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Methods for the analysis of short-term variability of heart rate and blood pressure in frequency domain

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VTT Information Technology

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Abstract

Cardiovascular variability signals provide information about the functioning of the autonomous nervous system and other physiological sub-systems. Because of large inter- and intra-subject variability, sophisticated data analysis methods are needed to gain this information. An important approach for analysing signals is the analysis in the frequency domain.

In this thesis, spectral analysis of cardiovascular variability signals was addressed by two different approaches. The first approach was based on univariate spectral analysis. The novelty of the approach is the quantification of the shift in spectral power *within a frequency band*. Three different estimators for the spectral shift were compared. The band-wise mean and median frequencies were found to provide better performance than the parameter used in earlier studies, namely central frequency. The band-wise median frequency was successfully applied to real clinical data.

In the other approach multivariate closed-loop analysis of the cardiovascular system was studied. A framework based on linear time series modelling and spectral decomposition was presented. The application of multivariate autoregressive (MAR) modelling on real cardiovascular data was addressed in detail, and a method for overcoming the problem of correlating noise sources in MAR modelling was applied successfully. A non-causal model for controlling the effect of respiration on cardiovascular system was proposed. Practical considerations of applying multivariate linear time series modelling to real cardiovascular data were discussed. Methods were demonstrated using real data.

One day an extremely bad hangover woke Fiodor up in the middle of the night. He was terribly thirsty. Without putting on the light he went into the kitchen, felt a bottle on the shelf and started to drink. Having gulped the very first mouthful he realised he had made a mistake - it wasn't water in the bottle, as he had thought, but kerosene.
Fiodor however had mastered Zen so well that he found the courage not to correct the mistake, and calmly drank up the whole contents.

Vladimir Shinkarev:" Maxim and Fiodor"
(translated by Tatjana Puskelmann)

Preface

This work was carried out in the Multimedia research area of VTT Information Technology during the years 1994 - 1997 and in the Department of Clinical Physiology, Tampere University Hospital, during the years 1992 - 1994.

I wish to express my gratitude to Professor Väinö Turjanmaa, the *primus motor* behind a great deal of the work presented in this thesis, for continuous support and inspiration during the thesis. I sincerely want to thank Dr Hannu Nieminen, my advisor in my thesis work, who played an important part especially at the initiation phase of the work. I also want to thank Professor Niilo Saranummi for encouragement and support during the different phases of the work, and Dr Seppo Kalli for introducing the topic of the thesis to me. I also wish to thank Professor Arto Uusitalo, the leader of the Blood Pressure research group in Tampere, for support throughout the work.

I wish to thank Dr Risto Suoranta for his invaluable criticism, and Professor Philip Saul for his precious comments during the preparation of this thesis. This criticism enhanced the thesis considerably.

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I owe my thanks to all the members of the Blood Pressure research group in Tampere. Especially I wish to thank Dr Martti Tuomisto, Dr Silja Majahalme, Mrs Pirjo Järventausta and Mr Matti Sydänmaa, MSc. I wish to thank Dr Luca Mainardi and Dr Guy Carrault for their co-authoring of two of the publications. I would also like to express my gratitude to Mr Seppo Haataja, MSc, Dr Jari Viitanen, Mr Jukka Perälä, MSc, Dr Mark van Gils and all the present and former employees in the VTT Information Technology Tampere group for an inspiring atmosphere and pleasant collaboration during these years. I am grateful also to Dr Christophe Vermeiren, who provided invaluable

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Tampere, May 1997

Ilkka Korhonen

Contents

List of publications

This dissertation is based on the following five publications referred to by roman numerals (I - V) in the text:

I. Takalo R., Korhonen I., Turjanmaa V., Majahalme S., Tuomisto M., Uusitalo A. 1997. Frequency shift in baroregulatory oscillation in borderline hypertensive subjects. *Am J Hypertension*, 10(5):500-504.

II. Korhonen I., Mainardi L., Loula P., Carrault G., Baselli G., Bianchi A. 1996. Linear multivariate models for physiological signal analysis: theory. *Comp Meth Progr Biomed* 51:85-94.

III. Korhonen I., Mainardi L., Carrault G., Baselli G., Bianchi A., Loula P. 1996. Linear multivariate models for physiological signal analysis: applications. *Comp Meth Progr Biomed*, 51:121-130.

IV. Korhonen I., Takalo R., Turjanmaa V. 1996. Multivariate autoregressive model with immediate transfer paths for assessment of interactions between cardio-pulmonary variability signals. *Med Biol Eng Comp*, 34:199-206.

V. Korhonen I. Multivariate closed-loop model with non-causal respiratory input for the analysis of cardiovascular dynamics. *Meth Inform Med* (in press).

List of symbols and abbreviations

AIC	Akaike Information Criterion
ANOVA	Analysis of variance
ANS	autonomous nervous system
AR	autoregressive
ARMA	autoregressive moving average
BHT	borderline hypertensive
BP	blood pressure
CO	cardiac output
DBP	diastolic blood pressure
ECG	electrocardiography
f	frequency
f_s	sampling frequency
f_C	central frequency
f_{MEAN}	mean frequency
f_{MED}	median frequency
f_{MOD}	mode frequency
FFT	fast Fourier transform
$\boldsymbol{H}_{x:y}$	transfer function from variable y to variable x
HF	high frequency
HR	heart rate
HT	hypertensive
$\boldsymbol{I}$	identity matrix
ILV	instantaneous lung volume
L	number of variables
LF	low frequency
M_X	order of matrix polynome $\boldsymbol{X}(q)$
MAR	multivariate autoregressive
MARXAR	multivariate autoregressive with autoregressive exogenous input
N	data length, in samples
NN	normal-to-normal R-waves; time interval between two successive normal R-waves in electrocardiograph
NSC	noise source contribution
NSCR	noise source contribution ratio
NT	normotensive
PSD	power spectral density

q	unit delay operator
RMSSD	root mean squared difference between successive normal-to-normal intervals
RR	time interval between two successive R-waves in electrocardiograph
RRI	RR-interval time series
$S(f)$, $S(\omega)$	power spectrum
SBP	systolic blood pressure
SD	standard deviation
SDNN	standard deviation of the normal-to-normal interval series
SV	stroke volume
t	time index
$^{\mathrm{T}}$	matrix transpose operator
TPR	total peripheral resistance
$u(t)$, u	input signal
$\boldsymbol{u}(t)$, $\boldsymbol{u}$	vector of input signals: $[u_1(t)\ u_2(t)\ \ldots\ u_{\mathrm{L}}(t)]^{\mathrm{T}}$
Var	variance
VLF	very-low frequency
$y(t)$, y	output signal
$\boldsymbol{y}(t)$, $\boldsymbol{y}$	vector of output signals: $[y_1(t)\ y_2(t)\ \ldots\ y_{\mathrm{L}}(t)]^{\mathrm{T}}$
ω	normalised frequency
*	matrix conjugate transpose operator

1. Introduction

Periodicities present in cardiovascular variability signals, such as heart rate (HR) and blood pressure (BP), have been studied for generations, and even more extensively during the last three decades (Kamath & Fallen 1993). Interest has increased because of several factors. The main driving force has been the observation that these periodicities reflect the functioning of the autonomous nervous system (ANS) and hence physiological or pathophysiological processes. Alterations in cardiovascular rhythms have been linked with various physiological or medical provocations, like changes in posture (e.g. Turjanmaa et al 1990, Saul et al 1991, Taylor & Eckberg 1996), hypovolemic stress (e.g. Triedman et al 1993), isometric (e.g. Taylor et al 1995) and dynamic (e.g. Yamamoto et al 1991) exercise, mental stress (e.g. Roy & Stephoe 1991), introduction of vasoactive drugs (e.g. Saul et al 1990) and pharmacological autonomic blockade (e.g. Saul et al 1991), just to mention a few. Even more interestingly, altered oscillations have been linked with several pathologies, e.g. sudden infant death syndrome (Hon & Lee 1963), diabetes mellitus (Bennett et al 1978, Kitney et al 1982, Freeman et al 1995), myocardial infarction (Kleiger et al 1987), hypertension (Guzzetti et al 1988, Pagani et al 1988, Parati et al 1988), myocardial dysfunction (Malliani et al 1991), and reinnervation after cardiac transplantation (Fallen et al 1988). Also, they have been linked with different sleep stages (Scholz et al 1993), level of workload (Jorna 1992), personal fitness (Jorna 1985) and smoking (Hayano et al 1990).

The increased research on cardiovascular variability has become possible and attractive thanks to the vast technological progress in measurement devices and computational power. Currently, acquisition of rhythms in HR and BP may be carried out non-invasively, safely and accurately using the standard electrocardiogram (ECG) and devices like the Finapress (Ohmeda, Inglewood Cliffs, New Jersey, USA), and signals may be easily digitised and stored on a personal computer which provides sufficient computational power for most analyses. There are also commercial products which provide a readily integrated platform for acquiring and analysing these signals. Hence, a window to otherwise elusive human central neural integrative mechanisms is open to practically any researcher or clinician.

Despite the intensive research efforts, clinical use of cardiovascular variability analysis is still limited. This is largely due to the general complexity of the human physiology which is reflected in the signals. This complexity gives rise to large inter-subject variability and disposes the signals to measurement artefacts and noise due to other physiological activities. Hence, no consensus or clear definitions for the analysis methods have been found. Only simple time-domain parameters, like SDNN (standard deviation of the all normal-to-normal (NN) heart intervals), or RMSSD (square root of the mean squared differences between adjacent NN intervals) are slowly reaching a standardised position (Task Force of ESC & NASPE 1996). The details for the application of more advanced parameters are still the subject of heated debate.

Among the advanced parameters used for the quantification of the HR and BP variability are the parameters derived by spectral analysis. Analysis of cardiovascular variability signals in the frequency domain has been one of the most intensively applied methods since the early 70's (Sayers 1973). Despite this long time period, no standardised methods have been agreed upon. A recent Task Force report (Task Force of ESC & NASPE 1996) makes an attempt towards reaching a standardisation of the analysis methods for univariate spectral analysis but, it still fails to reach recommendations that would not be subject to serious criticism. Hence, detailed methodological knowledge, concerning questions like signal pre-processing and the spectral estimation method, etc., is still needed to carry out spectral analysis of cardiovascular signals.

As the cardiovascular system is inherently a multivariable one, use of a multivariable approach for the analysis would appear to be quite a natural choice. A recent Task Force report denotes multivariate analysis of cardiovascular variability as one of the most promising approaches (Task Force of ESC & NASPE 1996). During the last decade there have been some efforts towards multivariate modelling of cardiovascular system (Kalli et al 1986, Baselli et al 1988b, Turjanmaa et al 1990, Grönlund et al 1995, Barbieri et al 1996b), but as yet no breakthrough has been made. This is largely due to the complicated nature of the multivariate methods. To gain widespread use in biomedical research, any analysis method proposed must be robust, valid and reproducible by other research groups (Saranummi et al 1997). The multivariate methods proposed so far fail to meet these requirements. Some methods have

been criticised as biased (Kalli et al 1988a), while some lack adaptability due to their custom structure (Baselli et al 1988b). No methods have been validated in large clinical studies. To gain the use of multivariate modelling in the analysis of the cardiovascular system, research based on a solid theoretical foundation and building on general system theory is needed, and collaborative studies by clinicians and engineers have to be carried out to validate the methods.

2. Background

2.1 The early days of cardiovascular variability signals

Periodic fluctuations in arterial BP were observed first by Stephen Hales (1733). During his classical experiment Hales noticed rhythmic changes in the level of blood in a glass pipe connected to the carotid artery of a horse. He did not relate these variations to respiration or anything else but merely described them (Hales 1733):

> When it was its full height, it would rise and fall at and after each pulse two, three, or four inches; and sometimes it would fall twelve or fourteen inches, and have there for a time the same vibrations up and down at and after each pulse, as it had, when it was its full height; to which it would rise again, after forty or fifty pulses.

In the same also, Albrecht von Haller (1778) recognised that there exist fluctuations in HR, too, and that these fluctuations are in synchrony with respiration. After this finding it took till 1847 before fluctuations in BP were connected to respiration. The observation was made by Carl Ludwig (1847), who recorded physiological signals from dogs and horses on smoked drums. Ludwig explained the finding by the direct mechanical effect of intrathoracic pressure changes on BP. This explanation became obsolete when improved measurement technology enabled accurate quantification of BP and intrathoracic pressures: the BP fluctuations were too large to be just a result of purely the mechanical effect of intrathoracic pressure on arteries. A century after Hales, Traube (1865) documented in mechanically ventilated curarized dogs the occurrence of rhythms after the ventilator was turned off. The animal studies carried out by Hering (1869) around the same time showed the contribution of vasomotion on BP waves: he showed that the rhythmical waves persisted after the exclusion of heart from the circulation. These studies drew the early picture of respiratory-related cardiovascular variability.

BP rhythms slower than respiratory rate, with a period of about 10 seconds, were observed first by Cyon (1874), but carry the name of Dr Mayer, who observed these respiratory-independent oscillations three years later (Mayer

1877) - yet still ascribed them to respiration! The independence of the respiration-related, so-called Traube-Hering waves, and slower Mayer waves was suggested five years after Mayer's study by Fredericq (1882), and was much later on supported by Scweitzer (1945). The foundation of the analysis of short-term cardiovascular variability was completed by Burton and Taylor (1940), who discovered the third main oscillatory component, with a period slower than 0.05 Hz.

2.2 Short-term autonomous control of cardiovascular system

The aim of the cardiovascular system is to provide sufficient blood for tissues and especially the vital organs under all conditions. To carry out this demanding task, a variety of different interacting control systems are needed. In this thesis, only the short-term control of the cardiovascular system is presented. This control includes mechanisms which are capable of acting with a delay lasting from milliseconds to some minutes.

The heart is the prime actor of the cardiovascular system, causing the blood to flow and hence BP. Although the inherent rhythmicity of the heart is due to a natural pacemaker situated in the sinoatrial node, the rhythm is continuously modulated by the input from sympathetic and parasympathetic nerve impulses delivered from the brain to the sinus node (Kamath & Fallen 1993). Together, the sympathetic and parasympathetic nervous branches comprise the peripheral ANS. Specifically for the heart, sympathetic nerve fibres terminate at the sinus node pacemaker, conduction system, atria, ventricles and coronary vessels, while the parasympathetic fibres of the vagus nerve terminate at the sinoatrial and atrioventricular nodes, atrial and ventricular musculature and coronary vessels (Kamath & Fallen 1993). The final pace of the heart is defined by the balance between sympathetic and parasympathetic impulses, such that an increase in sympathetic nerve impulses speeds up the HR while increased parasympathetic activity tends to slow down the HR. The latencies of the sympathetic and parasympathetic branches differ significantly, the former having a typical response delay of a few seconds and the latter providing faster, near-immediate response to stimulations (Eckberg 1995).

BP is a consequence of the contraction of the heart, which forces the stroke volume into the aorta (Guyton 1986). Because of vascular resistance this initial flow causes the BP inside the vascular tree. The pumping action of the heart together with peripheral resistance maintains a continuous pressure difference between the arterial and venous site of the vascular system, which is a prerequisite for tissue perfusion (Guyton 1986). The principal relation between mean BP, stroke volume (SV) and total peripheral resistance (TPR) is that of Ohm's law (Poiseuille 1828):

$$BP_{mean} = SV \bullet HR \bullet TPR \qquad (1)$$

Hence, BP is dependent on HR, the force of the contraction of the heart and the state of the vascular bed. The main determinant of the SV is the degree of the filling of the heart and hence the venous return (Frank-Starling mechanism) (Braunwald et al 1967). The TPR is controlled by vasoconstriction and vasodilation predominantly by the sympathetic ANS branch (Kamath & Fallen 1993). Via local control of vascular resistance the regulation of the blood flow distribution between the different tissues is achieved (Guyton 1986).

The ANS is characteristically a feedback control system. Although the central command controls the overall behaviour, several reflexes provide rapid feedback mechanisms to respond effectively to specific demands (Kamath & Fallen 1993). The most intensively studied of these reflexes is the (arterial) baroreflex. The baroreflex is based on pressure or stretch receptors (baroreceptors) located in the heart, carotid sinus, aortic arch and other large vessels (Karemaker 1987). These stretch receptors are sensitive both to mean arterial pressure and to the pressure derivative (Karemaker 1987). The reflex is mediated by a specific baroreflex arc (Kirchheim 1977), and both the parasympathetic and the sympathetic firing are affected by baroreceptor stimulation (Rea & Eckberg 1987). The baroreflex modulation of vagal firing of the sinus node causes a fast and opposing change in HR and myocardial contractility due to a change in arterial BP (Karemaker 1987, Eckberg & Sleight 1992). In humans, the baroreflex latency has been reported to be between 200 and 600 ms (Eckberg & Sleight 1992). Hence, it provides a fast regulating mechanism for stabilising the BP level.

