NTNU
Department of Engineering Cybernetics

NORWEGIAN UNIVERSITY OF SCIENCE AND TECHNOLOGY

SPECIALIZATION PROJECT

Frequency analysis of hemodynamic parameters in sepsis patients using a Winkessel model.

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Abstract

Sepsis is one of the leading causes of death for hospitalized patients. Early symptoms are challenging to identify, as they are subtle, and other conditions with a common physiologic response meet the same criteria of diagnosis. During sepsis, the depressed vascular properties of the circulatory system are the main contributor to decreased blood perfusion. The reduced vascular tone will cripple the autoregulatory mechanisms that the body controls to maintain appropriate blood perfusion by controlling pressure and vascular dilation.

In a healthy patient, the autoregulation is observed as distinct slow variations in the hemodynamic parameters, such as systemic vascular resistance (SVR) and arterial compliance. Provided velocity and pressure measurements, we can calculate the arterial impedance, which can be analogized to a 2-element Windkessel model (WK). The model resembles a parallel RC circuit, in which the resistance is the SVR, and the capacitance is the arterial compliance. During septic shock, the autoregulatory mechanisms will be unstable and show a more stochastic behavior in the 2-element WK model as it attempts to stabilize the blood flow. This stochastic behavior should be derivable as an increase in the magnitude of the low autoregulatory frequencies and its neighbors.

The 2-element WK model parameters were found from 3-minute blood pressure and velocity measurements of seven patients. The parameters were then transformed into the frequency domain through a digital Fourier transform (DFT), where the possibility of distinguishing the severity of the septic shock from looking at the average magnitude of the working frequencies of the autoregulation was investigated. Although there seems to be some correlation, there is not enough evidence to employ this as a diagnostic measurement for sepsis. I do believe there is potential for further and more comprehensive studies on this matter, and I do see the potential to develop related research with this project's results and potential for development as a baseline.

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Abbreviations

SVR	=	Systemic Vascular Reisistance
WK	=	Windkessel
RC	=	Resistance and Compliance
NE	=	Norepinephrine
SIRS	=	Systemic Inflammatory Response Syndrome
DIC	=	Disseminated Intravascular Coagulation
NO	=	Nitrous Oxide
MAP	=	Mean Arterial Pressure

Chapter 1

Introduction

1.1 Motivation

Sepsis is one of the leading causes of death for hospitalized patients. About half the patients who have a septic shock will die within the first month of their diagnosis.[5] It is estimated that there will be 18 million cases of sepsis every year [8]. Early symptoms are challenging to identify, as they are subtle, and many other conditions with a common physiologic response meet the criteria of diagnosis. Early treatment of sepsis is associated with improved likelihood of recovery. [17] Innovations within detecting cardiovascular abnormalities with signal processing would be a good addition to existing biomarkers.

In theory, there is some correlation between impairments in autoregulation due to its difficulties in controlling the vascular dilation as the immune response tries to fight off the invading pathogens. These impairments are visible in hemodynamic parameters such as systemic vascular resistance (SVR) and arterial compliance. The possibility of looking at the changes in SVR and compliance to detect sepsis, or at least its increased severity, could significantly help improve sepsis diagnostics.

1.2 previous work

There are no relevant literature which has looked at the lower frequencies of the hemodynamic parameters to identify if a patient has sepsis.

Tips her Hans? Droppe seksjonen?

1.3 Research aims and objectives

The project was completed at the Department of Engineering Cybernetics (ITK) in collaboration with Department of Circulation and Medical Imaging (ISB), NTNU. It is a 7.5 specialization project (TTK4551), where the goal is to specialize in the selected area of

research based on scientific methods, collect supplementary information based on literature search and other sources, and combine this with own knowledge into a project report.

The research aim and motivation stems from oral and electronic communication with dr. Daniel Bergum, who works with intensive care medicine at the Faculty of Medicine and Health Science. The main goal of this project is to analyze variations in vascular parameters, such as systemic vascular resistance (SVR) and arterial compliance, as a tool of diagnosis, in patients with sepsis.

1.4 Outline of the report

The project report is divided into five chapters, excluding the introduction, followed by references.

The second chapter (after introduction) will introduce the relevant theory and citations needed to comprehend the objectives and methodology of the project. The severity and pathophysiology of sepsis and how it affects the hemodynamic parameters will be explained — followed by the possibility of transforming the parameters into an analogous parallel RC-circuit using a simple lumped 2-element Windkessel (WK) model.

Chapter 3 demonstrates how to estimate the parameters of a 2-element WK model. It operates on the theory that irregularities will occur in the slow varying changes in systemic vascular resistance (SVR) and arterial compliance controlled by autoregulation. The method is summarized by showing how to potentially detect these irregularities by analyzing the parameter's spectral components. The results of the project are then shown in chapter 4 and thereafter discussed in chapter 5.

At the end of the report, chapter 6 concludes the report with a brief summary, with a few of the principal features and details being addressed.

Chapter 2

Theory

The primary purpose of the circulatory system is to deliver oxygenated blood to tissue, where the supply of oxygen is the product of flow and oxygen content[18]. The body has developed innate self-regulatory systems to maintain appropriate blood flow and tissue perfusion. In a healthy individual, hemodynamic parameters fluctuate as autoregulatory mechanisms keep the cardiovascular system within a stable region.

The hemodynamic parameters, such as the *systemic vascular resistance* (SVR) and *compliance*, can be used to create a simple but robust model of the arterial system. Analogous to a parallel RC circuit, the diameter of the veins decides the systemic resistance that must be overcome for blood to pass through the arterial system, while compliance represents the ability of the arterial system to distend as a function of the slow changes in pressure. This kind of lumped model used for representing the arterial system is known as a Windkessel (WK) model.

In a septic patient, the autoregulatory mechanisms, as well as other efforts to maintain homeostasis, are impaired. The distinguishable slow autoregulatory changes in the arterial parameters will then be less stable, causing noticeable differences in the impedance of the arterial system.

2.1 Sepsis

Sepsis is a serious and crippling clinical condition that significantly changes the lives of those affected. The word septic originates from the old Latin term meaning rotten, in the same way, sepsis is derived from the Greek word for ”decomposition” or ”decay” [7]. Something being in a state of *shock* means decreased tissue oxygenation (reduced oxygen delivered to cells as a result of problems with the circulatory system) and low blood pressure. Combining the terms one gets something rotten, or infected material, causing a decreased oxygenation of organ tissue.

