with multiple components, or broad spectrum modulating factors.

(b) Another possibility of tackling this problem might consist of first extracting a single component (by filtering out all other components), determining its modulating factor, and subsequently removing the influence of the modulating factor from the original signal. This allows for a reiterative approach. Exploring this option was beyond the scope of this report.

5. This method may be used for enhancing the available models, or for designing new models for the heart rate regulation. New or enhanced models may be used to further increase the range of applicability of the method, by adding the possibility of extracting specific modulating factors and by adding the possibility of removing the influence of specific modulating factors.

6. Models for the cardiac output and for the Sino-Atrial node may be able to explain some of the encountered non-linearities. Other fields that need to be researched include physical models for the sympathovagal balance, the physical influence of respiration and the baroreflex.

7. Many processes, such as stress, —as well as other factors that are difficult to control— have a substantial influence on the heart rate. Furthermore, the influence on the heart rate has a rather arbitrary nature, and is difficult to model. Therefore, these influences have to be avoided; unfortunately is the consequence hereof, that stressful circumstances decrease the applicability of the method during stress, and thus during the hours preceding and succeeding delivery. Further modelling may be able to circumvent these problems.
7. DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS
## Appendix A

### List of Symbols

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<thead>
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<th>Symbol</th>
<th>Description</th>
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<td>The instantaneous frequency of a modulating factor</td>
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<td>The initial estimate of the instantaneous frequency</td>
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</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
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<tr>
<td>( f )</td>
<td>The heart wave</td>
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</tr>
<tr>
<td>( \hat{f} )</td>
<td>The recovered heart wave</td>
<td>43</td>
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<tr>
<td>( \Delta )</td>
<td>The action-potentials of the Sino-Atrial node</td>
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<tr>
<td>( \hat{\Delta} )</td>
<td>The recovered action-potential sequence of the</td>
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<tr>
<td>( \ell )</td>
<td>The waveform corresponding to a single heart beat</td>
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<td>( \ell^{-1} )</td>
<td>The time-reversed electric waveform</td>
<td>42</td>
</tr>
<tr>
<td>( \mathcal{L} )</td>
<td>The electrocardiogram</td>
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<td>( \mathcal{L}^* )</td>
<td>The electrocardiogram without noise</td>
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<td>( v_c )</td>
<td>The noise component</td>
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<td>( v_c^{-1} )</td>
<td>The noise-whitening filter</td>
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Appendix B

List of Notations

\[ j \] Imaginary part of a complex number: \( j^2 = -1 \)
\[ \mathbb{C} \] The domain of all complex numbers
\[ \Re\{c\} \] The real part of a complex number \( c \in \mathbb{C} \)
\[ \mathcal{H}\{s\}(t) \] The analytic signal of \( s(t) \)
\[ \mathbb{E}\{s\} \] The energy of \( s(t) \)
Appendix C

List of Equations

\[ \beta(t) = \langle \beta \rangle + v_\beta(t) \]  \hspace{1cm} (3.1) [27]

\[ \alpha(t) = \langle \alpha \rangle + v_\alpha(t) \]  \hspace{1cm} (3.2) [27]

\[ m(t) \triangleq \lambda \cdot \Re \left\{ \exp \left[ j \int_0^t \alpha(\tau) d\tau \right] \right\} \]  \hspace{1cm} (3.3) [27]

\[ h(t) = \beta(t) + m(t) \]  \hspace{1cm} (3.4) [28]

\[ f(t) \triangleq \Re \left\{ \exp \left[ j \int_0^t h(\tau) \right] 2 d\tau \right\} \]  \hspace{1cm} (3.5) [29]

\[ \Delta(t) = \sum_{n=0}^{\infty} \delta(t - t[n]), \quad f(t[n]) = 0 \quad \& \quad f'(t[n]) > 0 \]  \hspace{1cm} (3.6) [30]

\[ \mathcal{L}^*(t) = \{ \Delta * \ell \}(t) \]  \hspace{1cm} (3.7) [33]

\[ \mathcal{L}(t) = \mathcal{L}^*(t) + v_\mathcal{L}(t) = \{ \Delta * \ell \}(t) + v_\mathcal{L}(t) \]  \hspace{1cm} (3.8) [33]
\[ \dot{\mathcal{L}}(t) = \left\{ \mathcal{L} \ast v_c^{-1} \right\}(t) \]  
\hspace*{1cm} (4.1) [41]  
\hspace*{1cm} (rev.3.8) [33]