The other cardiovascular reflexes include low-pressure sensitive cardiopulmonal baroreceptors and chemoreceptors responding to metabolic needs (Karemaker 1987, Eckberg & Sleight 1992, Toska 1995). Furthermore, renal control of blood volume and the renin-angiotensin-aldosteron system (Toska 1995) and thermoregulation (Sayers 1973) may play a role in short-term cardiovascular regulation.

In healthy normal subjects, in normal conditions, HR increases and BP decreases during inspiration while the opposite is true during expiration. Respiratory influence enters cardiovascular variability in several ways. At the brain stem level, respiration modulates the sympathetic and parasympathetic efferent activity to the heart and vasculature through direct coupling between the respiratory and autonomic centres and through modulation of central sensitivity to baroreceptor and other afferent inputs (Saul et al 1991, Eckberg & Sleight 1992, Toska 1995). The efferent modulation of HR by respiration is carried out both by the parasympathetic and the sympathetic branches of the ANS, the former being dominant in respiratory frequencies over 0.15 Hz, and the relative importance of the latter increasing with decreasing respiratory rate (Saul et al 1991). At the direct mechanical level, intrathoracic pressure changes modulate arterial and central venous pressures and flows and affect preload and afterload, which in turn affect SV and hence BP (Saul et al 1991, Toska 1995). Furthermore, direct mechanical stretching of the sinus node and baroreceptors due to respiration may play a role in modulating the HR (Schmidt & Thews 1983, Toska 1995). The closed-loop coupling between HR and BP also plays a role in the respiratory variability of HR and BP. Respiratory sinus arrhythmia proceeds to BP as alterations in RR interval affect the resulting BP by the run-off effect and Frank-Starling mechanism (feed-forward) (Smith & Campine 1980, Guyton 1986, Taylor & Eckberg 1996), while the arterial baroreflex causes variations in HR when BP changes (feed-back) (deBoer et al 1987, Saul et al 1991).

2.3 Analysis of cardiovascular variability signals

In this chapter a short review over the methodology of analysing short-term cardiovascular variability signals is given. Short-term variability is defined as the variability reflecting the short-term control of the cardiovascular system,

expressed by the time series in the recordings of the length between a few minutes and a few tens of minutes. The analysis of longer data sequences is referred to only when appropriate from the short-term analysis point of view.

2.3.1 Cardiovascular variability signals

Instantaneous HR, or HR time series, is defined as a reciprocal of the time difference of the successive heart beats. In the supine healthy human, the mean value of the inter-beat interval is typically around 1000 ms, and the standard deviation (SD) 60 ms (Task Force of ESC & NASPE 1996). To guarantee proper identification of the HR variability, the resolution of $\leq$4 ms should be achieved (Task Force of ESC & NASPE 1996). In certain pathologies, even better resolution is needed (Kitney et al 1982, Merri et al 1990). In practise, this requirement implies use of good-quality ECG and robust definition of the fiducial point of the QRS-complex (Task Force of ESC & NASPE 1996). Usually, the peak of the R-wave is used as the fiducial point. Interpolation methods may be used to increase the localisation resolution and hence to enhance the HR series accuracy (Bianchi et al 1993, Loula et al 1994). The resulting time series is called the RR-series, or RR interval (RRI) series, the reciprocal of which is the HR series. Due to this non-linear relation between RRI and HR signals (Figure 1) linear quantification of HR variability is somewhat dependent on the choice of signal. Paradoxically, in case the of a different mean HR between the tests to be compared, the quantified HR variability may sometimes increase if HR is considered, but decrease if RRI is selected instead, or vice versa (Castiglioni 1995).

A continuous BP signal may be recorded invasively by intra-arterial catheter, or non-invasively by a device utilising the Penaz principle (Penaz 1973). The non-invasive method provides a resolution comparable to invasive recordings for spectral analysis (Omboni et al 1993) and is becoming more and more popular due to its ease-of-use and patient safety. Usually, the continuous BP signal is parametricised into a beat-to-beat time series of systolic BP (SBP; the maximum BP during each beat) diastolic BP (DBP; the minimum BP during each beat), and mean arterial pressure (MAP; true mean pressure between two successive diastolic time instants). Also pulse pressure (PP = SBP-DBP) may be used (Saul et al 1991). The parametrisation is carried out to emphasise the partially differing control mechanisms of DBP and SBP.

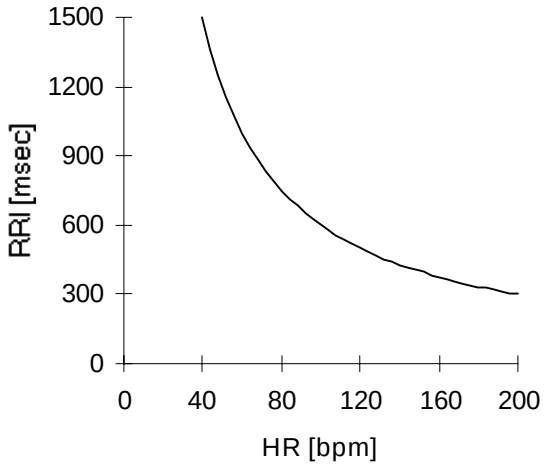

Figure 1. Non-linear relationship between HR and RRI.

In non-hospitalised subjects, respiration is usually quantified by measuring instantaneous lung volume (ILV) instead of the effective variable, intrathoracic pressure. The ILV is usually measured either by strain gauge over the chest (Baselli et al 1988b, Saul et al 1989, 1991) or by the transthoracic electric impedance method (Triedman et al 1995). Both methods provide inexpensive and non-invasive modalities. The strain gauge method is more sensitive to movement artefacts, while the impedance method may reflect also some variations of blood volume inside the chest (AAMI 1989). To obtain more accurate respiratory waveforms, an ergospirometer may be used (Tulppo et al 1996). This method is, however, somewhat uncomfortable to the subject and may hence affect his/her psychophysiological state.

Also other cardiovascular or cardiovascular-related signals have been considered for the analysis of their short-term variability. Toska (1995) analysed beat-to-beat SV, cardiac output (CO) and TPR measured by the ultrasound Doppler method during physiological provocations in the time domain. Grönlund et al (1995) used transcephalic electrical impedance together with ILV, SBP and HR to analyse control of cerebral circulation in new-born babies. Recently, Barbieri et al (1996a) included central venous pressure in their model of cardiovascular control. Many groups have studied the co-occurrence of cardiovascular rhythms and muscle sympathetic activity (Eckberg et al 1985,

Wallin et al 1994). In addition, cardiovascular variability has been related to signals such as electroencephalograph (EEG) during anaesthesia (Loula et al 1994), electro-oculograph, EEG and electromyograph (EMG) to assess vigilance (Värri et al 1994), and leg EMG to study sleep disorders (Vermeiren et al 1995a), just to mention a few cases.

2.3.2 Signal pre-processing

The inherent property of the beat-to-beat cardiovascular time series is their non-equidistant sampling in time. Hence, application of frequency domain analysis methods to these signals needs special attention. One way to solve the problem is to carry out the frequency domain analysis in the cycles/beat-plane instead of the usual cycles/second-plane (Hz-plane) (Sayers 1973, Baselli et al 1986, Malliani et al 1991). In this approach, all the signals are sampled at heart beats (R-waves) (Baselli et al 1986, 1988a) and the analysis is carried out directly on these signals. The transition to Hz-plane is made by dividing the cycles/beat-abscissa by the mean inter-beat interval. This transform is based on the assumption of zero HR variability and is hence non-uniform in every case of practical interest. It has been shown that this approach leads to spectral sideslopes and distortion on the Hz-plane depending on the amount of HR variability (deBoer et al 1984, Rompelman 1986, TenVoorde et al 1994). However, no studies have shown any practical importance for this distortion presented, and hence the method is in general use (Baselli et al 1994, Malliani et al 1991, Task Force of ESC & NASPE 1996). The second approach to overcome non-equidistant sampling is to use resampling methods to transform the time series into equidistantly sampled signals (Task Force of ESC & NASPE 1996). Two main approaches are introduced: the interpolation-resampling approach (Luczag & Laurig 1973) and window-averaging-resampling (Rompelman 1986, Berger et al 1986). The interpolation between consecutive heart beats may be carried out in a step-wise manner (Luczag & Laurig 1973), linearly (Luczag & Laurig 1973), or by spline function (Saul et al 1991). Proper resampling methods do not suffer from the distortion (Berger et al 1986) and provide an equal time scale for signals of beat-to-beat (e.g. HR and SBP) and other (e.g. ILV or sympathetic nerve activity) origin. The price paid for this is the increased computational load.

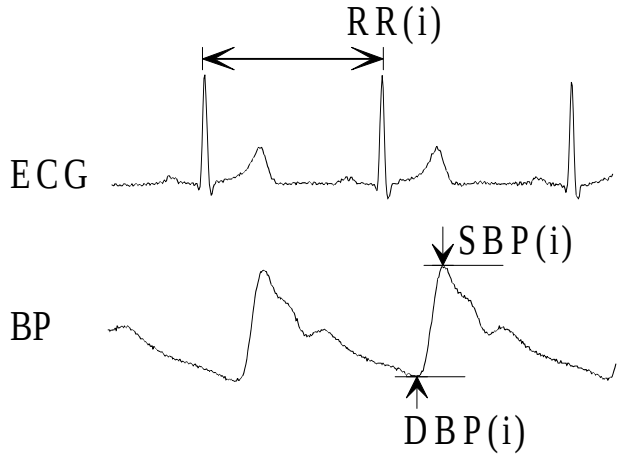

Figure 2. Derivation of beat-to-beat parameters from ECG and BP signals.

Table 1. Different constructions of the cardiovascular time series.

Authors	Correspondence to Figure 2	
	SBP(i)*	DBP(i)*
Baselli et al 1986, 1988	SBP(i+1)	DBP(i)
de Boer et al 1987	SBP(i+1)	DBP(i+1)
Rompelman & TenVoorde 1995	SBP(i)	DBP(i)

* Notations referring to Figure 2. Notations of different authors are described as referring to each RR(i) in Figure. This shows how different authors indicate the fiducial points in ECG and BP signals.

To accurately analyse intersignal properties, special care must be taken to restore the phase relationships between the signals. This means the use of linear phase filters with equal delay for all the signals, but it also emphasises the construction of the beat-to-beat series, i.e. what are the exact time instants of the fiducial points detected at the signals [e.g., RR(i): the R-wave beginning or ending each RR(i) (Eckberg 1995)] and what is the mutual correspondence between them (Table 1). The selection of construction affects the phase relations between the signals. Unfortunately, there exists no consensus on the topic and the use of different constructions hampers the comparison of different studies.

The final step in data pre-treatment includes data validation and removal of unwanted parts of the signal. Generally, any sequences containing artefacts,

ectopic beats, or other random-like physiological disturbances are excluded from the analysis unless this exclusion introduces a significant selection bias (Task Force of ESC & NASPE 1996). Proper interpolation methods may be used to decrease the effect of missing data or random physiological events (Kamath & Fallen 1995).

2.3.3 Spectral analysis

Power spectral density (PSD) of a signal is a linear transformation of a signal from the time plane to the frequency plane and describes the distribution of the signal power over the frequency plane. The complex spectrum of a signal is a complete presentation of the second order properties of the signal (mean and correlation function) (Picinbono 1993). In the case of a random, or stochastic, signal the PSD is also a stochastic variable. Spectral estimation of stochastic signals is dealt with intensively in the literature (Marple 1987, Kay 1988).

The spectral analysis of cardiovascular signals is based on the stochastic approach. The main consequence of this is the presumption of local stationarity of the signal (Kay 1988). Local stationarity means that the correlation function is unchanged during the recording and that the length of the recording is significantly longer than the correlation time (Picinbono 1993). In a stationary signal, expectation values may be accurately estimated by time averaging and hence from a single recording (Picinbono 1993). The presumption of stationarity is well recognised in analysing cardiovascular variability signals (Task Force ESC & NASPE 1996), and formal tests for the second-order stationarity are generally applied (Bendat & Piersol 1986, Task Force ESC & NASPE 1996).

Two different PSD estimation methods are most often used with cardiovascular signals: Fast Fourier Transform (FFT) based methods (Sayers 1973, Akselrod et al 1981) and AR spectral estimation (Baselli & Cerutti 1985). The main advantage of the FFT based methods is their computationally efficient implementation compared with AR methods (Task Force ESC & NASPE 1996). The AR methods, in turn, are claimed to provide 1) smoother and more easily interpretable spectral shapes (Task Force ESC & NASPE 1996), 2) better spectral resolution in the case of short data lengths (Kay 1988), and 3) straightforward decomposition of spectra into root components without the need for predefined spectral bands (Baselli et al 1987, Malliani et al 1991). In

general, both methods provide very comparable results (di Rienzo et al 1989, Task Force ESC & NASPE 1996).

The mainstream of studies apply traditional spectral estimation methods, like FFT or AR methods, directly to beat-to-beat time series, or then to resampled data (Task Force ESC & NASPE 1996). Fourier transform based spectral estimation methods applicable directly to non-equidistantly sampled data have been proposed by Rompelman et al (1982), deBoer et al (1984) and recently by TenVoorde et al (1994). These methods have not been widely applied despite their having some advantageous properties (TenVoorde et al 1994).

Usually three main spectral components of HR and BP short-term variability are recognised in humans:

1) high frequency (HF) component, around 0.15 - 0.4 Hz, arising mainly due to respiratory influence (Hyndman et al 1971, Eckberg & Sleight 1992);

2) low frequency (LF) component, around 0.05 - 0.15 Hz, referring to Mayer waves and usually associated with baroreceptor function (Akselrod et al 1985, deBoer et al 1987), pressure-pressure feedback loop (Baselli et al 1988a, 1994, Taylor & Eckberg 1996) and vasomotor activity (Hyndman et al 1971); and

3) VLF component, around 0.01 - 0.05 Hz, the origin of which is largely unknown but is proposed to be associated with thermoregulation (Sayers 1973, Kitney et al 1985), vasomotor activity (Kamath & Fallen 1993), or the renin-angiotensin system (Akselrod et al 1981).

The different latencies of the sympathetic and parasympathetic ANS branches are largely responsible for the fact that frequency domain analysis may be effectively utilised to analyse ANS function: the functioning of different branches is partially separable in the frequency domain. The HF component is associated mainly with parasympathetic activity (Akselrod et al 1985, Saul et al 1989, 1991), but the LF component is dominated both by sympathetic and parasympathetic control (Akselrod et al 1985, Saul et al 1991, Taylor & Eckberg 1996).

The parameters computed from the PSD estimates of short-term variability are usually the spectral power of different frequency bands and the LF/HF ratio (Task Force ESC & NASPE 1996). The LF/HF ratio has been claimed to provide a measure of so-called sympatho-vagal balance (Pagani et al 1986, Malliani et al 1991), but this statement is also criticised for lack of a physiological foundation (Eckberg 1995). The spectral power may be normalised, i.e. divided by the total spectral power under the LF and HF band to reduce the intersubject or intertest total power variability (Task Force ESC & NASPE 1996). The normalisation may in certain situations, however, mask the real patterns of changing regulation (Taylor & Eckberg 1996).

No studies have shown any practical significance as regards the selection of the spectral analysis method (FFT or AR spectral estimation) as long as the method selected is properly applied and the spectral powers on different frequency bands are considered as the output variables.

2.3.4 Multivariate spectral analysis

Multivariate spectral analysis allows quantification of the intersignal correlation in the frequency domain by means of cross-spectral analysis (Baselli et al 1986). The cross-spectral density function is defined as a Fourier transform of the cross-covariance function between the signals (Kay 1988). Hence, it may be used to assess the correlation between the signals at different frequencies. As to correlation analysis in general, it does not state anything about the cause-effect relationships between the signals. In an open-loop system, when the cause-effect relationship is known *a priori*, the analysis may be extended to provide transfer functions between the signals (Ljung 1987). In practical applications the cross-spectral density function is usually converted to coherence function, phase spectrum, or transfer function.

Analysis of weighted squared coherence function between HR and respiration was proposed by Porges at al (1980). Since then on the cross-spectral analysis of cardiovascular variability has gained increasing attention, and especially squared coherence and phase spectrum between cardiovascular signals have been studied in multiple works (e.g. deBoer et al 1985, Berger et al 1989a, Saul et al 1989, 1991). The computation of these functions by multivariate AR (MAR) spectral analysis was introduced by Baselli et al (1986). An important

application of cross-spectral methods has been the analysis of baroreflex sensitivity by cross-spectral analysis of RRI and SBP (Robbe et al 1987).

Berger et al (1989a) computed the open-loop transfer functions between the input and output signals. The coherence function is used as a frequency-dependent measure of linear coupling between the signals; a squared coherence value greater than 0.5 has been considered as the limit of confidence for transfer function measures, e.g. transfer phase (Kamath & Fallen 1993). Phase spectral and transfer function analysis has lead to fundamental results especially in analysing respiratory sinus arrhythmia or respiratory variability of BP (Berger et al 1989a, Saul et al 1989, 1991, Taylor & Eckberg 1996). However, it has been justifiably criticised as unable to depict the interactions between the closed-loop variables like BP and HR (Saul et al 1991, Taylor & Eckberg 1996).