Table 2.1: Criteria for the systemic inflammatory response syndrome (SIRS), defined as fulfilling two or more of the listed criteria. [15]

Criterion	Value
Temperature	$> 38°C$ or $< 36°C$
Heart rate	> 90 bpm
Respitory rate	> 20 or PaCO2< 32 mmHg
White bloodcell count	$> 12,000/\mu L$ or $< 4,000/\mu L$, or $< 10\%$ band

2.1.1 Epidemiology

Sepsis is most commonly caused by a bacterial infection, but it may also be fungal, viral, or protozoan [5]. In 1991 a universal and easy-to-apply set of clinical parameters were invented during a consensus conference working toward identification and treatment of the disease. This set of parameters is known by the term "systemic inflammatory response syndrome" (SIRS) [3]. SIRS affects the whole body and is defined by the presence of two or more of the criteria listed in table 2.1. The diagnosis of sepsis requires both evidence of an infection along with the patient being in a SIRS disease state. Sepsis can be divided into three stages: sepsis, severe sepsis, and septic shock. The SIRS criteria need to be present before the doctor can diagnose sepsis. Severe sepsis is a more severe stage of sepsis, associated with hypotension, hyperfusion, or organ dysfunction.[12] Septic shock is the final and most severe stage of sepsis and is associated with the same cardiovascular and organ deviance as for severe sepsis, but at critical levels, which can cause acute failure of multiple organs. Septic shock is defined as sepsis associated with hypotension and perfusion abnormalities despite the provision of adequate fluid (volume) resuscitation [12].

2.1.2 Pathophysiology

Sepsis starts out as a typical inflammatory response to an infection. The body's immune system reacts to invading pathogens in several ways. The initial response happens when white blood cells, also called leukocytes, encounter any invading antigen and immediately activates. When white blood cells activate, they recruit more white blood cells to eradicate the harmful organism. Since the infected material is usually located in the interstitial tissue, and not in the bloodstream, the white blood cells release molecules like Nitrous Oxide (NO) [10]. The nitrous oxide signals the surrounding smooth muscle to relax, resulting in vasodilation. This increase in vessel diameter causes a decrease in systemic vascular resistance, which means an increase in blood flow to the area in combination with increased permeability, or leakiness, of the vessel walls [4]. Both of these factors help the immune cells to reach the affected area. With the increased leakiness, fluid will build up in the tissue, making it difficult for red blood cells to oxygenate the surrounding tissue. This starvation of oxygen is essentially what causes a septic shock.

The goal of the white blood cells is to get rid of the infected material by releasing lytic enzymes and reactive oxygen species whose job it is to damage the pathogen [1]. These enzymes end up damaging the blood vessels as well as the pathogen. Whenever a blood vessel is damaged, a physiological process called hemostasis changes the blood from a

fluid liquid to a more gelatinous state. Hemostasis slows down the blood flow and forms blood clots to prevent blood from spilling into extravascular space [13]. The coagulation factors cannot keep up with the ruptures, and blood clots will start blocking blood flow to any parts of the body, including limbs and organs. This vicious cycle caused by the body's inability to restore homeostatic conditions, contributing to multiple organ dysfunctions is called Disseminated Intravascular Coagulation (DIC) [14].

To sum up the two main cardiovascular occurrences, from initial inflammatory response to septic shock:

1. White blood cells release enzymes and reactive oxygen species to fight the infection.
2. Increased relase of NO causes an increase in vasodilation to reach pathogens in the interstitual tissue $\longrightarrow$ increased permeability and leakiness.
3. The reactive oxygen species will cause the vessels to rupture, further increasing the leakiness.
4. By now, fluids have built up in the tissue, making it difficult to oxygenate tissue.
5. Hemostasis initiated by the ruptures creates blood clots all over the vascular system, obstructing blood flow, making it even harder to oxygenate tissue and critical organs.
6. The incapability to oxygenate will lead to varying degrees of organ failure and tissue death.

The main takeaway is that there are hemodynamic changes in parameters such as pressure, blood flow, venous resistance and dilation, and other parameters as the sepsis develops. During these events, the body's ability to autoregulate and maintain homeostasis is severely deprecated.

2.2 hemodynamics

Hemodynamics is the dynamics that govern blood flow. Like a control system controlling hydraulic circuits, e.g., pumps and pipes, the circulatory system is kept in stable condition by homeostatic control mechanisms. The heart is the pump of the circulatory system, pumping oxygen-rich blood to organs and tissue through contracting and relaxing. During the cardiac cycle, the period of contraction is called systole, and the period of relaxation is called diastole. The pulsating characteristics of the hemodynamics stem from this hydrostatic pressure gradient and the cardiovascular impedance. As blood is ejected into the aorta and to the rest of the arterial system, the elastic fibers of the arteries will help maintain the pressure and flow gradients as they dilate and resist any immediate changes. The content of this and the following section is mostly taken from "Snapshots of Hemodynamics: An Aid for Clinical Research and Graduate Education" [18].

2.2.1 Blood pressure and velocity

As the pulsatile flow and pressure are a result of a sudden change in pressure and the impedance of the arterial system, it is expected to have a periodic character, which is what

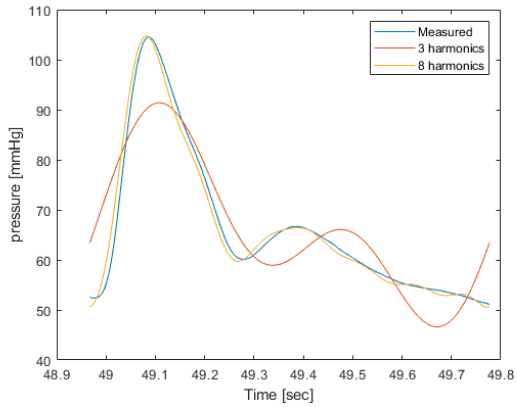


Figure 2.1: Measured pulsatile pressure vs. reconstructed pressure using the harmonic frequencies

we refer to as the cardiac cycle. Milnor WR. in the book "Hemodynamics" [6] states that the flow and pressure profile is a complex waveform built up of various harmonics, given by a series of sine waves produced by the heart pumping blood through the different chambers of the heart. These waveforms can be represented as superpositions of several harmonics:

$$p = \sum_{n=0}^{N-1} p_n e^{j\omega_n t} \quad \text{and} \quad q = \sum_{n=0}^{N-1} q_n e^{j\omega_n t} \tag{2.1}$$

where q_n and p_n are the complex Fourier components given by the angular frequencies ω_n. The actual flow and pressure can then be extracted as the real part of the complex functions in equation 2.4. If one were able to obtain the frequency response of either pressure or flow, one would be able to reconstruct the signal without too much deviation by using its first few harmonics. Figure 2.1 demonstrates how much information that is held within the first harmonics of one blood pressure measurement. One could successfully reconstruct the whole signal by simply employing the first 8-10 harmonics.