\[ \hat{\Delta}(t) = \text{PD} \left\{ \hat{\Delta} \ast \ell^{-1} \right\} \]  
\hspace*{1cm} (4.2) [42]  
\hspace*{1cm} (rev.3.7) [33]

\[ \tilde{f}(t) = \left\{ \hat{\Delta} \ast \text{[interpolation filter]} \right\}(t) \]  
\hspace*{1cm} (4.3) [43]  
\hspace*{1cm} (rev.3.6) [30]

\[ \hat{h}^*(t) = \mathcal{H}[\tilde{f}](t) \]  
\hspace*{1cm} (4.4) [43]  
\hspace*{1cm} (rev.3.5) [29]

\[ \hat{h}(t) = \left\{ \hat{h}^* \ast v_\delta^{-1} \right\}(t) \]  
\hspace*{1cm} (4.5) [45]  
\hspace*{1cm} (rev.3.1) [27]

\[ \langle \dot{\beta} \rangle(t) = \left\{ \hat{h} \ast \text{averaging filter} \right\}(t) \]  
\hspace*{1cm} (4.6) [45]

\[ \dot{m}(t) = \dot{h}(t) - \langle \dot{\beta} \rangle(t) \]  
\hspace*{1cm} (4.7) [46]  
\hspace*{1cm} (rev.3.4) [28]

\[ \hat{\alpha}^*(t) = \mathcal{H}\{\hat{m}\}(t) \]  
\hspace*{1cm} (4.8) [47]  
\hspace*{1cm} (rev.3.3) [27]

\[ \hat{\alpha}(t) = \left\{ \hat{\alpha}^* \ast v_\alpha^{-1} \right\}(t) \]  
\hspace*{1cm} (4.9) [47]  
\hspace*{1cm} (rev.3.2) [27]

\[ \langle \alpha \rangle(t) = \{ \hat{\alpha} \ast \text{averaging} \}(t) \]  
\hspace*{1cm} (4.10) [47]  
\hspace*{1cm} (rev.3.2) [27]

\[ \hat{e}_\alpha = \text{var} \{ \hat{\alpha}(t) \} \]  
\hspace*{1cm} (4.11) [49]

\[ \bar{m}(t) = \mathfrak{R} \left\{ \exp \left[ j \int_0^t \hat{\alpha}(\tau) \, d\tau \right] \right\} \]  
\hspace*{1cm} (4.12) [50]

\[ \hat{\lambda}(t) = \left\{ \mathcal{A} \ast \sqrt{\|\bar{m}\|^2(t)} \right\}(t) \]  
\hspace*{1cm} where \( \mathcal{A} \) is an averaging filter
\hspace*{1cm} (4.13) [50]  
\hspace*{1cm} (rev.3.3) [27]

\[ \hat{e}_\lambda(t) = \text{var} \hat{\lambda}(t) \]  
\hspace*{1cm} (4.14) [50]
Appendix D

List of Abbreviations

BPM  beats per minute
ECG  electrocardiogram
ECGs electrocardiograms
IBI  inter-beat-interval
IBIs  inter-beat-intervals
IHR  instantaneous heart rate
IHRs instantaneous heart rates
SNR  signal-to-noise ratio
SNRs signal-to-noise ratios
Appendix E

Glossary

**Autonomic Nervous System** the part of the *nervous system* of vertebrates that controls involuntary actions of the smooth muscles and heart and glands.

**Cardio-Vascular System** (the circulatory system): the organs and tissues involved in circulating blood and lymph through the body, thereby providing blood, nutrients and other substances to all organs.

**Cell** the basic structural and functional unit of all organisms.

**Depolarisation** the loss of polarisation (see *polarisation*).

**ECG** see *Electrocardiogram*.

**Electrocardiogram** a graphical recording of the electric waveform reflecting the polarisation and depolarisation of the heart during the cardiac cycle.

**Instantaneous Heart Rate** the heart rate that would result from the influence of the all heart rate regulating mechanisms at a specific point in time.

**Inter-Beat-Interval** the time interval between two successive heart beats.

**Neonate** newly born baby.

**Nervous System** the sensory and control apparatus consisting of a network of nerve *cells*.

**Organ** a fully differentiated structural and functional unit in an animal that is specialised for some particular function.

**Polarisation** having or giving polarity; medically often used to indicate the lower (electric) potential within the boundaries of cell as opposed to the interstitial potential.
**Repolarisation** the reestablishment of the standard polarisation.

**Nyquist Frequency** see Shannon Frequency

**Shannon Frequency** (also known as Nyquist Frequency).

Note: some of these glossary terms have been copied from WordNet©2003 (see http://www.dict.org).
Bibliography