2.3.5 Multivariate modelling

Unlike multivariate spectral analysis, multivariate modelling provides a means to analyse cause-effect relationships present in a system. Roughly speaking, multivariate models of cardiovascular signals may be divided into two categories: 1) models for the analysis of cardiovascular variability data and 2) models imitating the behaviour and structure of the cardiovascular system in order to gain an understanding of the functioning of the system. In this thesis, the emphasis is laid on the former category.

The models for the analysis of the cardiovascular system try not to imitate the structure of the real system but rather to describe and quantify the interactions between the acquired signals. These models may be further divided into two sub-categories: open- and closed-loop models.

Sophisticated open-loop ARMA (AR moving average) modelling was applied by Triedman et al (1995) to analyse the effects of SBP and respiration on HR using impulse response estimates. Their ARMA model explains HR through linear transfer functions from BP and ILV. A further developed version of the model was recently introduced by Perrott and Cohen (1996). The special feature of the new model was its anti-causal respiratory effect: ILV was allowed to affect HR with a negative delay of max. 5 seconds. This made it possible to

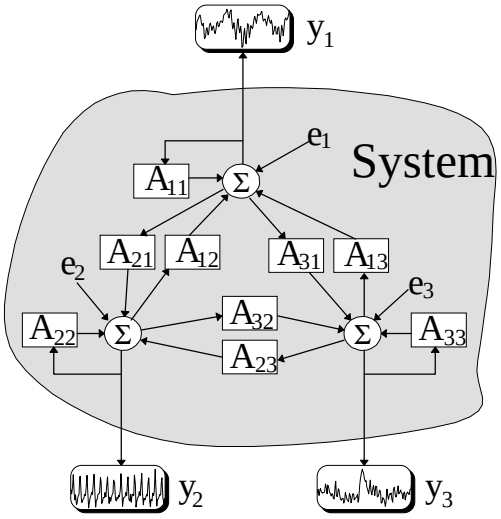

Figure 3. MAR model of three-variable system. y_i*:s represent measured signals,* e_i*:s unknown disturbances and* A_{ij}*:s the transfer functions between signals. (From publication IV) (Suoranta & Rantala 1991)*

control the reported phase lead of HR to ILV due to central control mechanisms of HR (Saul et al 1989, 1991).

A need for models capable of depicting the closed-loop interactions between signals was recognised a decade ago (Akselrod et al 1985). Kalli et al (1986, 1988b, Turjanmaa et al 1990) proposed MAR modelling of cardiovascular closed-loop interactions between HR and BP (Figure 3). In their approach, the quantification of the interactions between different variables was based on noise source contribution (NSC) analysis; the NSCs provide a division of spectral power in each signal into relative shares originating in different variables (for details, see chapter 4.2.3). Since then the method has been extended to cope with more variables and applied for the analysis of cardiovascular control of neonatal lambs (Kalli et al 1988a, Grönlund et al 1991) and human neonates (Grönlund et al 1995). Recently, Barbieri et al have applied bivariate (1996a, 1996b) and trivariate (1995) MAR modelling to estimate the gain of interactions between HR, BP and ILV. The MAR modelling provides an approach that is easy to adapt to different sets of variables (Kalli et al 1986, 1988a). The most

critical factor limiting its use is the assumption of the noise source independence; if this assumption is not fulfilled, the estimation of intersignal interactions becomes biased (Kalli et al 1988a).

A more sophisticated custom model was proposed by Baselli et al (1988b). This linear model described closed-loop interactions between SBP and HR together with respiratory influence. The analysis of interactions was based on spectral decomposition and estimation of intersignal gains. The model has been applied to experimental data from conscious dogs and humans in different physiological conditions (Baselli et al 1994).

Appel et al (1993) introduced a model comparable to Baselli's approach. Recently, they have developed the model further (Appel et al 1989, Mullen et al 1997). Their model is based on AR moving average (ARMA) equations and in structure comes close to the MAR model with exogenous input, or the MARX model. The main difference is that their model is effectively divided into two branches of very different time scale: an HR branch with a sampling frequency of 3 Hz and an arterial BP branch with a sampling frequency of 90 Hz. The former branch describes the ANS control of HR while the latter depicts the mechanical effects of HR and respiration on BP. The separation is further emphasised by the inclusion of a sinus node block in the model, allowing for the use of HR as a variable in analysing the ANS control, and the use of an impulse sequence modelling the firing of the sinus node in analysing the mechanical function of the circulatory system. The analysis of interactions was based on the estimated inter-signal impulse responses.

The studies published so far on multivariate time series modelling of cardiovascular signals are predominantly methodological papers which try to emphasise the proper function of the model and which are based on a relatively limited number of subjects. Hence, no fundamental physiological findings using these methods have yet been published. Despite that, multivariate modelling has been considered one of the most encouraging fields of cardiovascular signal analysis (Task Force ESC & NASPE 1996).

The other class of models consists of physiologically established mathematical models of the cardiovascular system. Probably the first model of the short-term variability of HR was introduced by Hyndman (Hyndman et al 1971). Interest in

modelling has continued ever since, and several different approaches have been proposed, including both linear (deBoer et al 1985, 1987, Saul et al 1989, 1991) and non-linear models (Kitney 1979, Leaning et al 1983, Akkerman et al 1995, TenVoorde et al 1995). The modelling has usually been considered successful when the model could reproduce (cross-)spectral properties of the experimental data in various conditions (deBoer et al 1987, Saul et al 1989, 1991, TenVoorde et al 1995). The aim of these modelling studies has been to gain an understanding of the cardiovascular system function and to provide a theoretical foundation for hypothesis building.

2.3.6 Time-variant spectral analysis

The methods mentioned above assume stationary data. However, the need to analyse signals during dynamic conditions, too, is largely recognised. To overcome the assumption of stationarity, Bianchi et al (1993, Mainardi et al 1995) introduced time-variant AR spectral analysis of cardiovascular signals. Novak and Novak (1993) proposed the use of Wigner distribution to analyse the signals in the time-frequency plane. These methods allow one to analyse spectral power variations in nonstationary conditions, such as physiologically dynamic provocations (Pola et al 1995). Kitney and Darvish (1995) gave a short review over the time-frequency methods applied to cardiovascular variability signals, and concluded that they provide ‘an important development’.

Recently, time-variant multivariate modelling has been applied to study the cardiovascular system. Mainardi et al (1993) and Barbieri et al (1996b) used time-variant MAR modelling to study cardiovascular responses during syncope and tilt, respectively.

Another approach to meet the need for dynamic analysis in the frequency domain has been complex demodulation which provides time tracking of the signal phase and amplitude around a given frequency (Shin et al 1989). Complex demodulation has been used to track respiratory related changes in the amplitude of HR variability (Shin et al 1989), amplitude of LF and HF oscillations in HR and BP during a tilt test (Hayano et al 1993) and for the assessment of phase relationships between HR, BP and ILV (Vermeiren et al 1995b).

As with multivariate modelling, time-variant analysis has not yet been largely adapted for clinically oriented studies; rather the emphasis has been on methodological development and trials on small numbers of subjects.

2.3.7 Non-linear methods

Inherent non-linearity of the cardiovascular system is a long-known phenomenon (Levy 1971). Still, the vast majority of studies assume linearity during stationary conditions when signals are exhibiting only small variations around their mean values (Cerutti et al 1994). The significance of non-linearity is assumed to play a significant role mostly in dynamic conditions or long-term recordings (Cerutti et al 1994). This is supported by findings that in stationary short-term conditions linear models may explain typically >65 % (Baselli et al 1994), or even more (Appel et al 1989), of the variability of the signals. Furthermore, the assumption of linearity, though not strictly justified, has in any case been the basis for most of the physiologically significant findings in the field so far.

Recently, interest in non-linear analysis has increased. Studies have shown non-linearity to play a significant role not only in long-term recordings but also in stationary short-term conditions (Korhonen & Turjanmaa 1995). Chon et al (1996) estimated that 10 - 15 % of the HR variability in static conditions is associated with the non-linear couplings. Quantification of the non-linearity during short-term conditions has been proposed by using non-linear time series models, like non-linear extensions of ARMA models (Bennett et al 1993), but especially the Volterra-Wiener series (Marmarelis 1993). Loula et al (1994) applied the Volterra-Wiener theory to compute second- and third-order kernels from the respiratory input to the HR output, and Chon et al (1996) identified second-order kernels in the case of a dual-input (ILV and BP) to HR. These studies have demonstrated that the short-term variability of cardiovascular signals exhibits significant non-linear components and that these components may be identified. The major problem with this approach, in addition to the more complex methods to be applied, has been and is still the physiological interpretation of the results.

During the last few years, application of chaos theory, also called non-linear dynamics, to cardiovascular variability signals has gained explosive popularity

(Cerutti & Signorini 1996), as has the research on chaos theory in general (Gleick 1987). Measures to estimate complexity and sensitivity to initial conditions of a non-linear system from the time series data have been applied predominantly to long-term HR variability data only, mainly due to the demands set for data length by the estimation methods (Cerutti & Signorini 1996). Only a limited number of studies have been carried out with short-term data (Kaplan et al 1991), and so far, interesting observations from the long-term data, like increased risk of death after myocardial infarction (Bigger et al 1996), have not been repeated in short-term conditions.

2.4 Estimation of spectral shift in myoelectric signals

Estimation of the characteristic frequency of the spectrum of a signal is a common problem while analysing myoelectric signals (Stulen & DeLuca 1981, DeLuca 1985, Hägg 1991). Lindström et al (1970) showed that the spectral shift (i.e. change in characteristic frequency of the spectrum) describes the changes in myoelectric signals during fatigue more accurately than the tracking of the signal power. There are three commonly preferred candidates for the characteristic frequency: the mode, the mean and the median frequency of the spectrum (Stulen & DeLuca 1981). The mode frequency, f_{MOD}, is the frequency of the maximum power, i.e. the highest spectral peak, of the power spectrum $S(f)$:

$$f_{MOD} = \left\{ f ; S(f) = \max\left[S(f) \right] \right\} \tag{2}$$

The mean frequency, f_{MEAN}, is the centre of gravity of the spectrum and is defined as

$$f_{MEAN} = \frac{\int_{f=0}^{\infty} f S(f) df}{\int_{f=0}^{\infty} S(f) df} \tag{3}$$

The median frequency, f_{MED}, is the frequency which divides the spectrum into two regions with equal power:

$$\int_{f=0}^{f_{MED}} S(f)df = \int_{f=f_{MED}}^{\infty} S(f)df \tag{4}$$

Superficially, the mode frequency might appear to be most appropriate estimate for the characteristic frequency. However, in the case of a stochastic process, like a myoelectric or cardiovascular variability signal, this is not the case. The variance of the spectral estimate would strongly influence the estimation accuracy of the mode (Stulen & DeLuca 1981) and the coefficient of the variation for the estimate of the mode has been empirically found to be five times higher than that for the mean frequency for myoelectric signals obtained from the human diaphragm (Schweitzer et al 1979). Hence, the mode frequency is not usually used in spectral shift estimation. The mean and median frequencies provide comparable results in analysing muscle fatigue by myoelectric signals (DeLuca 1985) and they have been found to be highly correlated with real myoelectric data (Hägg 1991). The median frequency has been claimed to be least sensitive to noise (Stulen & DeLuca 1981), but Hägg (1991) concluded that there is little reason to select one over another due to methodological errors.

2.5 Author's former research on the topic

This thesis is based on our former research (Takalo et al 1994a, 1994b, Grönlund et al 1995) in which some specific methodological problems were addressed and others came to light. This chapter briefly describes the work in order to provide a closer understanding of the set-up of this thesis.

2.5.1 Univariate spectral analysis of HR and BP variability in border-line hypertensive and mildly hypertensive subjects

Takalo et al (1994a, 1994b) applied univariate spectral analysis to HR and BP signals to quantify differences in cardiovascular regulatory mechanisms between normotensive (NT), borderline hypertensive (BHT) and mildly

hypertensive (HT) subjects under standard laboratory conditions with the subjects in supine, sitting and standing positions and during sleep.

Rationale. According to the guidelines of World Health Organisation (WHO Expert Committee 1978), NT are those whose SBP≤140 mmHg and DBP≤90 mmHg, HT those whose SBP≥160 mmHg or DBP≥95 mmHg and BHT those who do not fall in either of the previous categories. Most subjects with borderline hypertension will not progress to permanent, established hypertension (Julius 1991). It would be beneficial if the subjects with increased risk of cardiovascular morbidity could be identified among those who have elevated BP. Spectral analysis of HR and BP can provide information about autonomic nervous system function in hypertension (Malliani et al 1991). Guzzetti et al (1988) found by spectral analysis of HR variability enhanced sympathetic and depressed vagal activity in mildly hypertensive subjects. An increased sympathetic tone in BHT subjects has been documented by different experimental methods (Julius 1991). For example, Anderson et al (1989) observed an increased sympathetic nerve activity in direct intraneural recordings in BHT subjects. Furthermore, autonomic abnormality is typically found in young subjects with borderline hypertension, but not necessarily in established hypertension (Julius 1991). The phenomenon of abnormal spectral characteristics may hence be transient, or at least different, with BHT and HT groups, and division into two groups (NT and HT), or any mis-categorisation of the subjects, may effectively mask any findings of the ANS function analysis.

The study set-up. Three carefully classified groups - NT, BHT and HT - were studied in standardised conditions, i.e. during quiet laboratory conditions in three different postures (supine, sitting, standing) and during sleep. The different postures provided standard and repeatable activation to ANS, and the performance in strictly controlled laboratory conditions aimed to standardise the other inputs to ANS. The subjects were allowed to breathe spontaneously, which minimised any autonomic disturbance due to paced breathing. ECG and intra-arterial BP were measured from the subjects by using the Oxford method, and the signals were transformed into resampled (linear interpolation, 1 Hz resampling frequency) beat-to-beat time series of HR, SBP and DBP. Spectral analysis of BP and HR variability was carried out in each posture (N=300). In principle, analysis of BP variability could be more sensitive for detecting changes in sympathetic nervous system function than the analysis of HR

variability which may be more efficient in detecting parasympathetic (vagal) dysfunctions (Akselrod et al 1985, Japundiz et al 1990, Taylor & Eckberg 1996).

Spectral estimation. AR spectral estimation with a high model order was used in order to guarantee accurate quantification of the complex cardiovascular rhythms present in HR and BP signals. The model order was selected to be 30. This exceeds that given by the most usually employed model order selection criteria, like the Akaike Information Criterion (AIC) (Akaike 1974). A typical model order proposed by the AIC is from 10 to 15 with the time series analysed in these studies. The reason for this selection lies in the fact that the model order selection criteria are optimised for pure AR time series, and with non-AR or noisy data they have a tendency to underestimate the model order needed (Landers & Lacoss 1977, Marple 1987, Kay 1988). Hence, with real HR or BP data, the model order proposed by some objective criterion, like AIC, is not always sufficient to resolve all the spectral details present in the signal (Pinna et al 1996). Pinna et al (1996) propose an iterative and interactive procedure to optimise the model order, but this procedure is not attractive in the case of large data sets due to its need for subjective judgement of the goodness of the model. Kay (1988) states that model order may be increased up to N/3 or N/2 (N being the data length) without any danger of spurious peaks in spectral estimate due to overestimated model order. Hence, we selected a constant model order of 30, which significantly exceeds that proposed by AIC but provides a reasonable resolution for spectral details in all the cases studied and does not introduce the chance of spurious spectral shapes due to artificially high model order. This selection allowed an accurate and robust spectral estimation by an automatic procedure.

Spectral analysis. In the spectral analysis, our main attention was on the quantification of the LF rhythms around 0.1 Hz, which are generally associated with baroreceptor function (Akselrod et al 1985, deBoer et al 1987), pressure-pressure feedback loop (Baselli et al 1988a, 1994, Taylor & Eckberg 1996) and vasomotor activity (Hyndman et al 1971). These oscillations are mediated by both the sympathetic and parasympathetic nervous systems (Akselrod et al 1985, Saul et al 1991, Taylor & Eckberg 1996) and may hence be modified by changes in either branches of the ANS. In general, the parasympathetic control plays the more dominant role the higher the frequency in the frequency-domain, and the

sympathetic control becomes relatively more important when the frequency is decreased (Saul et al 1991). To gain more exact quantification of these rhythms, the LF band was further divided into two sub-bands: LF_{low} (0.02 - 0.075Hz) and LF_{high} (0.075 - 0.15Hz) (Robbe et al 1987, Parati et al 1988).

Results. In the BHT group, either the relative power on the LF_{low} band is greater, or that on the LF_{high} band smaller than in the NT or HT groups. This finding is the most significant on the DBP oscillations and suggests that the HR and BP oscillations on the LF band are shifted to lower frequencies in the BHT group compared with the NT and HT groups.

Conclusion. The observed changes in the spectral powers suggested that there exists a shift in the frequency of oscillations on the LF band (0.02 - 0.15 Hz) in the BHT group compared with the NT and HT groups. To quantify this kind of phenomenon, the calculation of spectral power in different bands does not provide an optimal method but rather some other methods had be found.