2.2.2 Impedance

The impedance of a segment of the vascular system is the relation between the local difference in pressure and flow. It is a measure of the system's ability to resist an immediate motion of fluids when subjected to an increase in pressure. As explained in the previous section, both pressure and flow can be represented by a linear combination of their harmonics. The vascular impedance is defined as the ratio between the complex pressure (P) to complex flow (V) for the harmonic frequencies:

$$Z(\omega) = \frac{P(\omega)}{V(\omega)} \tag{2.2}$$

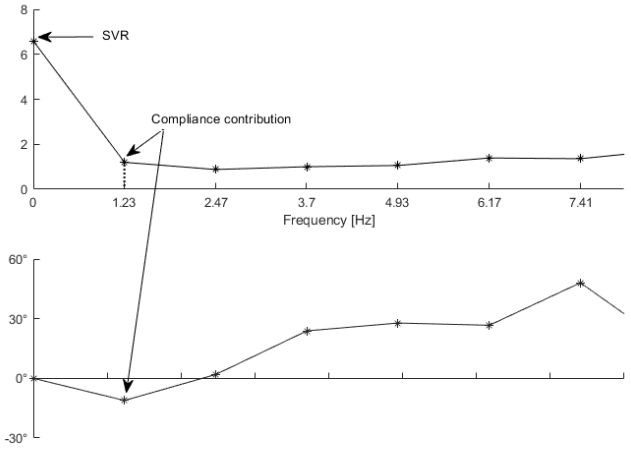


Figure 2.2: Impedance magnitude and phase of the pressure plot shown in figure 2.1 as a function of the harmonic frequencies. The magnitude at zero frequency is the SVR, and the steady decrease in magnitude is contributed by the arterial compliance.

Figure 2.2 shows the magnitude of the impedance as a function of its harmonic frequencies from a cardiac cycle[1]. In theory, the magnitude should approach a constant value, and the phase angle close to zero, which is the contribution of the characteristic impedance [6]. Without reflections in the arterial system, the input impedance would equal characteristic aortic impedance, and the pressure and flow would have the same wave shape. For low frequencies, the reflections at the periphery, the 'diffuse reflections,' are large and cause the impedance to be high. At high frequencies, local 'distinct reflections' play a role, and they determine the oscillations in the impedance about the characteristic impedance. At zero frequency is the SVR, while the first harmonic provides a measure of the arterial compliance.

The compliance of the cardiovascular system is due to the elastic properties of the cardiovascular system. The vascular tissue is mainly composed of elastin, smooth muscle and collagen [18][2]. Elastin fibers are highly extensible and demonstrate viscoelastic properties, i.e. a rapidly applied force to the material will require more force to achieve the same widening as a purely elastic material. The vessel wall's ability to expand and contract as pressure increase or decrease is known as compliance (C), and is quantified as a change in volume (ΔV) divided by a change in pressure (ΔP) [6].

[1] If the original sequence is one cycle of a periodic function, the digital Fourier transform provides all the non-zero values of one DTFT cycle, and the frequency vector is spaced by multiples of the harmonic frequency ($\Delta f = \frac{f_s}{N_{fft}}$)

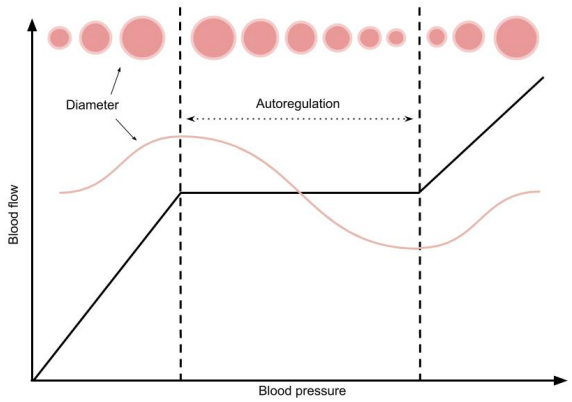


Figure 2.3: Pressure-flow autoregulation. The autoregulatory region is between the dashed lines, where appropriate blood flow is maintained by controlling pressure and vasodilation.

2.2.3 autoregulation

Autoregulation is the intrinsic ability of an organ to regulate blood pressure, flow, and hence maintain appropriate perfusion. If the blood perfusion to an organ is reduced as a result of a drop in blood flow, autoregulation will return it towards normal levels within anything from 20 seconds to 3 minutes.[11] When the body is within the autoregulatory region, between the dashed lines in figure 2.3, it maintains constant blood flow by regulating pressure and the resistance of the arterial system, i.e., the dilation and contraction of the blood vessels. If the blood pressure falls, the vasculature of the system will after a short period (minute) dilate, and hence decrease the vascular resistance to regulate the relationship

$$Q = P \times R \tag{2.3}$$

between pressure, flow and resistance. The reason for the slow homeostatic response of the autoregulatory system is believed to be due to slow metabolic and molecular mechanisms. The myogenic mechanism alter the ability of the vascular smooth muscle to constrict or dilate in response to differences in transmural pressure, while the release of endothelial factors, such as NO, contributes to vasodilation. [2]

Autoregulation in sepsis

The primary purpose of the circulatory system is to deliver oxygenated blood to tissue, where the supply of oxygen is the product of flow and oxygen content.[18] The body has developed innate self-regulatory systems to maintain the appropriate blood flow and tissue perfusion. In a healthy individual, hemodynamic parameters fluctuate as autoregulatory mechanisms keep the cardiovascular system within a stable region. In a septic patient, however, the autoregulatory mechanisms as well as other efforts to maintain homeostasis are impaired, as the normal slow autoregulatory changes in the arterial parameters will be less stable, causing noticable changes in the impedance of the arterial system.

2.3 Modeling the cardiovascular system

In section 2.2 the dynamics of blood flow, called hemodynamics, was introduced in terms of blood pressure, SVR and arterial compliance. In figure 2.6 is an analogy between the fire engine Windkessel and the arterial system. The peripheral resistance of the cardiovascular system is the summed resistance of all small arteries, arterioles, and capillaries, while total arterial compliance is the sum of the compliance of all arteries. The WK model helps us understand how the arterial system functions, and is widely used for modeling the arterial system.

2.3.1 Windkessel Model

The Windkessel model is a *lumped-parameter model*, where a more accurate description of the pressure-flow relation may be acquired by including more elements. As an example, figure 2.5 shows an analogy to an electrical representation of a two- and three-element Windkessel model, where another input resistance is added to represent the characteristic impedance of the aorta [18], resulting in a description of the higher frequencies given by the aortic input impedance.

Although increasing the complexity of the lumped model provides a better prediction of the relationship between pressure and flow, i.e., the impedance of the system, it becomes more challenging to determine the parameters and how much a disease like sepsis influences them. It has ,been shown that the three-element WK model inadequately estimates arterial compliance, i.e., the initial declining slope of the impedance in figure 2.6, [16] which is one of the most important parameters when analyzing the effects of sepsis.