2.5.2 Multivariate modelling

In Grönlund et al (1995) we used MAR modelling to quantify intersignal relationships of HR, BP, transcephalic impedance and respiration in neonates with cerebral haemorrhage. MAR modelling was applied as proposed by Kalli et al (1986, 1988a) and mean NSC was analysed in different spectral bands. The main finding of this study was the observation that the inherent variability of the transcephalic impedance, which reflects the intra-cerebral blood circulation, was lower in babies with haemorrhage than in healthy ones. This was interpreted as a possible marker of pressure passivity in the cerebral circulation following peri-intraventricular haemorrhage. Despite this finding which supports the use of MAR modelling in the analysis of the cardiovascular system, we met the problem denoted earlier by Kalli et al (1988a): with real cardiovascular data the noise sources in the identified MAR model tended to become correlated, which created some unreliability in the results. The exact amount of this error has not been studied. To benefit from the potential of multivariate linear modelling in cardiovascular research, the error had to be analysed and methods to overcome the problem had to be developed.

In addition, we noted that the mean NSC analysis did not provide a convenient parametrisation of the inter-signal relationships in the case where the spectrum of the system is not broad-band: if the spectral energy is not distributed over the whole frequency band of interest, the mean NSC tended to be sensitive to numerical inaccuracies (non-published results). This is due to the fact that the model identification tends to fit better those frequencies with more spectral power than those with less power. In the analysis of mean NSC, all the frequencies gain equal weight. This increases the sensitivity of the mean NSC analysis to modelling inaccuracies. As the cardiovascular signals like HR and BP tend to be narrow-band signals if no special methods, like broad-band respiration (Berger et al 1989b), are applied, this predisposition of the mean NSC becomes inconvenient. Hence, more robust parametrisation of multivariate modelling results had to be defined.

3. Aims of the thesis

The scope of this thesis was the frequency-domain analysis of short-term variability of HR, BP and respiration signals using time series modelling. The objectives of the study were to:

1. define simple parameters to quantify the spectral shift in HR and BP variability signals,

2. apply linear multivariate time series modelling for frequency domain analysis of interactions between cardiovascular signals,

3. develop portable modelling approaches which utilise generally available algorithms and software,

4. define simple, robust and clinically interpretable parametrisation of the multivariate modelling results,

5. address practical considerations of applying linear multivariate modelling for the analysis of cardiovascular interactions.

4. Summary and discussion on publications

This thesis consists of five publications related to the analysis of cardiovascular variability signals in the frequency domain, especially concerning HR and BP. Publication I addresses quantification of the spectral shift on a limited spectral band and introduces a new parameter to quantify this spectral shift. In this summary, the estimation of the band-wise spectral shift is discussed in some more detail. Publications II - V deal with multivariate time series modelling of cardiovascular variability signals. Publications II and III present a general framework for linear multivariate modelling of physiological signals, cardiovascular signals being the application field of interest. Publication IV presents a method for overcoming a problem of noise source dependence in MAR modelling of the cardiovascular system. Publication V introduces a new model for analysing the closed-loop interactions between HR and BP and to quantify respiratory effects on cardiovascular dynamics.

4.1 Quantification of spectral shift

In this thesis, spectral analysis was applied to HR and BP signals to quantify differences in cardiovascular regulatory mechanisms between NT, BHT and HT subjects under standard laboratory conditions with the subjects in supine, sitting and standing positions and during sleep. This objective has guided the study. Concerning univariate spectral analysis, the aim of this thesis was to develop a robust method for quantifying the spectral shift observed on the LF band in BHT subjects (Takalo et al 1994a).

4.1.1 Estimation of band-wise spectral shift in cardiovascular variability signals

Estimation of spectral shift of myoelectric signals by monitoring the characteristic frequency of the signal spectrum is a widely used method for measuring muscular fatigue (DeLuca 1985). Several estimators of the characteristic frequency of the entire spectrum of the myoelectric signal were presented in Chapter 2.4. In the case of a myolectric signal, the whole frequency

range of the spectrum reflects the same physiological process, namely the muscle action potentials. Hence, it is relevant from the physiological point of view to estimate spectral shift over the entire spectrum. In the case of cardiovascular variability signals, different physiological processes are involved in the generation of the oscillations. The oscillations may be partly separated in the frequency domain (Task Force ESC & NASPE 1996) and consequently, alterations in different physiological processes may be detected in alterations in different spectral bands in the frequency domain. Hence, detection of spectral shift caused by different physiological processes needs focusing on different spectral bands.

To focus on the quantification of the spectral shift within a specific spectral band, three estimators of the characteristic frequency were studied: the band-wise mean (f_{MEAN}), the band-wise median (f_{MED}), and the band-wise central (f_C) frequencies[1]. The central frequency has been proposed by Baselli et al (Baselli et al 1987) and thereafter used in some studies (Pagani et al 1986, 1988, Guzzetti et al 1988). The computation of the f_C is based on the decomposition of the AR spectrum into root components with power P_i and frequency f_i and computing a weighted mean of the frequencies of the roots:

$$f_C = \frac{\sum_i f_i P_i}{\sum_i P_i} \tag{5}$$

where i is an index of the roots which fall inside the frequency band of interest (Mainardi et al 1995)[2]. Usually only components which exceed 5% of the total power of the spectrum are accounted for (Pagani et al 1986). The band-wise f_{MEAN} is defined as the centre of gravity of the spectral band:

[1] The same abbreviations as used in Chapter 2.4. are used here for simplicity of notation. From here on, these abbreviations refer to band-wise estimates.
[2] The details of computing the f_C were verified by personal communication with Dr Luca Mainardi (Polytechnic University of Milan, Milan, Italy).

$$f_{MEAN} = \frac{\int_{f=f_1}^{f_2} fS(f)df}{\int_{f=f_1}^{f_2} S(f)df} \quad (6)$$

The band-wise f_{MED} is introduced as the frequency which divides the spectral band into two regions with equal power:

$$\int_{f=f_1}^{f_{MED}} S(f)df = \int_{f=f_{MED}}^{f_2} S(f)df \quad (7)$$

These estimators aim to locate the characteristic frequency of the oscillations within a specified frequency band. The spectrum within a frequency band may be considered as a distribution function with limited tails. The shape of the distribution is strongly dependent on the signal, spectral estimation and selected frequency band (Figures 4 - 5). The optimal location parameter is dependent on the shape of the distribution function and selected criteria for optimality. For example, the sample median is the maximum likelihood estimate of location with the Laplacian distribution, while the sample mean is that of the normal distribution (DeGroot 1975, Suoranta 1995). In practice, the selection of an optimal estimator is often ambiguous, and instead we need to select an appropriate estimator. This problem has been discussed by Suoranta (1995).

In Figures 4 - 5, AR spectral estimates of the HR signal are presented together with f_{MEAN}, f_{MED} and f_C estimations on the LF band [0.04 - 0.15 Hz (Task Force ESC & NASPE 1996)]. The AR model order is varied from that proposed by AIC (Akaike 1974) to 30 and 50. The higher model orders should in principle provide more realistic spectral estimates with real data (Chapter 2.4.1). It may be noted that the shape of the spectral distribution on the LF band is highly dependent on the model order, and with higher model orders the band contains typically multiple peaks. Consequently, especially the f_C is seen to be strongly dependent on the selected model order, while the f_{MEAN} and the f_{MED} show less variations with the model order.

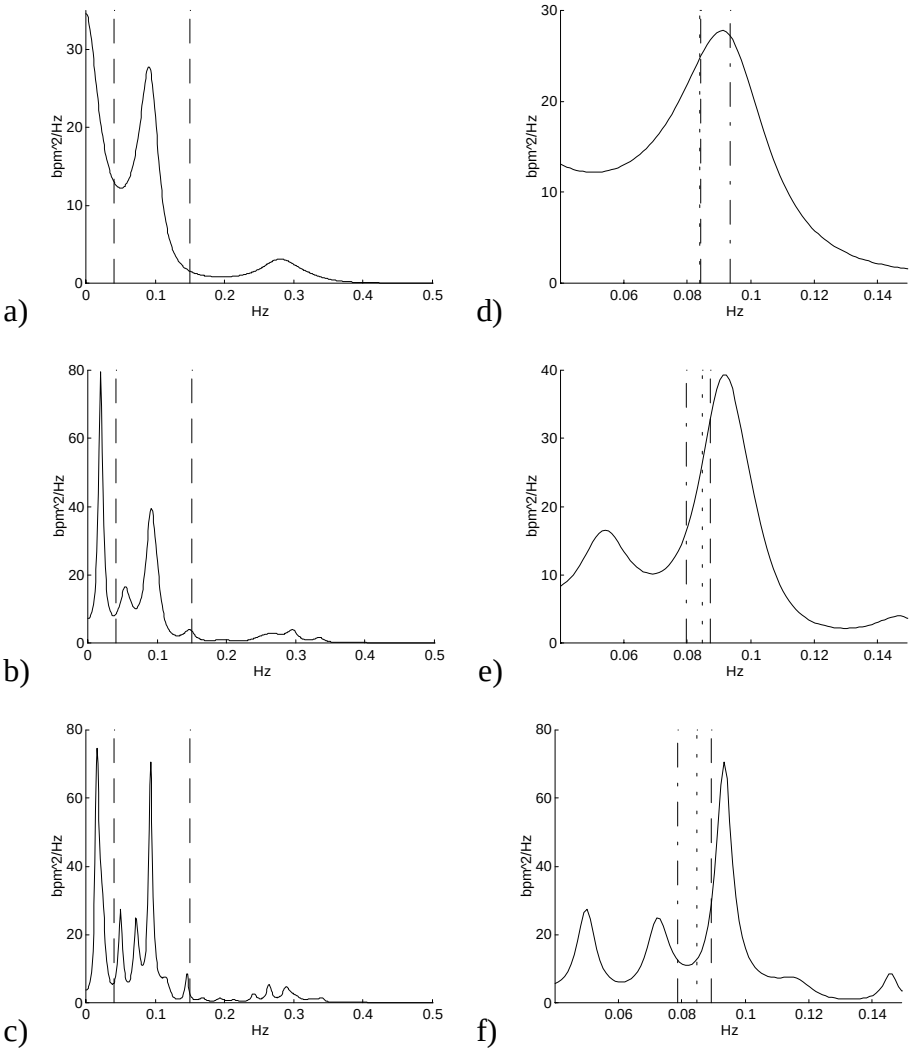

Figure 4. Typical HR spectral estimates with different AR model orders (data length 300). In leftmost panels, vertical lines indicate spectral band between 0.04 - 0.15 Hz. In rightmost panels, vertical lines indicate f_{MED} *(dashed line),* f_{MEAN} *(dotted), and* f_C *(dashed-dotted). Model order is: a) and d) 7, according to AIC (Akaike 1974); b) and e) 30; c) and f) 50. Note dependence of spectral shape, and consequently in particular of* f_C*, on model order.*

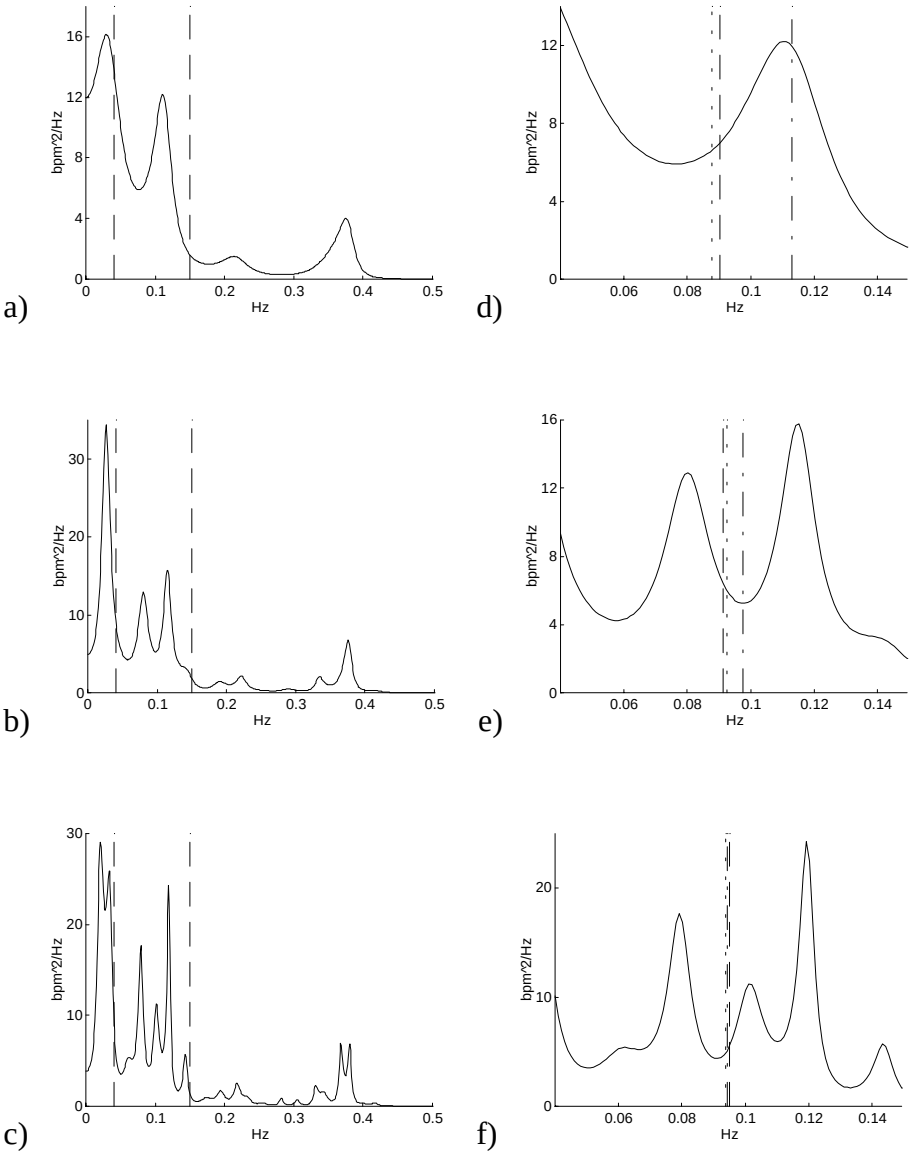

Figure 5. Another set of typical HR spectral estimates with different AR model orders (data length 210). In leftmost panels, vertical lines indicate spectral band between 0.04 - 0.15 Hz. In rightmost panels, vertical lines indicate f_{MED} *(dashed line),* f_{MEAN} *(dotted), and* f_C *(dashed-dotted). The model order is: a) and d) 10, according to AIC (Akaike 1974); b) and e) 30; c) and f) 50.*

To study the performance of these three location estimators with real data, the data of publication I was reanalysed and band-wise f_{MEAN}, f_{MED} and f_C computed. Supine, sitting and standing positions were considered. Goodness of the parameters was assessed in four terms:

1. Parameter standard deviation is the standard deviation of the parameter computed over 100 overlapping (3.3 %) periods (N=301) of stationary data (N=1301). Stationary data was generated by first fitting an AR model (model order 30) to real time series data and then generating data by filtering synthetic stationary white noise with the AR model coefficients. This procedure made it possible to obtain stationary data which match the spectral characteristics of the real cardiovascular data. In parameter computation, AR spectral estimation (model order 30) was used.

2. Sensitivity of the parameter to variations in the model order is defined as a standard deviation of the parameter computed by estimating the spectrum of each time series using several AR model orders. The model orders 10, 15, 20, 25, 30 and 40 were used.

3. Sensitivity of the parameter to variations in the frequency band is defined as a standard deviation of the parameter computed for each time series by estimating the parameter using several frequency band limits. Variations in the LF band limits were introduced as described in publication I (lower limit between 0.02 and 0.06 Hz, upper limit between 0.11 and 0.15 Hz, resulting in 9 different estimations).

4. Ability of the parameter to discriminate between the NT, BHT and HT groups. F and P values were obtained by ANOVA for repeated measurements. Discrimination power was analysed with different model orders and frequency bands, but model order 30 and frequency band 0.04 - 0.15 Hz were used in the final analysis.

The use of real data from various postures and subject groups guaranteed that a large variety of realistic spectral shapes were represented in the analysis.

Table 2 Mean parameter standard deviation of the different characteristic frequency estimators with varying model order. Unit is 10^{-3} Hz.

		Supine			Sitting			Standing			
		NT	BHT	HT	NT	BHT	HT	NT	BHT	HT	Mean
SBP	f_{MEAN}	3.2	3.5	3.1	3.4	3.4	3.0	2.8	2.5	3.0	3.1
	f_{MED}	5.0	5.9	4.8	5.1	5.5	4.5	4.4	3.8	4.0	4.8
	f_C	5.2	5.5	4.7	5.2	5.5	4.6	3.9	3.6	4.3	4.7
DBP	f_{MEAN}	3.6	3.5	3.4	3.1	2.9	3.2	2.8	2.6	2.7	3.1
	f_{MED}	5.6	5.9	5.7	5.3	4.6	4.8	4.2	3.8	3.7	4.8
	f_C	5.5	5.5	5.3	5.2	4.3	4.4	3.9	3.7	4.0	4.7
HR	f_{MEAN}	3.3	3.2	3.6	3.3	3.2	3.9	3.1	2.8	2.8	3.3
	f_{MED}	5.1	5.3	6.1	5.7	6.0	5.8	4.5	4.2	4.1	5.2
	f_C	7.0	7.0	7.4	6.6	6.4	6.6	5.6	4.8	5.0	6.3

Table 3. Mean standard deviation of the different characteristic frequency estimators with varying model order. Unit is 10^{-3} Hz.