Two-element Windkessel model

In this project, only the two-element WK model is used. The two-element WK model assumes that the impedance of the system solely relies on peripheral resistance and total

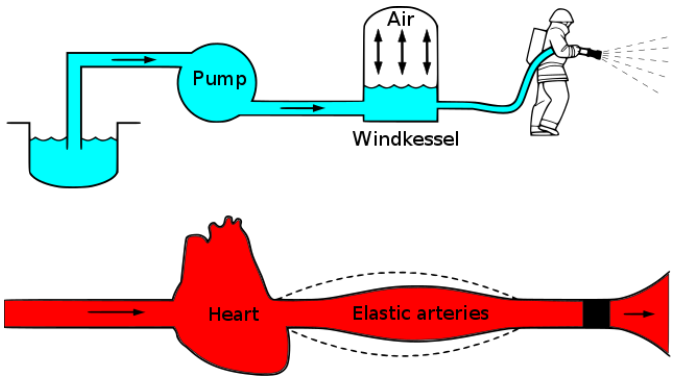


Figure 2.4: The analogy between a fire engine with a Windkessel from the 18th century and the artial system. The image is made by Kurzon - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=31288770

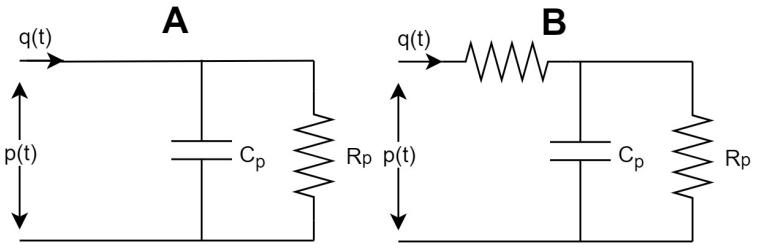


Figure 2.5

arterial compliance. By analogy to an electric circuit, all the inflow volume must be equal to the capacitance and the outflow through the resistance in figure 2.5. The relationship between pressure and flow through the model is given by the impedance:

$$Z(\omega_n) = \frac{R}{\frac{1}{R} + j\omega_n C} \tag{2.4}$$

Where R is the SVR, C the arterial compliance, and ω_n the n-th harmonic.

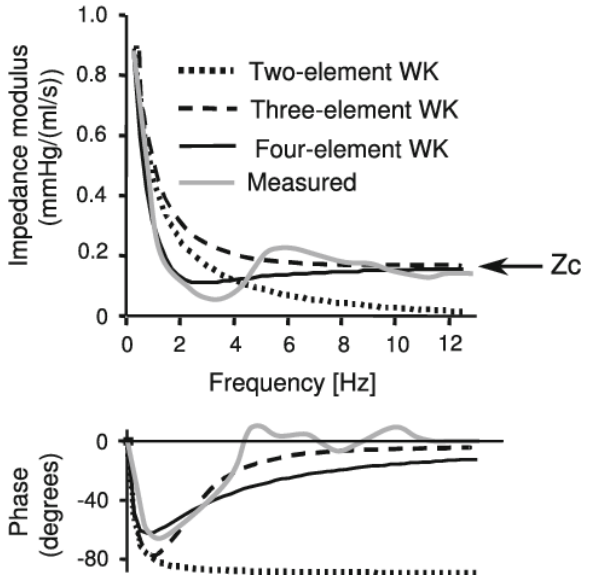


Figure 2.6: An example of measured aortic input impedance plotted together with impedances predicted by the two-element Windkessel, the three-element Windkessel, and the four-element Windkessel (Adapted from Westerhof et al. [76])

Chapter 3

Methods

The goal of this chapter is to demonstrate how to estimate the parameters of the 2-element WK model that was introduced in section 2.3.1. When analyzing the frequencies of a healthy individual, the changes in SVR and arterial compliance show a distinct, slow variation in the time domain, which relates to a narrow band of frequencies in the lower end of the spectrum. The theory is that in the presence of a disease like sepsis, irregularities in these slow varying changes will manifest itself in the systems attempt to maintain blood perfusion through its ability to modify parameters like SVR and arterial compliance. This will cause the lower frequencies of a digital Fourier transform (DFT) to correlate more with the parameter signals and increase their spectral density, which we should be able to detect. All of the digital processing and digital signal analysis was performed in MATLAB.

3.1 Measurements

Blood pressure and velocity measurements were aggregated into a MATLAB workspace MAT-file, commonly at least four columns; one for time, blood pressure, and blood velocity variable:

- *Tmean*: The mean value of each cardiac cycle.
- *Tmax*: The maximum value of each cardiac cycle
- *Tmin*: The minimum value of each cardiac cycle.
- *Ts*: Raw measurement sampled at $f_s = 200Hz$.

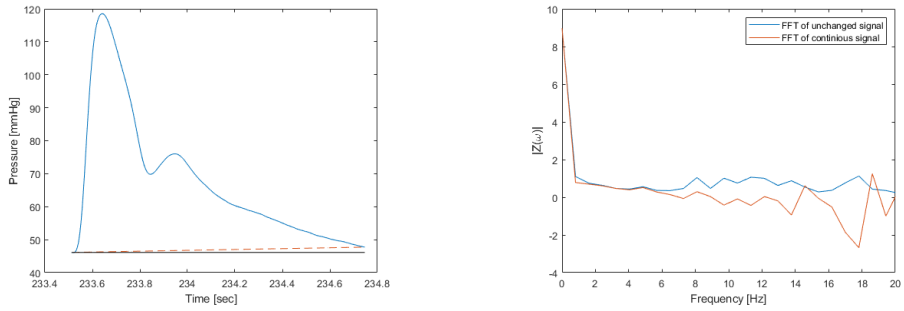
An algorithm that registers each cardiac cycle by comparing the gradient of the previous cardiac cycle was used to calculate and register the mean, max, and minimum values of each measurement. Each of the measurements was four minutes long; the time variable of Tmean, Tmax, and, Tmin were the timestamps of the beginning of each cardiac cycle; while the time variable of Ts contains the actual time axis of the measurement sampled at 5ms intervals (200 Hz).

The data of a total of 7 out of 19 patients affected by sepsis were provided. The reason being that faulty pulse registrations and negative velocities corrupted some of the pressure and velocity measurements. Each patient had four recordings taken at different stages of the disease, with no knowledge as to which stage the patient was in at any specific recording. The length of each recording primarily contained 4 minutes worth of measurements[1].

3.2 Preprocessing

Before estimating the parameters of the impedance of each cardiac cycle, there are a few things that need to be adjusted for the Fourier analysis to be as accurate as possible. Although dealing with a simple 2-element WK model makes the parameters more robust, it is still important to remove minor spectral biases such as spectral leakage, so that we can be more sure about the spectral contributions from the disruptive properties of the sepsis.

3.2.1 Detrending the cycle



(a) **(b)**

Figure 3.1: A linear function between the start and end values are used to remove the sharp transition that occurs when the measured value at the beginning and end of the cardiac cycle is different (a). This reduces the spectral leakage that would transpire as the Fourier analysis has to try to recreate the signal.

Usually, a window function like Hamming, Hanning, etc., are used to mitigate the effects of spectral leakage. If we were to apply such a window to our signal, it would attenuate our calculated compliance, and make it more difficult to detect changes deviations that originate from the disease. To remove the sharp transitions from one cycle to the next and reduce the effect of spectral leakage, A linear function between the start and end values, shown as the red dashed line in figure 3.1a, was subtracted from the signal. Afterward, the signal, now centered around zero, was moved back to the mean value of the previous start and end value. This way, we avoid the potential of spectral leakage when there is a discontinuity between the beginning and end of the pressure and velocity measurements.