		Supine			Sitting			Standing			
		NT	BHT	HT	NT	BHT	HT	NT	BHT	HT	Mean
SBP	f_{MEAN}	1.9	2.1	1.8	1.8	1.6	1.7	1.1	1.1	1.4	1.6
	f_{MED}	2.6	3.2	2.8	2.4	2.6	2.6	1.4	1.3	1.4	2.6
	f_C	7.4	7.2	8.2	7.1	7.3	8.1	4.2	4.0	4.0	6.4
DBP	f_{MEAN}	1.8	1.9	1.7	1.6	1.4	1.5	1.1	1.1	1.0	1.5
	f_{MED}	2.5	3.2	2.6	2.4	2.4	2.4	1.5	1.4	1.3	2.2
	f_C	7.3	8.9	6.7	7.0	6.9	6.5	4.0	4.4	4.1	6.2
HR	f_{MEAN}	3.1	2.9	2.7	2.3	2.0	2.1	1.8	1.3	1.5	2.2
	f_{MED}	4.1	3.8	3.6	3.5	3.1	3.2	2.5	1.8	2.2	3.1
	f_C	8.4	8.5	6.7	8.9	8.7	9.0	6.5	5.6	7.0	7.7

Table 4. Mean standard deviation of the different characteristic frequency estimators with varying frequency band. Unit is 10^{-3} Hz.

		Supine			Sitting			Standing			
		NT	BHT	HT	NT	BHT	HT	NT	BHT	HT	Mean
SBP	f_{MEAN}	6.4	7.5	7.0	5.8	6.3	6.3	3.6	3.7	3.8	5.6
	f_{MED}	5.6	8.1	6.7	5.0	6.0	5.8	2.3	2.4	2.1	4.9
	f_C	7.9	9.5	8.5	7.5	7.8	8.3	4.6	4.8	4.8	7.0
DBP	f_{MEAN}	6.5	7.5	6.9	5.9	6.0	6.2	3.7	4.0	3.9	5.6
	f_{MED}	5.7	8.2	6.8	5.3	5.0	5.6	2.6	2.6	2.2	4.9
	f_C	8.0	9.1	8.5	7.7	7.6	7.8	4.7	4.8	4.7	7.1
HR	f_{MEAN}	9.9	10.0	9.5	10.1	9.8	8.6	7.6	7.0	7.5	8.9
	f_{MED}	11.1	11.0	10.7	12.0	11.0	9.3	7.4	6.5	6.7	9.5
	f_C	11.5	12.6	12.0	12.6	11.5	11.3	9.1	8.4	9.4	10.9

Table 5. Group mean values of the different characteristic frequency estimators. Unit is 10^{-3} Hz.

		Supine			Sitting			Standing		
		NT	BHT	HT	NT	BHT	HT	NT	BHT	HT
SBP	f_{MEAN}	88	84	86	88	83	84	85	82	83
	f_{MED}	84	80	84	85	79	80	82	78	79
	f_C	85	82	82	85	80	81	82	79	81
DBP	f_{MEAN}	87	83	86	86	82	84	85	82	82
	f_{MED}	84	80	84	83	78	79	82	78	79
	f_C	85	79	83	84	80	80	83	79	80
HR	f_{MEAN}	96	93	95	92	87	89	88	84	85
	f_{MED}	94	89	94	90	84	86	85	81	81
	f_C	95	94	93	91	87	88	87	81	83

Table 6. Discrimination power of the different characteristic frequency estimators obtained by ANOVA of repeated measurements.

	f_{MEAN}		f_{MED}		f_C	
	F	P	F	P	F	P
DBP	7.88	0.0005	6.52	0.0017	7.15	0.0009
SBP	7.37	0.0008	5.85	0.0033	6.15	0.0024
HR	5.52	0.0045	5.74	0.0036	5.00	0.0074

The results are reported as mean values for each posture and subject group in Tables 2 - 6. The f_{MEAN} showed the lowest parameter standard deviation (Table 2). The f_{MED} and the f_C showed equal standard deviation with BP time series, but with HR time series the former had a lower standard deviation than the latter. With real data and low model order (<25), the f_C could not always be computed as the spectral estimate did not show poles on the LF band. When the model order was selected by the AIC, 23 out of 276 HR spectral estimations did not have a pole on the LF band. The cases which did not show spectral peaks on the LF band with all the model orders tested are excluded from the results in Table 3. The f_C showed clearly the highest sensitivity for the model order or the frequency band variations (Tables 3 - 4). The f_{MEAN} showed a lower sensitivity to model order variations than the f_{MED} (Table 3), while the sensitivity of these parameters to frequency band variations was equal (Table 4).

The parameter standard deviation and especially the sensitivity to model order or frequency band variations were highest in the HR spectral estimates. This indicates that the HR spectral shapes are somewhat different to those of BP on the LF band. There were no clear between-group differences in the behaviour of the estimates. In the standing position, the standard deviation and sensitivity of

the parameters were lower than in the sitting or supine positions. This may be a consequence of the enhanced LF component in standing position reported earlier (Turjanmaa et al 1990). This phenomenon suggests that in the standing position an elevated sympathetic modulation may give rise to more regular LF oscillations which, in turn, may be seen as clearer spectral shapes. Estimation of the characteristic frequencies with clear spectral shapes may not be as sensitive to variations in spectral estimation and frequency band selection as is the case with more complex shapes.

The different parameters provided comparable group mean values (Table 5), though there was a tendency for $f_{MED} \leq f_C \leq f_{MEAN}$. The selection of the model order and frequency band limits did not show a strong influence on the discrimination power of the estimates (data not shown). There were no significant differences in the discrimination power of the different estimates (Table 6).

It may be summarised that the band-wise f_C was found to be the poorest estimate of the characteristic frequency due to its higher sensitivity to model order and frequency band variations. Another disadvantage of the f_C was the fact that it can not be estimated if the AR spectral estimate does not show poles on a selected frequency band. The band-wise f_{MEAN} and f_{MED} were found to provide comparable results, the former showing slightly better performance in general.

4.1.2 Summary and Discussion of publication I

The band-wise f_{MED} was successfully applied to the HR and BP variability data on the LF band. The frequency limits were optimised for the maximal group differences between NT, BHT and HT groups. The finding of our previous study (Takalo et al 1994a) was confirmed: the frequency shift in the LF oscillations occurred in the BHT group when compared with the NT and HT subjects. The study showed the importance of focusing on the spectral shift in the spectral analysis of cardiovascular signals.

Earlier studies have not reported any spectral shift in hypertension when the f_C was used to quantify the frequency of oscillations (Pagani et al 1986, 1988, Guzzetti et al 1988). This may be partly due to methodological factors. In this thesis it was found that the f_C was the poorest estimate of the spectral shift. This

is further emphasized if a low model order as usually suggested by AIC is used: with low model orders the f_C may be strongly sensitive to the model order selection (Figures 4 - 5) and even not computable if no spectral pole is found on the frequency band of interest (Table 2). This may mask the inter-group differences. To quantify the shift, more robust estimates, such as the f_{MEAN} or f_{MED}, should be employed.

4.1.3 Implications

Former studies (Takalo et al 1994a, 1994b) and publication I emphasise the importance of appropriate methodology in the analysis of HR and BP variability. In particular:

- The selection of a high enough model order in the AR spectral analysis is needed to resolve the spectral details of the real data. Usually, a higher model order than that proposed e.g. by the AIC is needed. The upper limit has been stated to be between 33 - 50 % of the data length (Kay 1988).

- One needs to focus on the frequency content rather than the power of the signal spectrum to discriminate the BHT group from NT and HT groups.

- Quantification of the band-wise characteristic frequency may be carried out by computing parameters like f_{MEAN}, f_{MED} or f_C. Of these, the f_C provides the poorest performance. The f_{MEAN} and f_{MED} provide comparable results, the former showing slightly better performance.

- The f_{MEAN} and f_{MED} are simple to compute, and they can always be computed in any given spectral estimate and frequency band. They can be computed on the FFT based spectral estimates, too.

- The spectral estimation method and in particular selection of the frequency limits influence the estimation of the band-wise characteristic frequency. Care should be taken to apply appropriate spectral estimation methods and to select the desired spectral band.

4.2 Multivariate modelling

In this thesis, multivariate modelling methods were developed for analysing interactions between HR, BP and respiration. First, a general framework for linear multivariate time series modelling of physiological signals is presented. Then, the framework is used by adapting two special sub-class models for the modelling of cardiovascular signals, namely an MAR model and an MAR model with an exogenous AR input, or an MARXAR model. The models are presented from the theoretical point of view, their properties are discussed and examples using real data are presented. The application of the models to large amounts of physiological data is beyond the scope of this thesis.

4.2.1 Rationale

The cardiovascular system is inherently a multivariate closed-loop system. Hence, the need for multivariate closed-loop analysis methods to study the system was recognised long ago (Akselrod et al 1985). The main advantage of multivariate closed-loop modelling over univariate or open-loop modelling is its theoretical ability to describe intersignal relationships in a realistic manner. During the last decade, efforts have been made to develop closed-loop modelling methods to analyse the cardiovascular system (Kalli et al 1986, Baselli et al 1988b, Mullen et al 1997, Barbieri et al 1996a). Common to all these approaches has been the use of linear time series modelling between the acquired signals to describe closed-loop relationships. There are several reasons for the use of linear time series models for a non-linear system:

- during static short-term conditions, the cardiovascular system may be reasonably well approximated by a linear system. When the conditions are changed, a new model is identified (piece-wise linear approach)

- linear system theory has a strong theoretical foundation compared with the non-linear system theory

- linear analysis produces results that may be physiologically interpreted.

Yet, no closed-loop modelling approach has been implemented outside methodological studies. This may be speculated to be due to several reasons.

Most importantly, any method to reach wide-spread use in biomedical research must be based on sound theory and must be methodologically adaptable by other researchers (Saranummi et al 1997). The modelling approaches presented so far may be criticised as not fully meeting these conditions. MAR modelling, proposed by Kalli et al (1986) and later applied by Grönlund et al (1995) and Barbieri et al (1996a), provides an attractive method since it is easily adapted to different sets of signals and may be identified by standard procedures (Kalli et al 1988a). However, the analysis of interactions between signals is based on the assumption of independent noise sources in the model, a condition which is seldom met within cardiovascular data (Kalli et al 1988a). This causes some bias in the results and hence limits the use of the method. The advanced custom model proposed by Baselli et al (1988b) does not suffer from the problem of noise source dependence as the model involves a mechanism for handling the co-existing variability in the SBP and RRI, namely the 0-delay transfer path from SBP to RRI. Despite this inclusion, the model has failed to gain a widespread use, perhaps due to its custom structure and identification procedure. The application of the model to a different set-up of signals is laborious. Finally, the recent approach by Mullen et al (1997) introduced a sophisticated model which separately studies the mechanical and neural interactions between HR, BP and ILV, and also includes a non-linear element for mimicking sinus node function. The approach is based on the assumption of mutually independent noise sources, and may hence suffer from the same problems as the MAR modelling approach by Kalli et al (1988b).

The objective of this thesis was to develop multivariate analysis methods that would overcome the problems faced by previous approaches. One of the driving principles of the study was to gain approaches which do not suffer from the methodological deficiencies mentioned above, which are based on general system identification theory and which may be adapted by using the generally available software tools, like Matlab®. The final objective was to define methods that can be relatively easily applied in different set-ups and with large numbers of subjects to study.

4.2.2 Basic concepts

Only discrete time domain theory is presented in this thesis. The notation used in this thesis is adapted from Ljung (1987). The most central concepts are repeated here for clarity.

A vector signal $\boldsymbol{u}(t) = [u_1(t)\ u_2(t)\ \ldots\ u_L(t)]^T$ is an L-variate signal which obtains new values at each time instant t. For simplicity of notation, we usually write $\boldsymbol{u}$ instead of $\boldsymbol{u}(t)$. Any transfer functions are presented by using a delay operator q

$$q^{-1}\boldsymbol{u}(t) = \boldsymbol{u}(t-1) \tag{8}$$

which allows the notation for multivariate filtering operation:

$$\begin{aligned} \boldsymbol{y}(t) &= \sum_{k=1}^{\infty} \boldsymbol{g}(k)\boldsymbol{u}(t-k) = \sum_{\boldsymbol{k}=1}^{\infty} \boldsymbol{g}(k)\left(q^{-k}\boldsymbol{u}(t)\right) \\ &= \left[\sum_{k=1}^{\infty} \boldsymbol{g}(k)q^{-k}\right]\boldsymbol{u}(t) = \boldsymbol{G}(q)\boldsymbol{u}(t) \end{aligned} \tag{9}$$

where we introduce a notation for matrix polynomial

$$\boldsymbol{G}(q) = \sum_{k=1}^{\infty} \boldsymbol{g}(k)q^{-k} \tag{10}$$

In the eq. 9 - 10, $\{\boldsymbol{g}(k),\ k=1\ldots\infty\}$ is the L x L matrix polynomial which introduces the coefficients of the multivariate filter. According to Ljung's notation, $\boldsymbol{G}(q)$ (or just $\boldsymbol{G}$) is called the transfer function of a linear system. The term transfer function is usually reserved for the z-transform of $\{\boldsymbol{g}(k),\ k=1\ldots\infty\}$, but in this notation the difference does not tend to be observed (Ljung 1987).

The transfer function in the eq. 10 is transformed into frequency function by the substitution $q=e^{i\omega}$, where $-\pi\leq\omega\leq\pi$. The ω is called normalised frequency and can be transformed into normal frequency domain by $\omega = 2\pi f/f_s$, where f_s is the sampling frequency.

4.2.3 Framework

In publication II, a general multivariate linear modelling concept is adapted from Lung's presentation (Ljung 1987):

$$\boldsymbol{A}(q)\boldsymbol{y}(t) = \boldsymbol{F}^{-1}(q)\boldsymbol{B}(q)\boldsymbol{u}(t) + \boldsymbol{D}^{-1}(q)\boldsymbol{C}(q)\boldsymbol{e}(t) \tag{11}$$

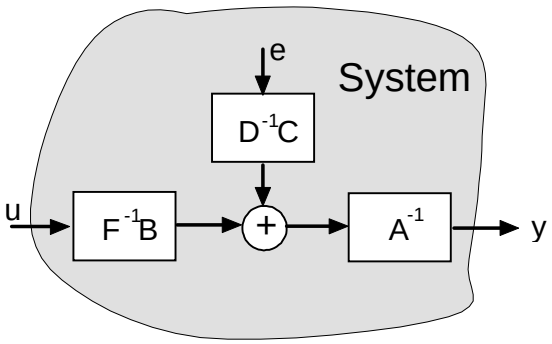

Figure 6. Schematic presentation of general linear time series model (From publication II).

where polynomials $\boldsymbol{A}(q)$, $\boldsymbol{C}(q)$ and $\boldsymbol{D}(q)$ have the identity matrix $\boldsymbol{I}$ in their zero-delay term. Vector signals $\boldsymbol{y}$, $\boldsymbol{u}$ and $\boldsymbol{e}$ represent output, input and unknown disturbance signals of the system, respectively (Figure 6). The model combines the most commonly used linear time series models and hence emphasises their mutual similarity. The most important property of the model in the eq. 11 is its convergence with the real transfer functions of almost any causal, linear, time-invariant, stationary system in the sense that

$$\begin{aligned} \boldsymbol{A}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{F}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{B}_{\boldsymbol{M},\boldsymbol{N}}(e^{i\omega}) &\to \boldsymbol{G}(e^{i\omega}) \\ \boldsymbol{A}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{D}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{C}_{\boldsymbol{M},\boldsymbol{N}}(e^{i\omega}) &\to \boldsymbol{H}(e^{i\omega}) \end{aligned} \tag{12}$$

uniformly in ω as $N>>M \rightarrow \infty$ (Ljung 1987). $\boldsymbol{G}$ and $\boldsymbol{H}$ are the real system transfer functions from the input to the output, and from the disturbance to the output, respectively, and M and N refer to model order and data length, respectively. Hence, provided that the data length is sufficient, and the model has high enough an order to approximate the real system properties, the model is capable of describing the system properties arbitrarily well in frequency domain. The same holds true of those reduced models which include some sub-group of the model coefficients [$\boldsymbol{A}$, $\boldsymbol{B}$, $\boldsymbol{F}$] and [$\boldsymbol{A}$, $\boldsymbol{C}$, $\boldsymbol{D}$]. These models include MAR model ($\boldsymbol{A}$ coefficient only), the MARXAR model ($\boldsymbol{A}$, $\boldsymbol{B}$, and $\boldsymbol{F}$) and dynamic adjustment models ($\boldsymbol{A}$ and $\boldsymbol{D}$). This lays a solid theoretical foundation for the multivariate linear time series modelling.