[1] A few of the measurements were cut short to about 3 minutes.

Although it did not make a big difference in the specific cycle shown in figure 3.1, it could potentially be a much larger transition, which would give rise to a more substantial amount of spectral leakage.

3.3 Parameter analysis

Section 2.2.2 and its figure 2.2 introduced that the SVR is given by the 0-frequency component of the impedance, while the arterial compliance by the magnitude of the first harmonic. Afterward, section 2.3 gave us an analogy to a 2-element WK model and an analogy to a parallel RC circuit. The next thing we need to do is calculate the parameters for each cardiac cycle and analyze the slow oscillations caused by the autoregulation.

3.3.1 Parameter estimation

Figure 3.2 shows a simple diagram of how the parameters are extracted from a 4-minute recording. The parameters are found for every cardiac cycle of the 4-minute recording. The SVR is simply the magnitude of the 0-frequency. To find the compliance, however, a simple parametric fit is used to determine the compliance that produces the lowest error for the impedance function given in equation 2.2.

When both SVR and compliance are found for the full 4-minute measurements, they are stored as MATLAB arrays. In figure 3.4, both SVR and the computed compliance are shown as a function of time. As a connection, one can take note of how both the SVR and compliance are showing the same respiratory oscillations as for the pressure and velocity. The main takeaway, however, is the presence of slow 20- to 100-second variations in all of the hemodynamic parameters. By comparing the plot of the parameters with the actual measurements in figure 3.3, we can see the theory introduced in section 2.2.3 and figure 2.3 concerning autoregulation in action. As the blood pressure rises, the compliance shows an opposite trend, most likely because of the myogenic autoregulatory mechanisms altering the elasticity of the vascular smooth muscle.

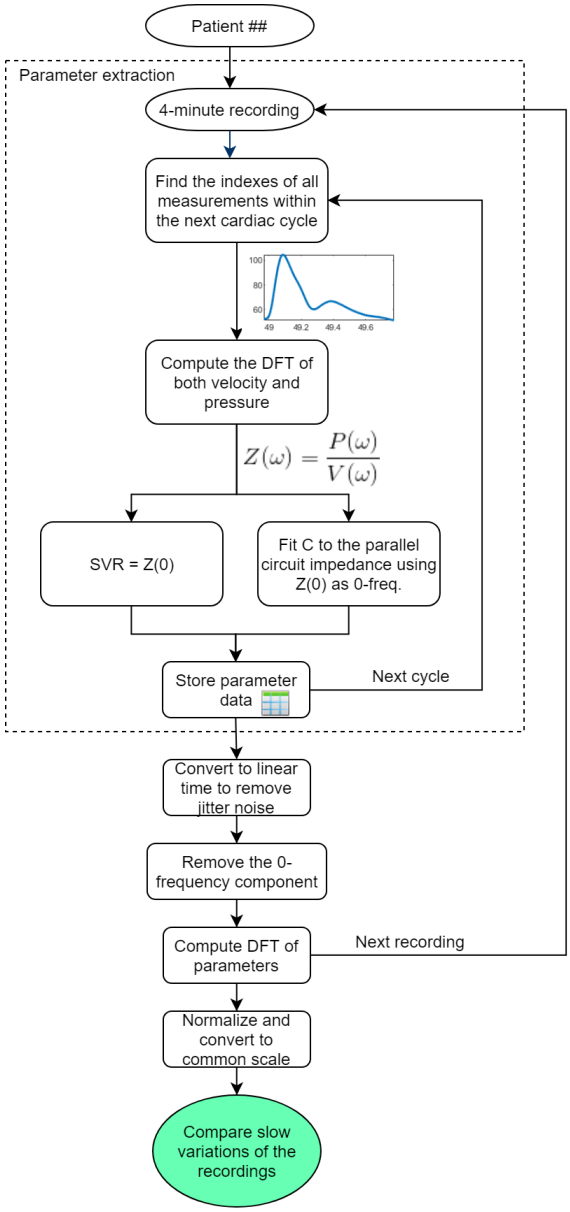


Figure 3.2: Diagram of how the parameters are extracted from a 4-minute recording and compared to the other recordings.

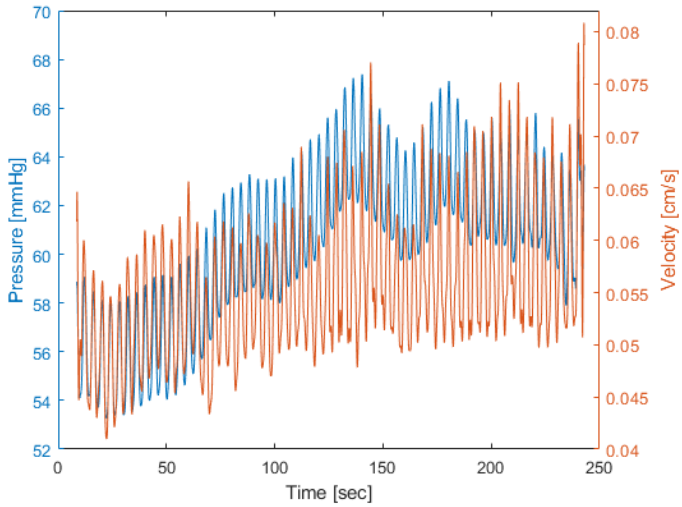


Figure 3.3: Filtered pressure and velocity recordings. The filter is used to remove the pulmanory frequency ($\sim$1.25) and other higher frequencies such that only the changes from the respiration and the autoregulation is visible.

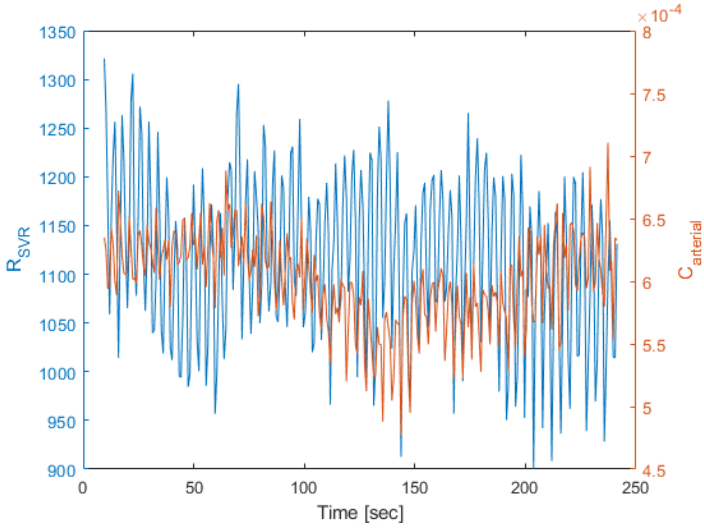


Figure 3.4: The 2-element WK parameters calculated from the full 4-minute recordings of pressure and velocity in figure 3.3. For each cardiac cycle, i.e., once every 0.6-0.8 seconds, the parameters are calculated. By comparing the slow variations of the pressure, velocity, and compliance, one can observe the autoregulation from section 2.2.3 and figure 2.3 in action.

3.3.2 Analyzing lower frequencies

We are now interested in analyzing the slow, autoregulatory variations of the parameters. The theory is that in the presence of a disease like sepsis, irregularities in these slow varying changes will manifest itself in the systems attempt to maintain blood perfusion through its ability to modify parameters like SVR and arterial compliance. This will cause the lower frequencies of a DFT to correlate more with the parameter signals and increase their spectral density, which we should be able to detect.

Converting to linear time

In the parameter extraction shown in figure 3.2, the time indices that make up a cardiac cycle are the ones within the registered timestamps of the pulses. The pulse does not work at a constant frequency, and hence the parameter measurements performed every cardiac cycle will not have a uniform time axis. This deviation from true periodicity is registered as jitter noise in the frequency analysis. A simple fix is to interpolate the signal. The MATLAB function interp1() was used to upsampling the signal by a factor of 10 and subsequently interpolating it using the 'PCHIP' (piecewise cubic Hermite polynomial) method.

Frequency analysis

Before finding the amplitude of the parameter's frequencies, we want to remove the 0-frequency component from the parameter data. The reason being that we are multiplying with a rectangular window as we are working with a finite number of samples, which will cause spectral leakage. The spectral leakage can be devastating for parameters of recordings with a much higher 0-frequency magnitude relative to the harmonic frequencies. When the parameters have been interpolated and had its 0-frequency component removed, the discrete-time sampled frequencies of the finite sequence of equally-spaced parameter samples are found by performing a digital Fourier transform (DFT):

$$X(k) = \frac{1}{N} \sum_{n=0}^{N-1} x(n) e^{-j(\frac{2\pi}{N})nk} \tag{3.1}$$

Since a DFT accumulate the amplitude of each sample for a given frequency, the magnitudes of the frequencies are normalized by a factor N-samples:

Comparing the recordings

After transforming the parameters of all the available recordings for a given patient into the frequency domain, we need to find a common scale as blood pressure and velocities can both vary on a day-to-day basis or depending on the patient has a disease like sepsis. If one parameter's mean value is much higher in one recording than the others, its variations will scale and become much higher as well, giving it seemingly the highest magnitudes. By dividing the frequency components of the parameters by its 0-frequency, we transform all of the recordings to a similar and relative scale.

Figure 1 shows the final DFT for a random recording, which will be the basis for comparing the contribution of the parameters from the lower frequencies. As a minor

validity test, one can check for the respiratory frequency at 0.25 Hz. The following chapter will compare the parameters found from the recordings of 7 patients.

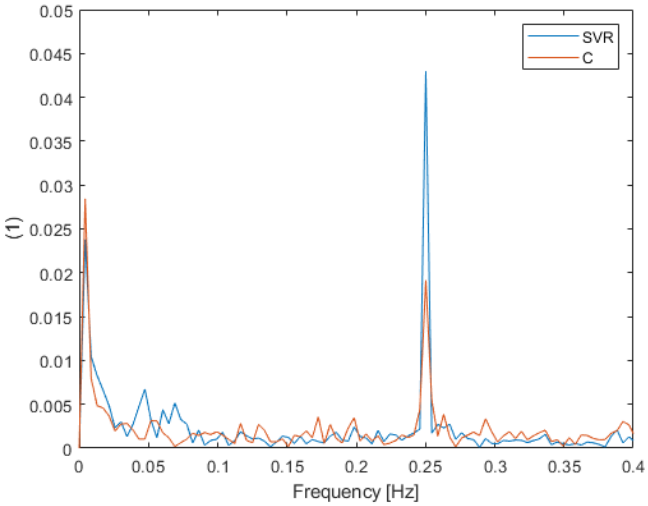


Figure 3.5: A sample of the final DFT of the parameters for a given recording, which will be used when comparing recordings. The y-axis is unitless relativity measure.

Chapter 4

Results

For this project, the pressure and blood flow velocities of seven patients were recorded. For each patient, four recordings taken on separate stages of the disease were used in the analysis. As thoroughly discussed in the previous chapters, in the absence of disease, the cardiac systems of the body can locally adjust their vascular resistance and compliance to maintain adequate blood flow and cardiac output to critical organs. During severe sepsis or septic shock, it is believed that these autoregulatory properties fail at maintaining homeostasis in the cardiovascular system. Since both the SVR and compliance are the two main parameters of the cardiovascular model, one should be able to identify a pattern of autoregulation malfunction by observing the lower frequencies of these parameters.

The patients' state at any stage of the recordings was not revealed before the final week of the project, i.e., one week before the project report deadline. The intention was that without any preliminary knowledge of the patients' state, one should be able to recognize if the patient was getting worse or recovering from sepsis.

The first section will follow the state and analysis of one patient, which will be referred to as patient 18. The following section will then show the results of multiple patients.

4.1 Sepsis severity indicator

The amount of Norepinephrine (NE), also called noradrenaline, given to the patient, along with the mean arterial pressure (MAP), can be used as a marker of the severity of sepsis. NE is used as a first-line agent in hypotensive patients affected by septic shock. NE is a vasopressor, which is a medicine that stabilizing blood perfusion by contracting (tightening) the blood vessels when the patient is suffering from extremely low blood pressure. [9] The NE infusion is proportional to the severity of the shock, i.e., the dosage is increased if the condition of the patient is more critical. Patient 18 were given the following dose in chronological order of the recordings taken at different dates:

- **19.01.2019**: 0.07 [micrograms/kg/min]
- **20.01.2019**: 0.12 [micrograms/kg/min]

- **21.01.2019**: 0.13 [micrograms/kg/min]
- **23.01.2019**: 0.11 [micrograms/kg/min]

From this, we can tell that patient 18's condition is better in the first recording, gets worse the next two days, and is less severe in the last recorded day as the patient responds to appropriate treatment.

4.2 Patient 18

This section will analyze the 2-element WK parameters in both time and frequency domain. First, the calculated parameters for each recording for the patient will be presented and examined, before a more in-depth investigation of their lower frequencies.

4.2.1 2-element WK parameters

The SVR and compliance were calculated for all four recordings according to the parameter extraction shown in the diagram in figure 3.2 in section 3.3.1. For patient 18, we saw a small spike in the NE dose from 19.01 to 20.01, which was then slightly reduced again in the last recording as the patient most likely responded to treatment. Before analyzing any deeper, it should be mentioned that the parameter values are converted to a relative, comparable, and unitless scale by dividing by the mean parameter value. The reason being that all the measurements with larger value ranges oscillated with much more magnitude relative to the others, which would make them outweigh the others in both time and frequency domain. From the SVR in figure 4.1, you can see the state of the patient get worse from the top plot of the figures until the second to last, by the parameter's stochasticity. For the compliance, however, it seems like the severity is worst in the first recording, and dampens off in the subsequent measurements. These kinds of discrepancies will be further discussed in the next chapter.