The analysis of interactions between different variables is based on spectral decomposition. Suoranta (1990) provides a complete presentation of the spectral decomposition in the case of the MAR model. In this thesis, the presentation is extended for the general linear model structure presented in the eq. 11.

The analysis of interactions is based on the mutual independence of the model noise sources $\boldsymbol{e}$ and the independence of the past input [$\boldsymbol{u}(t\text{-}k)$] and the noise sources $\boldsymbol{e}$. Assuming the input $\boldsymbol{u}(t\text{-}k)$ to be uncorrelated with the disturbance $\boldsymbol{e}$, the effect of $\boldsymbol{u}$ on the spectrum of the output $\boldsymbol{y}$, $\boldsymbol{S}_{\boldsymbol{y:u}}(\omega)$, is

$$\boldsymbol{S}_{\boldsymbol{y:u}}(\omega) = \boldsymbol{T}_{\boldsymbol{G}}(e^{i\omega})\boldsymbol{S}_{\boldsymbol{u}}(\omega)\boldsymbol{T}_{\boldsymbol{G}}(e^{i\omega})^{*} \tag{13}$$

where * denotes matrix conjugate transpose, $\boldsymbol{S}_{\boldsymbol{u}}$ is the spectrum of $\boldsymbol{u}$ and

$$\boldsymbol{T}_{\boldsymbol{G}}(e^{i\omega}) = \boldsymbol{A}^{-1}(e^{i\omega})\boldsymbol{F}^{-1}(e^{i\omega})\boldsymbol{B}(e^{i\omega}) \tag{14}$$

is the total transfer function matrix from the input to the output ($\boldsymbol{G}$ refers to the eq. 12). Provided that $\boldsymbol{u}$ are mutually uncorrelated, $\boldsymbol{S}_{\boldsymbol{u}}$ is diagonal and the effects of each u_i may be studied separately by the partial spectra

$$\boldsymbol{S}_{\boldsymbol{y:}u_i}(\omega) = \boldsymbol{T}_{\boldsymbol{G}}(e^{i\omega})\boldsymbol{S}_{u_i}(\omega)\boldsymbol{T}_{\boldsymbol{G}}(e^{i\omega})^{*} \tag{15}$$

where $\boldsymbol{S}_{ui}$is the input spectral matrix where other elements are zero, except $\boldsymbol{S}_{ui}(n,m) = \boldsymbol{S}_{u}(n,m)$ when $n = m = i$ (m and n being the column and row indexes, respectively). Similarly, the effect of the disturbance $\boldsymbol{e}$ on the output spectrum is

$$\boldsymbol{S}_{y:e}(\omega) = \boldsymbol{T}_{H}(e^{i\omega})\Sigma\boldsymbol{T}_{H}(e^{i\omega})^{*} \tag{16}$$

where

$$\boldsymbol{T}_{H}(e^{i\omega}) = \boldsymbol{A}^{-1}(e^{i\omega})\boldsymbol{D}^{-1}(e^{i\omega})\boldsymbol{C}(e^{i\omega}) \tag{17}$$

Σ is the variance-covariance matrix of the white noise sources $\boldsymbol{e}$, defining the spectra of the white noises. Again, if $\boldsymbol{e}$ are mutually uncorrelated (Σ is diagonal), their effect may be studied individually by noise conditioned spectra or partial spectra:

$$\boldsymbol{S}_{y:e_i}(\omega) = \boldsymbol{T}_{H}(e^{i\omega})\Sigma_{i}\boldsymbol{T}_{H}(e^{i\omega})^{*} \tag{18}$$

where the elements of Σ_i are zero, except $\Sigma_i = \Sigma(n,m)$ when $n = m = i$. To analyse the relative contribution of each disturbance e_i to the variability in each signal x_j, normalisation of the partial spectrum may be utilised. This yields the concept of NSC (Kalli et al 1988a, Oguma 1981)

$$\Gamma_{ij}(\omega) = \left| \frac{\boldsymbol{S}_{yj:ei}(\omega)}{\boldsymbol{S}_{yj}(\omega)} \right| \tag{19}$$

where $\boldsymbol{S}_{yj:ei}$ is the partial spectrum of y_j originating from the noise source e_i (eq. 18) and $\boldsymbol{S}_{yj}$is the spectrum of y_j. The contribution of the input u_i may be computed by replacing $\boldsymbol{S}_{yj:ei}$ by $\boldsymbol{S}_{yj:ui}$.

The mean NSC, i.e. the mean of Γ_{ij} over some frequency range, has been used in some studies (Kalli et al 1988b, Turjanmaa et al 1990, Grönlund et al 1991, 1995). The problem with the mean NSC is its sensitivity to numerical inaccuracies. The least squares model identification yields to a better fit on the frequencies with more spectral power. However, when computing the mean NSC, all the frequencies gain equal weight. This is inconvenient if the spectrum

of the system contains frequencies with low power and hence low weight in model identification. Instead, we may use the NSC ratio (NSCR) (Suoranta & Rantala 1991), which states how much of the signal power in y_i in the frequency range from ω_1 to ω_2 originates from the noise source of the other variable y_j:

$$\Gamma_{ij}(\omega_1,\omega_2) = \left| \frac{\int_{\omega=\omega_1}^{\omega_2} \boldsymbol{S}_{yj:ei}(\omega)d\omega}{\int_{\omega=\omega_1}^{\omega_2} \boldsymbol{S}_{yj}(\omega)d\omega} \right| \tag{20}$$

In the eq. 20, the NSC is weighted by the actual variability present in the signal on each frequency, and hence the NSCR is more robust than the mean NSC.

The analysis of spectral decomposition has several advantages:

- Frequencies with high power are more dominant in spectral decomposition analysis compared with frequencies of low power. This supports the least squares model identification, which yields a better fit with the high power ranges of variability.

- The method provides decomposition into root components of variability which is actually present in a signal.

- When applied in a band-wise manner (NSCR), the analysis is relatively insensitive to model order variations, provided that the model order is high enough (publication V).

It should be noted that any single transfer function (or impulse response) between the variables may be computed directly from the model coefficient matrices and that the models presented allow the analysis of transfer functions as well (Ljung 1987). However, the quantification of single transfer functions is more sensitive to modelling inaccuracies than spectral decomposition analysis.

The assessment of the goodness of the model involves both numerical validation and final validation. Numerical validation means inspection of the justification

of the assumptions made *a priori* (whiteness and mutual independence of $\boldsymbol{e}$, etc.). The multiple correlation coefficient (Ljung 1987)

$$R_{y\boldsymbol{i}}^2 = 1 - \frac{\sum_{t=1}^{N} e_i^2(t)}{\sum_{t=1}^{N} y_i^2(t)} \tag{21}$$

expresses the proportion of the total variability in y_i that is explained by the model. This proportion is often called the prediction ratio. It may be used for assessing the goodness of the model for the data especially when comparing the performance on the same data of competitive models. It should be noted that the model may fit the data perfectly even though the prediction ratio is <1. The final validation of the goodness of the model aims to discover whether the model is good enough for its purpose. As discussed in publication II, this task is highly context-dependent and usually involves subjective validation (Ljung 1987).

4.2.4 MAR modelling

MAR modelling provides a simple and well-known method for studying intersignal properties of a closed-loop system. Originally, the method was applied for analysis of the dynamics of a nuclear reactor (Oguma 1981, 1982, Upadhyaya et al 1980). Kalli et al (1986) proposed the method for the analysis of the cardiovascular system. They used the first canonical version of the model:

$$\begin{aligned} \boldsymbol{y}(t) &= -\sum_{k=1}^{M_A} \boldsymbol{a}(k)\boldsymbol{y}(t-k) + \boldsymbol{e}(t) \Leftrightarrow \\ \sum_{k=0}^{M_A} \boldsymbol{a}(k)\boldsymbol{y}(t-k) &= \boldsymbol{e}(t) \Leftrightarrow \\ \boldsymbol{A}(q)\boldsymbol{y}(t) &= \boldsymbol{e}(t) \\ \boldsymbol{A}(q) &= \boldsymbol{I} + \sum_{k=1}^{M_A} \boldsymbol{a}(k) q^{-\boldsymbol{k}} \end{aligned} \tag{22}$$

The model describes the present value of $\boldsymbol{y}$ as a linear combination of the *past* values of the signal plus the prediction error. This form of the model may be

unambiguously identified when given the model order M_A and the signal $\boldsymbol{y}$, i.e. no other definitions are needed (Ljung 1987). The model may be identified by solving a set of linear equations, e.g. by a multivariate extension of the well-known Levinson algorithm (Kailath 1985). These facts, together with the principle presented in the eq. 12 make MAR modelling especially attractive. However, the noise sources of the model in the eq. 22 usually become dependent when applying the model to cardiovascular data (Kalli et al 1988a). This makes the analysis of intersignal interactions biased. One method for making the noise sources independent is based on another canonical implementation of the MAR model, namely (Suoranta 1990)

$$\begin{aligned} \boldsymbol{a}(0)\boldsymbol{y}(t) &= -\sum_{k=1}^{M_A} \boldsymbol{a}(k)\boldsymbol{y}(t-k) + \boldsymbol{e}(t) \Leftrightarrow \\ \sum_{k=0}^{M_A} \boldsymbol{a}(k)\boldsymbol{y}(t-k) &= \boldsymbol{e}(t) \Leftrightarrow \\ \boldsymbol{A}(q)\boldsymbol{y}(t) &= \boldsymbol{e}(t) \\ \boldsymbol{A}(q) &= \sum_{k=0}^{M_A} \boldsymbol{a}(k) q^{-\boldsymbol{k}} \end{aligned} \tag{23}$$

The difference between eqs. 22 and 23 is that in the eq. 22 the zero-delay term of $\boldsymbol{A}$ is no longer $\boldsymbol{I}$, but has ones (1s) on the main diagonal and possibly non-zero values elsewhere. To keep the model stable, no closed-loop transfer is allowed on the zero-delay (Baselli et al 1988b). This condition is met when the zero-delay term of the model, $\boldsymbol{a}(0)$, is organisable into the form: $\boldsymbol{a}(0,i,j)=1$ with all $i = j$, and $\boldsymbol{a}(0,i,j)=0$ with all $j>i$ (lower triangular form), or $\boldsymbol{a}(0,i,j)=0$ with all $j<i$ (upper triangular form). This form is no longer unambiguous since the directions of the zero-delay transfer paths have to be defined *a priori*. However, this makes it possible to include the noise source dependence in the model coefficients, and hence to make the noise sources independent.

The method proposed for identifying the model is based on a four-step procedure:

1. Organise the signals in data vector $\boldsymbol{y}$ by using physiological knowledge so that the immediate transfer mechanisms (zero-delay term) can be allowed from the signals with smaller index to the signals with higher index.

2. Identify the conventional MAR model (eq. 22) by a standard model identification procedure (e.g. Levinson algorithm).

3. Apply Cholesky decomposition (Kay 1988, Suoranta 1990) to decompose the noise source covariance matrix Σ into $\Sigma = \boldsymbol{SDS}^*$, where $\boldsymbol{D}$ is a diagonal matrix with $\boldsymbol{D}(1,1) = \Sigma(1,1)$, $\boldsymbol{D}(i,i) \leq \Sigma(i,i)$ for all $i>1$, and $\boldsymbol{S}$ is a lower triangular matrix with ones (1s) on the main diagonal.

4. Use $\boldsymbol{D}$ as a new noise source covariance matrix and transfer the model coefficients $\boldsymbol{A}(q)$ identified in step 1 into new ones by multiplying from the left by $\boldsymbol{S}^{-1}$. This transformation yields another canonical presentation of the system spectra in which the noise sources of the model are made definitely independent (diagonal noise source covariance matrix).

This procedure has several advantages: 1) it relies on generally available and well-known procedures (Levinson algorithm, Cholesky decomposition); 2) it makes the noise sources in the model definitely independent by including the independence in the model coefficients; 3) it does not affect model stability (Hannan & Deistler 1988). The disadvantage is that it needs correct *a priori* knowledge in order to yield correct results.

4.2.5 Summary of publications II - IV

In publication IV, the bias caused by noise source dependence in the MAR model is analysed and a method for making the noise sources definitely independent is presented. It was found that the noise source dependence may lead to serious errors (>100%) in NSCR analysis of HR, SBP and ILV signal interactions. The MAR modelling approach presented above was demonstrated to be suited for analysing intersignal relationships between HR, SBP and ILV. It was shown that the method works, i.e. it effectively makes the model noise sources independent. The results drawn from a single subject do not allow profound conclusions from the physiological point of view, but it can be seen that the analysis provides a reasonable assessment of cardiovascular control.

In publication III, the MAR modelling was demonstrated with a different set of signals, namely with ILV, HR, DBP and SBP. The study confirmed the findings of publication IV: the method presented is capable of making the noise sources independent, and hence it enables the use of MAR modelling even in the case where highly dependent variables (DBP and SBP) are used simultaneously in the model. Furthermore, time-variant MAR modelling and dynamic adjustment modelling of cardiovascular data were demonstrated. The dynamic adjustment modelling part was an application of the model proposed by Baselli et al (1988b). The time-variant MAR modelling was based on the conventional form of the model (eq. 22). The application demonstrates the ability of MAR modelling to adapt to various needs.

4.2.6 MARXAR model and summary of publication V

Despite its advantages, the MAR modelling has some disadvantages, too. First of all, it is not necessarily the structurally optimal model for studying cardiovascular dynamics. The MAR model is a model in which all the signals explain each other, i.e. transfer functions are allowed in all directions. However, this is not necessarily physiologically feasible. Especially, there is no evidence that a transfer mechanism from HR or BP to respiration exists. Theoretically, with a causal system and without any disturbances in measurements, this would not be a problem, but the non-existing transfer paths would reach zero-gain in identification. However, with real data, this may cause some problems. Respiratory activity is usually assessed by measuring the ILV signal which reflects the mechanics of the lungs. The ILV signal is then used in modelling to represent the total respiratory input to the cardiovascular system, the input which actually includes both the function of the respiratory centre and the mechanics of the lungs. Due to the central effects of the respiratory activity on the cardiovascular system, the change in HR during inspiration has been reported to precede the change in ILV (Saul et al 1989). This supports the assumption that there is some delay in transmission of the central command from the respiratory centre to the ILV signal (Perrott & Cohen 1996). Thus, the ILV may be considered as a delayed representative of the total respiratory input to the cardiovascular system. In causal modelling this may cause problems: the delay may shift the non-zero part of the cross-correlation function between ILV and HR (or ILV and BP) into negative which, in turn, means a shift of the transfer power from the transfer function $H_{\mathrm{HR:ILV}}$ (or $H_{\mathrm{BP:ILV}}$) to $H_{\mathrm{ILV:HR}}$ (or

$H_{ILV:BP}$). This means that the physiologically non-existing transfer paths ($H_{ILV:HR}$ or $H_{ILV:BP}$) may become non-zero. In addition, any disturbances correlating to HR or BP, and entering the ILV signal, may cause similar kinds of effects. For example, the impedance method for measuring ILV may reflect some cardiovascular variability due to variations in intrathoracic blood volume (AAMI 1989). In publications III and IV, these factors may cause the observed effect of HR and BP variability on the ILV signal. To overcome this problem, a more advanced model structure than that of the MAR model is needed.

In publication V, a new model for the analysis of cardiovascular interactions, namely the MARXAR model (Fig. 7), was introduced to overcome the problems with MAR modelling. The model introduces a negative delay in the ILV signal to control the 'non-causal' respiratory effect, i.e. the phase-lead of HR to ILV. In addition, the ILV signal is handled as a pure input to the system, i.e. no transfer paths from HR or BP to ILV are allowed. This structure mimics more closely the real physiological functioning of the cardiovascular system. The model is the first one to combine the non-causal respiratory input, proposed by Perrott and Cohen (1996), and closed-loop modelling. The model introduces also a phase-lead of SBP to ILV which has not been observed with real data. This was allowed to keep model identification simple. In principle, it should not

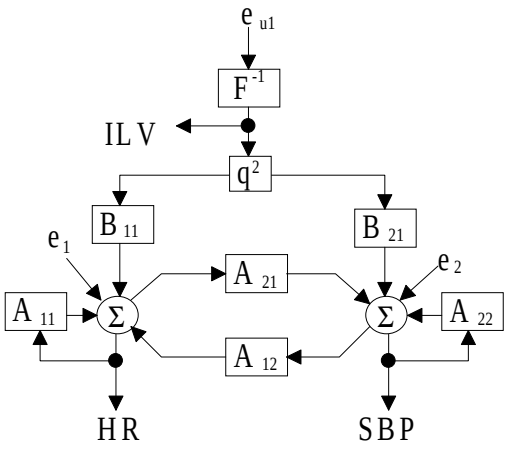

Figure 7. Schematic presentation of MARXAR model. (From publication V).

produce any problems as there exist no known influences of SBP on ILV; the coefficients corresponding to negative delays should become negligible with real data if no phase-lead of SBP to ILV occurs.