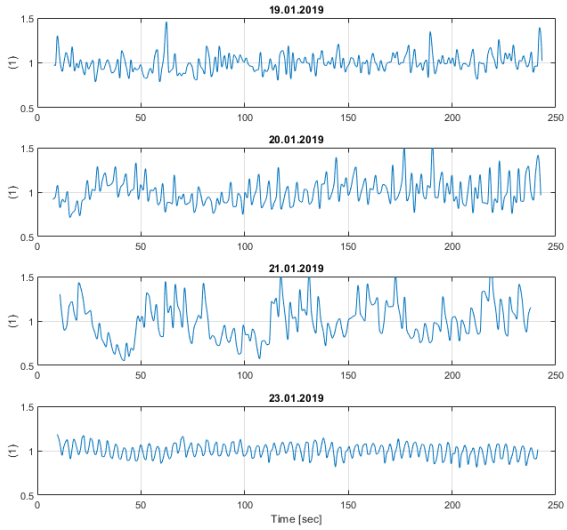


Figure 4.1: SVR of patient 18 calculated from 4 different recordings. Since each parameter measurement had different ranges and offsets, each of the measurements are divided by their own mean to convert them to a unitless and comparable scale.

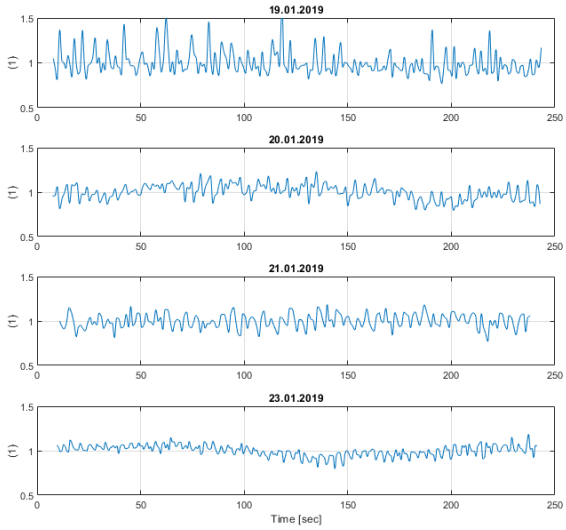
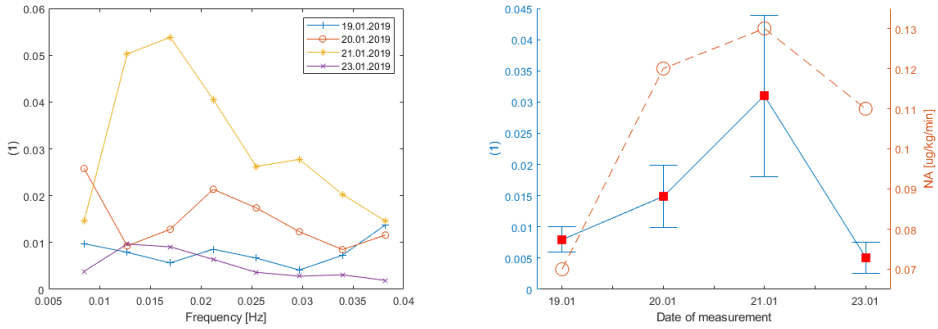


Figure 4.2: The arterial compliance of patient 18 calculated from 4 different recordings.

4.2.2 Parameter frequency analysis

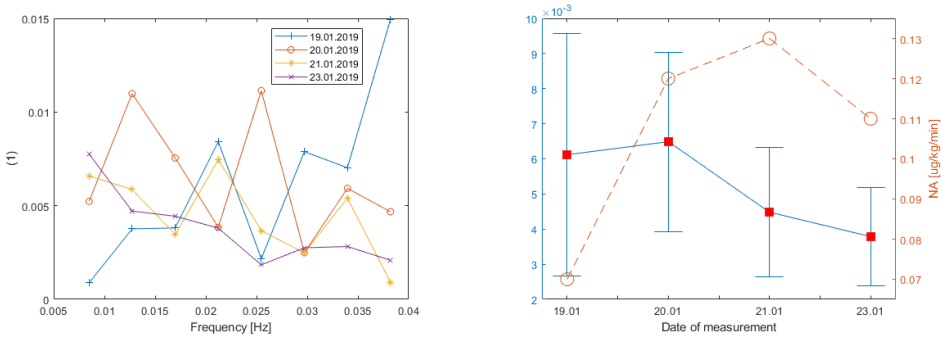
The frequency spectrum of the resistance is shown in figure 4.3 and compliance in figure 4.4. The magnitude of the frequency components has been converted to a comparable, unitless scale. In the left plot of both figures shows the magnitude of the frequency band 0.0085-0.0382 Hz (20-120 second oscillations) for each recording. From the frequency spectrum of the resistance in figure 4.3a, you can see the large contribution from the 40-80 second variations in the parameters. This is even more evident in the next plot in figure 4.3b, which shows the average magnitude of the whole frequency band, as well as the NE dosage given to the patient at the different dates of the recordings. The resistance seems to follow the state of the patient given by the increased dosage of NE. The compliance, however, seems to show a decreasing trend in the magnitude following the increased dosage if NE, which conforms with the analysis in the previous section.



(a) magnitude of the *slow* variations in resistance (∼20-125 seconds).

(b) Mean magnitude of the frequencies shown in (a).

Figure 4.3: The frequency analysis of the SVR of all recordings. The experimental theory is that the lower frequencies of the parameter, which will manifest itself as low-frequency noise and increase the average magnitude. Figure (b) shows the mean value of each recording of the frequency spectrum in (a).



(a) magnitude of the *slow* variations in resistance (∼20-125 seconds).

(b) Mean magnitude of the frequencies shown in (a).

Figure 4.4: The frequency analysis of the arterial compliance of all recordings. The experimental theory is that the lower frequencies of the parameter, which will manifest itself as low-frequency noise and increase the average magnitude. Figure (b) shows the mean value of each recording of the frequency spectrum in (a).

4.3 All patients

Figure 4.5 and 4.6 respectively shows the resistance and compliance of all the available patients with usable blood pressure and velocity measurements. They both show the mean magnitude of the frequencies within the band of interest, the same way it was presented in the r.h.s. plot of the figures from the previous section. There seems to a bit hard to correlate the average magnitude of the lower frequency band and the state of the patient, given the NE dosage. The relationship between the NE dose and the state of the patient is not always correct; some patients can either get better by themselves, respond to the treatment, or a combination of the two. It is fair to say, however, that the majority of the results seem to follow the hypothesis that there either is a larger average magnitude in the frequency band of interest corresponding with a greater NA dosage.