The model structure is that of the MARX model where the inputs are modelled as univariate AR processes, and the closed-loop process between HR and SBP is modelled by a MAR process presented in the eq. 23. The model structure has a strong physiological relevance, but it still relies on standard model structures. This enabled development of a model identification procedure which relies on generally available algorithms and software tools. This makes the model easily adaptable to other set-ups with slightly different signals or by other researchers.

The model identification procedure, the effect of model order and the stability of the NSCR estimates were studied. The analysis was based on simulation data, but also experimental data was considered. A linear simulation system was designed to match the general structure of the model (input-output relations) but to differ by transfer function structures (zero-pole transfer functions in the simulation system vs. all-zero transfer function blocks in the model). This design was to test the ability of the model to describe the dynamic interactions in case exact matching with system parameters is not possible. Model performance was studied by comparing the estimated NSCR estimates to theoretical values as a function of model order.

The results are presented in Figs. 8 - 11. It was found that the NSCR estimates were accurately estimated by the model in all the simulation cases studied, provided that the model order was sufficiently high (Figs. 8 - 9). The model order required was significantly higher than the order of the simulation system. This was due to different structures of the single transfer functions in the simulation system and the model. Moreover, it was found that after reaching a sufficient model order, a further increase in the order did not significantly affect the NSCR estimates. The NSCR estimates tended to vary as a function of the model order until a sufficient order was reached, and then stabilise. The sufficient order exceeded the values given by the objective model order selection criteria, such as the AIC (Akaike 1974). With simulation data, the AIC gave typically values of 5 - 7 for M_A and smaller values for M_B, while the NSCR estimate convergence required values $M_A \geq 12$ and $M_B \geq 7$.

The behaviour of the NSCR estimates was the same for experimental data (Figs. 10 - 11). With small model orders the NSCR estimates tended to vary as a function of the model order, but when the model order increased to $M_A \geq 25$ and $M_B \geq 20$ the estimates stabilised. A high model order was needed especially on the LF band, while on the HF band the stabilisation was reached with smaller model orders.

It should be noted that these estimations of sufficient model order exceed the model orders used in most previous studies which use objective criteria in selecting the model order (Kalli et al 1988b, Baselli et al 1988b, 1994, Barbieri et al 1996a). This finding that a relatively large model order is needed to accurately depict the dynamics of the cardiovascular system is not very surprising. It is a well-known property of the objective model order selection criteria that they tend to underestimate the model order when the real system transfer functions differ from those of the model by structure (e.g. all-zero vs. all-pole structure) (Ljung 1987, Kay 1988). As a high order of an all-zero system is needed to approximate a low order all-pole system, a high-order MARXAR (or MAR model) is required to portray the dynamics of a different linear system (like the simulation system in publication V), or the real cardiovascular system.

In publication V, the effect of different kinds of changes in the parameters of the system on the NSCR estimates was also demonstrated. The results show that the NSCR analysis is capable of describing slight changes in the system dynamics in an interpretable and robust way.

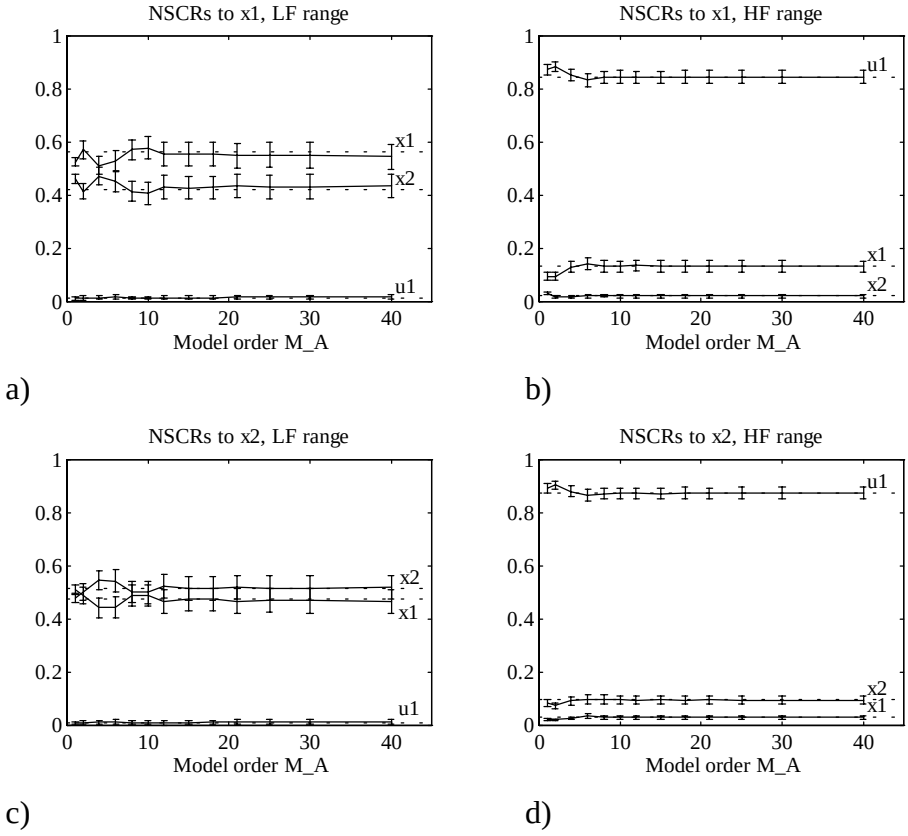

Figure 8. Effect of model order on NSCR estimates computed from simulation data. Solid lines present NSCR estimates for each variable according to model identification (mean + SD), while dashed lines show correct NSCR values. M_B=7 and M_F=5.

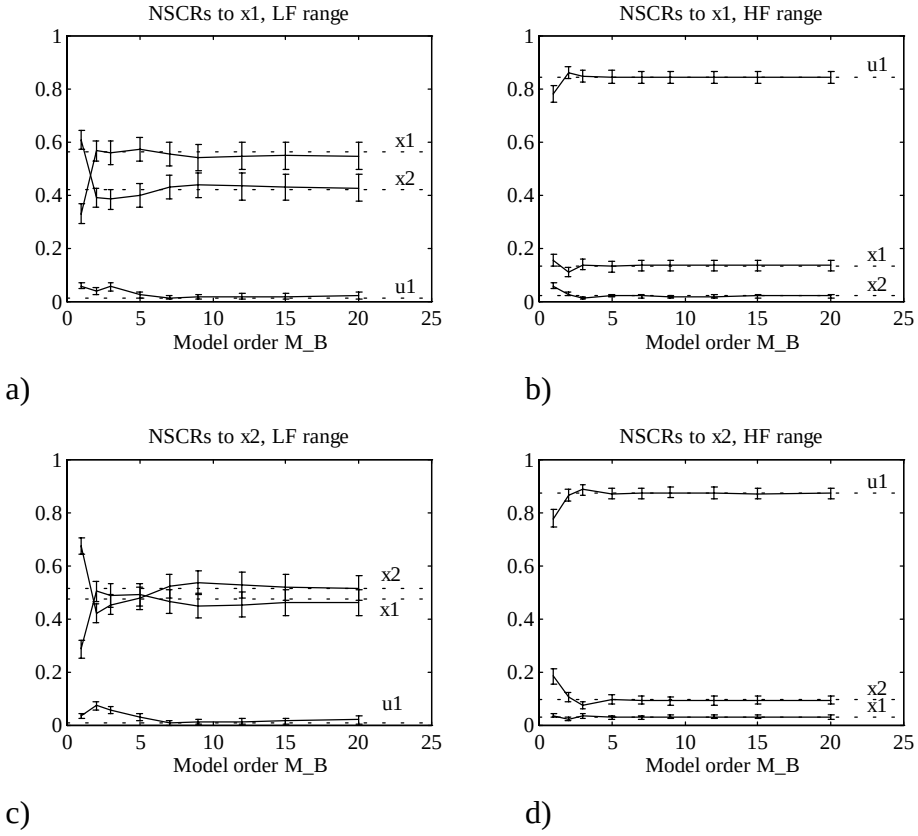

Figure 9. Effect of model order on NSCR estimates computed from simulation data. Solid lines present NSCR estimates for each variable according to model identification (mean + SD), while dashed lines show correct NSCR values. M_A=12 and M_F=5.

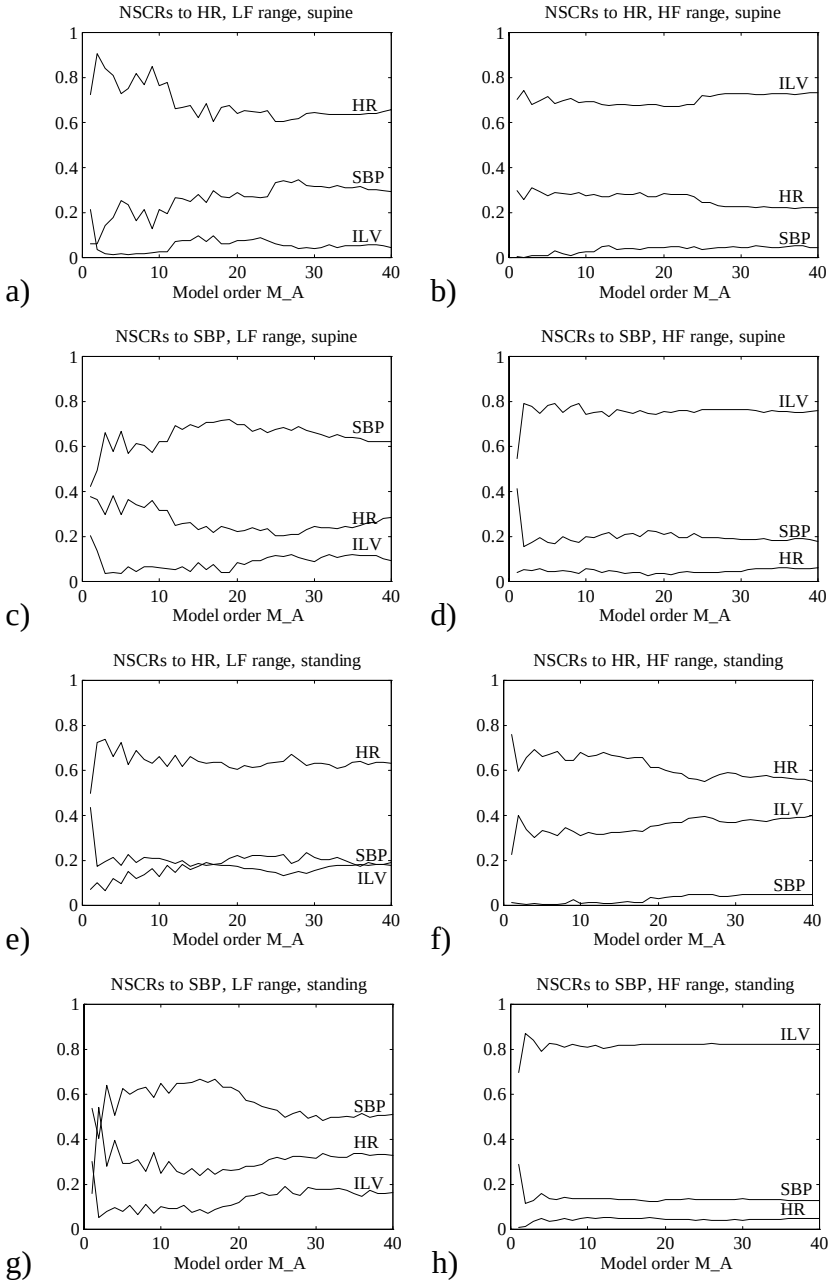

Figure 10. Effect of model order on NSCR estimates computed from experimental data, subject in supine (a - d) and standing (e - h) positions. Lines present NSCR estimates for each variable as a function of the model order. M_B=20 and M_F=10.

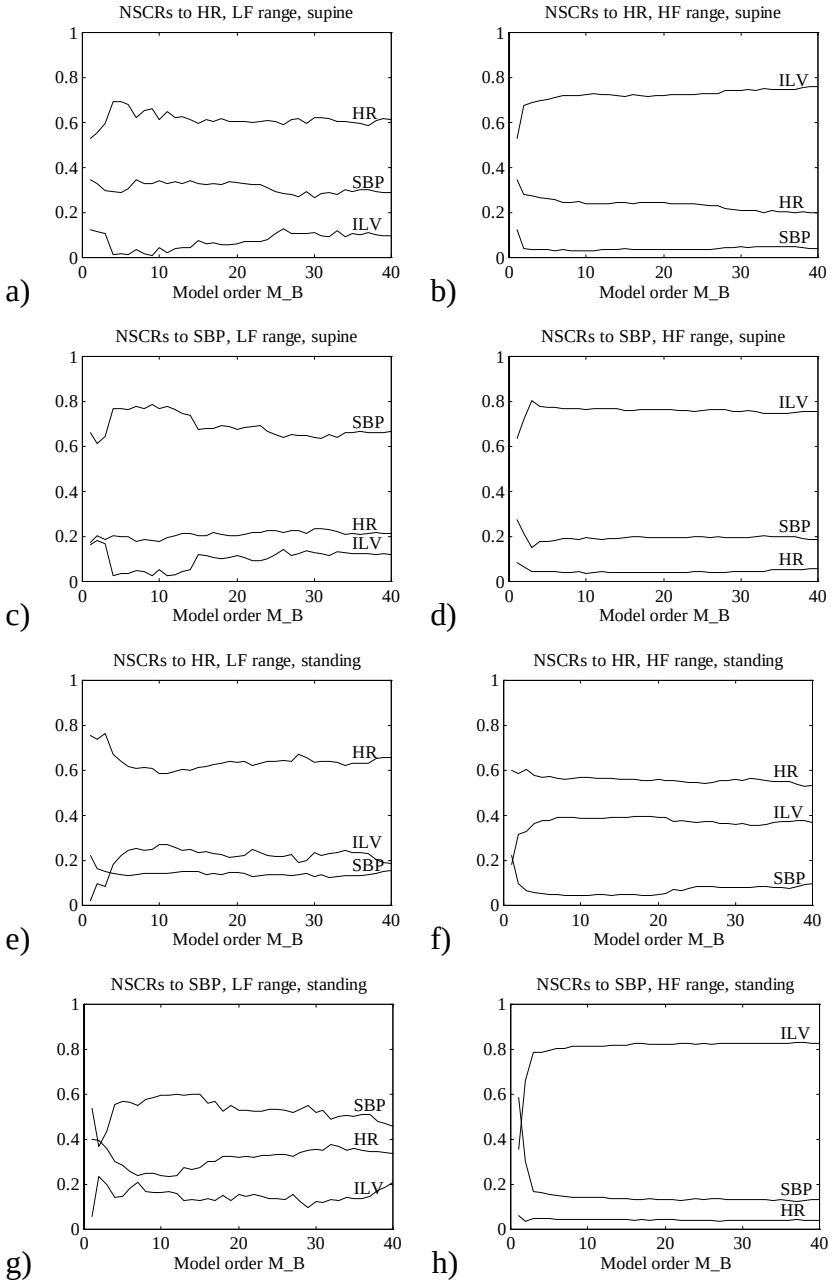

Figure 11. Effect of model order on NSCR estimates computed from experimental data, subject in supine (a - d) and standing (e - h) positions. Lines present NSCR estimates for each variable as a function of the model order. M_A=25 and M_F=10.

4.2.7 Interpretation of spectral decomposition analysis

Publication V showed the NSCR analysis to be robust over a large scale of model orders. In addition, it is related to actual variability present in a signal. Hence, it may not be as sensitive to modelling inaccuracies due to narrow-band signals as is, e.g., transfer gain analysis. This makes it an attractive method for quantifying multivariate modelling results. The analysis of NSCRs enables decomposition of the signal spectrum into root components of different origin. Assuming a complete model, a variable y_i reaches a high gain in NSCR analysis if and only if 1) the variable y_i is directly influenced by an external source of variability (external means here some source which is not included in the model as a variable) and 2) there exist transfer mechanisms from the variable y_i to other variables y_j, $i \neq j$. Hence, an increase in the NSCR estimate from y_i to y_j may be because of:

1. increased external modulation of the variable y_i

2. increased gain of the transfer functions from y_i to other variables (directly, or via other variables, to y_j)

3. decreased external modulation of other variables

4. decreased gain of other transfer functions than those from y_i.

The NSCR analysis quantifies only the original origin of the variability and does not allow direct assessment of the actual transfer pathways. For example in the models in publications III - V, the effect of respiration on HR and SBP variability is entirely attached to the NSCRs from ILV, despite the fact that some of the effects may be transferred to SBP via HR (Saul et al 1991, Taylor et al 1996). The actual transfer pathways may be analysed by accompanying the NSCR analysis with, e.g., the analysis of transfer gain functions and, most importantly, with *a priori* physiological knowledge.

The NSCRs provide *relative* decomposition of the variability into root components. Hence, the analysis should be completed with spectral analysis to assess what the amount of actual variability in each signal and in each frequency range is. For example, in publication III, the NSCR analysis shows that

respiration is the most important origin of the DBP variability in the HF range, as it is with the HR and SBP variabilities (publication III, Figure 2). NSCR analysis interpreted without spectral analysis might lead to the misinterpretation that all the involved signals - HR,DBP,SBP - exhibit similar variability in that range. However, the spectral analysis indicates (publication III, Figure 3) that the variability of DBP in the HF range is much less than that of HR or SBP. This example shows that appropriate interpretation of the multivariate modelling results requires combining information from multiple sources.

The role of pure inputs $\boldsymbol{u}$ in the model is usually more straightforward to interpret than the role of noise sources $\boldsymbol{e}$. The noise sources represent external stimulations of the variable, e.g. autonomous control acting primarily on that variable. For example, of the variables included in the models presented in this thesis (publications III - V), autonomous modulation of the vasculature controls primarily the SBP, while neural modulation of the sinus node controls primarily the HR. Hence, an increase in the sinus node modulation should be seen as an increase in the NSCRs from HR to other variables, and an increase in vascular modulation as an increase in the NSCRs from SBP.

4.2.8 Limitations

Simple black-box linear modelling of a complex physiological system necessarily involves many deficiencies. Some of them have been mentioned above, but here the most important ones are summarised and briefly discussed.

Nonlinearities

The cardiovascular control system and the transfer mechanisms between the different variables are nonlinear. For example, baroreceptor function has been found to have typical sigmoid-shaped response curve to arterial pressure (Karemaker 1987), the mechanical interactions involved in heart contraction exhibit nonlinear relations between BP and RRI (run-off effect, Frank-Starling mechanism) (Guyton 1986), respiratory sinus arrhythmia has been found to have a non-linear relation to tidal volume and respiratory frequency (Selman et al 1982), etc. In addition, the relationship between HR and RRI is nonlinear (Figure 1). Because of these nonlinearities, a linear model is by default just a linear approximation of the real system dynamics. However, it has been argued

that a linear approximation is justified over small ranges of operation (Kitney & Gerveshi 1982, Cerutti et al 1994). This assumption is supported by studies which apply time series modelling in stationary short-term conditions in human subjects and report the prediction ratio of the model: Baselli et al (1994) report the mean prediction ratio 75 - 84% with their linear model, while Chon et al (1996) report only 13% difference in the prediction ratio between a linear and a nonlinear model. The results of the present thesis agree with these studies: prediction ratios 81 - 99% were found with linear modelling. Hence, most of the dynamics of the signals may be regressed by a linear model in stationary short-term conditions. This supports the justification of linear approximation in short-term steady-state conditions. However, the difference in nature between the nonlinear physiological system and the linear model should be recognised when applying the modelling.

Incompleteness of the model

In practice, it is not possible to measure all the different variables involved in cardiovascular control. Hence, any time series model remains an incomplete representation of the true system. This hampers the interpretation of the results. If the missing variable affects only one included variable, its influence is completely represented by the noise source attached to that variable. However, in practice the missing variables may contribute to existing variables via various pathways with different delays. These influences sum up to the modelled transfer paths and noise sources in a complex way. A simultaneous external stimulation of many variables is seen as noise source correlation, while an influence entering different variables with different delays is seen as an artificial transfer mechanisms between these variables. Hence, the NSCR analysis may be affected by variables not included in the model in a complex way. This emphasises the need of in-depth understanding of both the physiology and the modelling methods while interpreting the results.

Use of *a priori* knowledge

A priori knowledge of physiology is involved both in constructing the model and defining the zero-delay transfer directions, and in interpreting the results. Consequently, there is a chance of biased results if the *a priori* knowledge is not correct. Hence, the modelling approach presented has limitations in yielding

fundamental results concerning the cardiovascular system. The most suited application of the methodology is the quantification of closed-loop interactions in various physiological or pathophysiological states where the basic mechanisms of interactions are quite well known.

Stationarity and model order selection

The time-invariant modelling presented assumes the data to be stationary. As true stationarity is never achieved in finite length recordings, the concept of local stationarity (Picinbono 1993) has to be applied: the system is studied under conditions during which the statistical properties of the signals do not change. If this yields records significantly longer than the correlation time of the system, the recording may be assumed locally stationary (Picinbono 1993), and the time-invariant modelling may be applied. In the cardiovascular system the maximum duration of a stationary recording is typically up to 10 minutes even during stable conditions. This sets certain limits on the accuracy of the modelling: the information content of a finite length recording is limited. This, in turn, sets limits for the convergence of the model with the real system (eq. 12). In publication V it was found that relatively large model orders are needed to model the cardiovascular dynamics. On the other hand, the data length sets a limit for the maximal model order. An upper limit $3\sqrt{N/L}$, where N is the data length and L the number of variables, has been proposed for the model order (Kay 1988).

In publication V, it was shown that the NSCR estimation is not sensitive to model order overestimation. The same may not hold true with transfer function analysis or analysis of impulse responses. Increasing model order increases variance of the model parameters (Ljung 1987). Hence, some optimisation of the model order may be needed if analysis is to be extended beyond spectral decomposition analysis.

Data quality

A factor limiting the potential of the model to describe the true system is the data quality. This means not only a high signal-to-noise ratio but also richness of the data from the information content point of view. Least squares model identification methods have most accuracy at those frequencies with most

spectral power and the estimates outside these frequencies are not reliable. The cardiovascular variability signals are usually band-limited, i.e., their spectral power is concentrated around a few frequencies. If physiologically feasible, special methods, such as broad-band respiration (Berger et al 1989b), may be used to broaden the spectral content of the signals and to overcome this problem. Moreover, the selection of the appropriate sampling frequency of the variability signals is a trade-off between the time resolution and the modelling efficiency. From the time series modelling point of view, the sampling frequency should not be higher than the time constants of the system (Ljung 1987). On the other hand, increasing the sampling rate may allow more accurate recognition of phase differences between the signals. A limiting factor in the selection of the sampling frequency is that we can obtain new samples of the heart function only at each new heart beat. The selection used in this thesis, 1 Hz, may be considered appropriate as it is close to the natural rhythm of the heart at rest. While analysing real patient material, experimenting with different sampling frequencies should be carried out to reach an appropriate trade-off.

4.2.9 Implications

Publications II - V yield some practical suggestions for the multivariate modelling of the cardiovascular system:

- Linear multivariate time series modelling seems to provide a reasonable approximation of the cardiovascular system during stationary short-term conditions.

- Independence of the noise sources in a closed-loop model is a pre-requisite for the analysis of the system interactions. Dependence may cause remarkable bias in the results.

- Inclusion of the immediate transfer paths in the model is essential to make the model noise sources independent. A simple method presented may be used to identify a MAR model with definitely independent noise sources.

- Ease of application and theoretical convergence with any linear causal time-invariant stationary system dynamics makes the MAR model an attractive modelling tool for the cardiovascular system. However, it may not be an

optimal model when pure input variables (e.g. respiration) are included in the model.

- The possible phase-lead of the HR to the ILV may cause problems in causal modelling. Special care should be taken to control the role of respiration in the modelling. A non-causal MARXAR structure was proposed for analysing the effect of respiration and the closed-loop interactions between the HR and the BP.

- Relatively high model order is needed to depict the dynamics of the cardiovascular system by linear modelling. The model order required is significantly higher than that suggested by objective model order selection criteria.

- Spectral decomposition analysis and NSCR analysis provide information about the intersignal relationships between the cardiovascular variables. The information is directly related to the actual variability present in the signals, which makes the analysis easier to interpret.

- The NSCR analysis is robust over a wide range of model orders when a sufficient model order is reached and exceeded.

4.3 Author's contribution to publications

The field of biomedical research is a multidisciplinary one and successful research in the area demands the collaboration of researchers from different fields. Because of that, this thesis work has been carried out partly at VTT Information Technology (the former Medical Engineering Laboratory of the Technical Research Centre of Finland) and partly at the Department of Clinical Physiology, Tampere University Hospital. The research work described has been carried out in very close co-operation with the clinicians, and part of the study (publication I) has been managed by them at Tampere University Hospital.

In publication I the author was the only technical expert participating in the analysis carried out. The author had the main responsibility for designing and

defining the analysis methods and he authored the analysis software. Especially, the author proposed the use of high-order AR spectral estimation and the use of f_{MED} to quantify the frequency shift on the LF band.

In publications II-V the author has been the principle author. In publication II the author elaborated the presentation of the general linear stochastic time series modelling framework for physiological signal analysis. The co-authors presented the multivariate dynamic adjustment and time-variant modelling parts of the paper (chapters 2.4.2 and 2.4.3). In publication III the author carried out the MAR modelling case, including laboratory measurements, data processing, modelling and analysis, and was the main author of the introduction and discussion. The presentation of the multivariate dynamic and time-variant modelling parts (chapters 2.2 and 2.3) was carried out by the co-authors. In publication IV the author proposed the application of the Cholesky decomposition method to make the noise sources of the model mutually independent, designed the study set-up, participated in the laboratory measurements, authored the analysis software, performed the data analysis and drew the main conclusions. Publication V was the work solely of the author, but in collaboration with the clinicians from Tampere University Hospital.

5. General discussion and conclusions

The spectral analysis of cardiovascular variability signals has been under intensive research for three decades. These analyses are gradually reaching the stage of clinical applications, and the methods are becoming more standardised. Yet, application of spectral analysis for research or clinical purposes needs special care to be taken in order for proper methodologies to be used. Despite some recommendations published recently (Task Force of ESC & NASPE 1996), all the details of analysis can often not be defined without an in-depth knowledge of the methods. For example, when using AR spectral estimation, no clear rule-of-thumb can be given for the model order selection. This thesis, and some other reports published in the recent past (Kay 1988, Pinna et al 1996), criticise the straightforward use of certain objective criteria in the model order selection. The existence of these kinds of open methodological questions underlines the importance of co-operation between physicians and engineers in the analysis of cardiovascular variability signals.

Because of long-lasting and intensive research in the spectral analysis of cardiovascular variability signals, no revolutionary methodological findings were expected. Usually, the spectral analysis is carried out by analysing the spectral power in certain pre-defined frequency ranges. Our experimental finding in Takalo et al 1994a and publication I was that in BHT subjects there is a shift in the frequency of oscillations *inside* the LF band. This shift may not be detected by conventional analysis of spectral power only. This emphasises the need for methods to quantify also the frequency of oscillations in addition to their power. In this thesis, three methods were compared to quantify this spectral shift. The outcome was the principle result of this thesis in univariate spectral analysis: band-wise f_{MED} and f_{MEAN} provide more robust quantification of this shift than the f_C which has been used in various previous studies.

Multivariate modelling has been addressed as one of the most promising approaches to the analysis of cardiovascular variability signals (Task Force of ESC & NASPE 1996). In this thesis some efforts were made to bring the methodology towards application in clinical research. The model identification procedures and the parametrisation of the modelling results were designed for this purpose. Still, when applying the methods to real experimental data, it should be kept in mind that the approach presented is designed more to draw

quantitative parameters related to the functioning of the cardiovascular control system than to be a realistic model of the underlying system. In particular, one should bear in mind the limitations in the performance of the linear models, the most important of which are related to the demands for stationarity, appropriate data length and quality and justification of the linearity assumption in different circumstances. The system identification cycle presented in publication II should always be followed in order to guarantee that the results obtained are correctly interpreted.

Insensitivity of spectral decomposition analysis to the changes in model order is a useful characteristic. The selection of model order is considered one of the most difficult problems in multivariate modelling. An important fact came to light: when multivariate modelling is used for data description rather than control purposes, it is not harmful to overestimate the model order within limits, but an underestimation may yield erroneous results. In publication V, a saturation of the NSCR estimates at a certain level was found when the model order was increased. This was true for both the simulation and the experimental data. If this is a general phenomenon with cardiovascular variability data, it might be utilised as a foundation for developing a simple model order selection criterion.

At present, only spectral decomposition analysis was applied for the analysis of interactions. In the future, use of other parameters like transfer functions and impulse responses should be considered and their behaviour in relation to the selected model order should be studied. In addition, the frequency content of the spectral decomposition might be studied using parameters such as f_{MED} or f_{MEAN}, as with the univariate spectral analysis. These studies might define other robust parameters to describe the model dynamics. Another interesting research direction in the analysis of the cardiovascular control system would be the consideration of other variability signals in addition to HR, BP and respiration. Recently, advances in impedance cardiography have greatly improved its reliability, and there exist devices which allow non-invasive beat-to-beat monitoring of SV (Kööbi et al 1997). This allows direct measurement of one of the most important variables in the dynamics of the cardiovascular system and hence could yield significant new insights into the control system. The methods presented in this thesis may be adapted with minor modifications to include SV or any other related signal.

In the present thesis, the multivariate modelling methods developed were applied to real experimental data only for demonstration purposes. In future studies, the methods should be validated against real physiological data from a relatively large number of subjects. Only after that can the methods presented considered valid and reliable.

In this thesis, a new parameter for quantifying spectral shift in HR and BP signals, namely band-wise median frequency, or f_{MED}, was proposed and applied to the analysis of experimental data from BHT and HT subjects. In addition, a general framework for multivariate linear modelling of cardiovascular signals was presented. The use of spectral decomposition for analysing the intersignal relationships in the model and methods for enhancing the MAR modelling were proposed. Finally, a new type of linear model for modelling cardiovascular dynamics was introduced. Identification procedures relying on generally available software tools were developed both for the new MAR model form and for the MARXAR model. The behaviour of the models was analysed, and the effect of model order selection was analysed with the MARXAR model. It may be concluded that the multivariate modelling approach was developed sufficiently to allow its future application to experimental data sets.

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Errata in publications

Publication II, page 2, 3rd paragraph:

> We divided the spectrum into three bands because it has been shown that the short-term variability in HR is affected by three major physiological factors attributable to respiratory, pressure vasomotor (at around 0.1 Hz) and thermal vasomotor (at around 0.05 Hz) activities. There is evidence that even the renin-angiotensin system may play a significant role in short-term cardiovascular control (at around 0.04 Hz). So there are certainly more than two oscillations involved in BP and HR variability above 0.03 Hz.

Publication II, equation 1:

$$\boldsymbol{A}(q)\boldsymbol{y}(t) = \boldsymbol{F}^{-1}(q)\boldsymbol{B}(q)\boldsymbol{u}(t) + \boldsymbol{D}^{-1}(q)\boldsymbol{C}(q)\boldsymbol{e}(t)$$

Publication II, equation 7:

$$\boldsymbol{A}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{F}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{B}_{\boldsymbol{M},\boldsymbol{N}}(e^{i\omega}) \rightarrow \boldsymbol{G}(e^{i\omega})$$
$$\boldsymbol{A}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{D}_{\boldsymbol{M},\boldsymbol{N}}^{-1}(e^{i\omega})\boldsymbol{C}_{\boldsymbol{M},\boldsymbol{N}}(e^{i\omega}) \rightarrow \boldsymbol{H}(e^{i\omega})$$

Publication II, equation 9:

$$\boldsymbol{T}_{\boldsymbol{G}}(e^{i\omega}) = \boldsymbol{A}^{-1}(e^{i\omega})\boldsymbol{F}^{-1}(e^{i\omega})\boldsymbol{B}(e^{i\omega})$$

Publication II, equation 12:

$$\boldsymbol{T}_{\boldsymbol{H}}(e^{i\omega}) = \boldsymbol{A}^{-1}(e^{i\omega})\boldsymbol{D}^{-1}(e^{i\omega})\boldsymbol{C}(e^{i\omega})$$

Publication II, equation 18:

$$\boldsymbol{y}(k) = -\sum_{i=1}^{M_A}\boldsymbol{a}(i)\boldsymbol{y}(k-i) + \boldsymbol{e}(k)$$

Publication IV, equation 1:

$$\sum_{i=0}^{M_A} \boldsymbol{a}(i)\boldsymbol{y}(k-i) = \boldsymbol{e}(k)$$

Publication IV, equation 10:

Correct reference is to SUORANTA and RANTALA, 1991.

Publication IV, Table 2:

NSCR from SBP to SBP in standing position, in MF range should be 119/74 (conventional/corrected).

Publication IV, page 4 (orig. 202), left column, 2nd paragraph:

Correct reference is to HANNAN and DEISTLER, 1988.

Publication V, equation 6:

$$\boldsymbol{A}(q) = \sum_{i=0}^{M_A} \boldsymbol{a}(i)q^{-\boldsymbol{i}};\ \ \boldsymbol{B}(q) = \sum_{i=-2}^{M_B-2} \boldsymbol{b}(i)q^{-\boldsymbol{i}};\ \ \boldsymbol{F}(q) = 1 + \sum_{i=1}^{M_F} \boldsymbol{f}(i)q^{-\boldsymbol{i}}$$

Publication V, page 2, *2.2. Model identification*, 2nd numbered issue:

Use MATLAB-function `arx.m` in System Identification Toolbox [8] to identify $\boldsymbol{A}'(q)$, $\boldsymbol{B}'(q)$ and $\boldsymbol{e}'(t)$ according to (4).