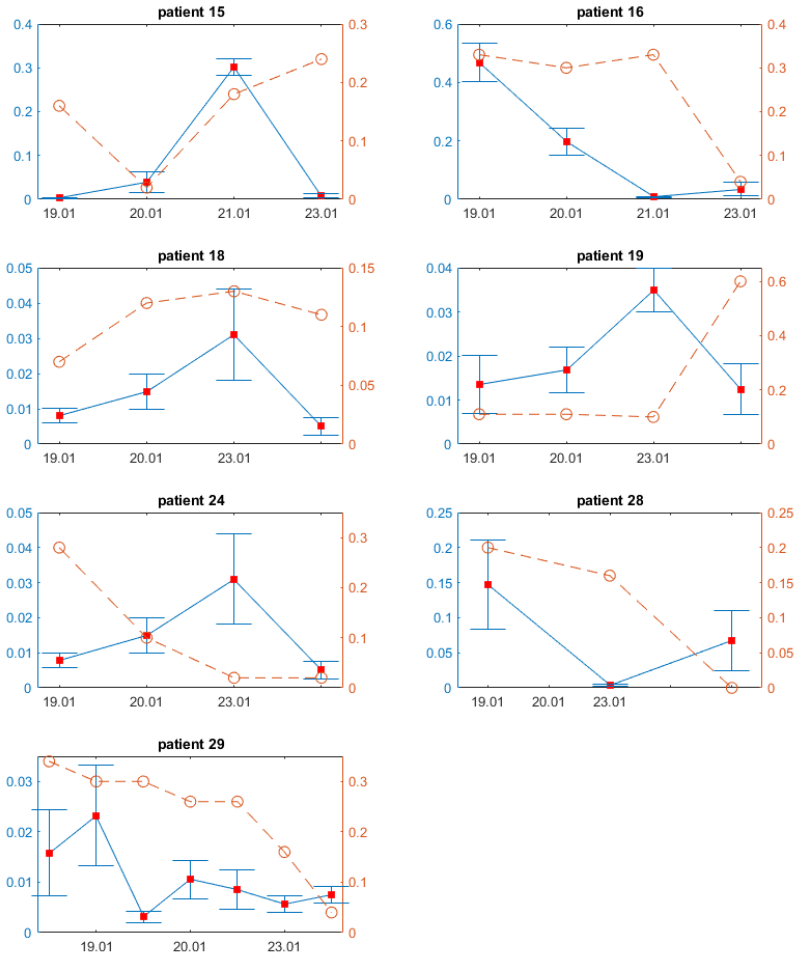


Figure 4.5: Mean SVR magnitude within the frequency band of interest for all patients.

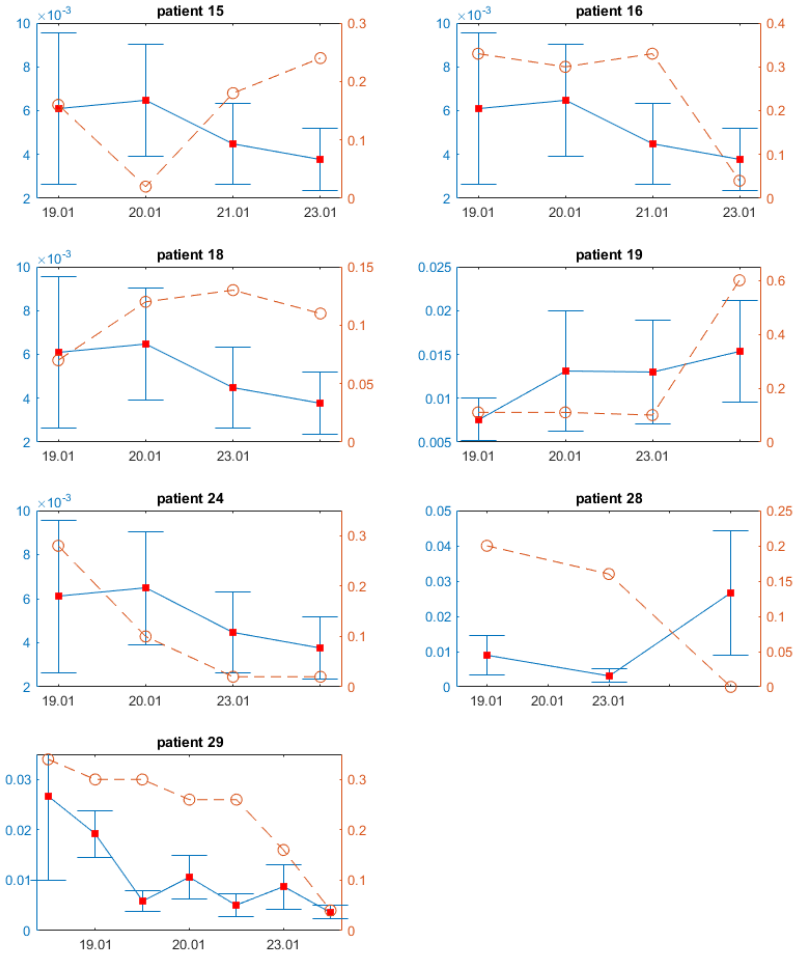


Figure 4.6: Mean compliance magnitude within the frequency band of interest for all patients.

Chapter 5

Discussion

The theory regarding the autoregulatory mechanisms in a septic patient, in that they are impaired and observable in the hemodynamic parameters, have been proven in the relevant literature. There are abnormalities in both the systemic vascular resistance and the arterial compliance in association with the severity of the septic shock. From figure 4.1, one can see that there is a correlation between the resistance and the NE dosage. The compliance in figure 4.2, however, seems to show an opposite trend. Most likely, this discrepancy is caused by the vasopressor effects of the NE, as a decrease in the vascular system's ability to dilate will reduce the compliance. The same results seem to be true for the examination of the magnitudes of their frequency components in figure 4.3 and 4.4. The vasopressor effects should, however, not have too large of an impact on the relative magnitude measures when we divide by the DC component. By transforming the signal to a relative and comparable scale, it should have suppressed the differences in vascular dilation capabilities.

It is evident that the autoregulatory oscillations become unstable and start oscillating stochastically and with higher amplitudes. There is a correlation between the magnitude and the NE dosage, but it is less significant than I expected. It might have been useful to split the frequencies of interest into narrower bands to look for more specific autoregulatory deviances that following the severity of the disease. With more recordings, one could create a method that would crosscheck multiple frequency bands to the NE dosage.

I do believe there is potential for further and more comprehensive studies on this matter, and I do see the potential to develop related research with this project's results and potential for development as a baseline.

Chapter 6

Conclusion

This report has discussed the possibility that a disruption in the autoregulatory mechanisms for a septic patient is observable in hemodynamic parameters such as systemic vascular resistance (SVR) and arterial compliance. The main objective of the project was to investigate the possibility of detecting these disruptions. The hypothesis was that the abnormalities would manifest as an increase in the average magnitude of the lower frequencies of the parameters. The SVR and compliance of seven patients were successfully calculated and analyzed in both the time and frequency domain. Although there seems to be some correlation, there is not enough evidence to employ this to aid in diagnostics of sepsis. I do, however, believe there is potential for further and more comprehensive studies on this matter, and I do see the potential to develop related research with this project's results and potential for development as a baseline.

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