Doppler based ultrasound imaging methods for noninvasive assessment of tissue viability

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Abstract

Tissue viability can be defined as the combination of perfusion, metabolism and function. Perfusion means that blood is supplied to the tissue cells. Metabolism means that the cells are alive and able to utilize the nutrients and oxygen supplied by the blood to perform a function. The function can be different depending on the cell type. In this work, the focus will mainly be on muscle cells. One function of a muscle cell is to contract and relax.

The object of this thesis is to describe non-invasive Doppler methods to detect, measure and visualize two of these viability factors: Blood perfusion, and tissue deformation. First, other non-ultrasonic methods to assess the viability parameters are briefly described. Next, a review of ultrasound methods to assess the parameters is compiled. The review covers the topics blood flow detection and velocity estimation, tissue Doppler imaging, and strain and strain rate imaging.

Blood perfusion can to some extent be assessed through the Doppler measurement and detection of blood velocity. As a part of the processing of the received Doppler signal is the clutter filter that is needed to remove the echo from stationary or slowly moving tissue. Unfortunately this filter also removes the echo from slowly moving blood and thus prevents measurements of blood flow in the smallest vessels. Signal models for pulsed wave Doppler and color flow imaging are presented, as well as methods to estimate the lowest detectable velocity. A measured clutter signal from a muscle with involuntary vibrations is used to illustrate the method. For this clutter signal and a ultrasound frequency of 6 MHz, the results show a low velocity limit of 6.4 mm/s, indicating that capillary blood flow is not detectable, regardless of observation time. In color flow imaging, where the observation time is limited, the detection limit is even higher. A likelihood function for blood detection and expressions for the probability of detection are presented.

Tissue deformation can also be assessed by the ultrasound Doppler technique. The strain rate, i.e., the rate of deformation, of a tissue segment can be estimated from the tissue Doppler data by calculating the spatial velocity gradient. The optimal strain rate estimator and expressions for the lower bound variance are derived. A simplified estimator suitable for real-time performance in an ultrasound scanner is investigated in in vitro and in vivo experiments. A method to estimate the accumulated strain from the instantaneous strain rates is also presented.

The in vitro experiments involve cyclic compression of a gel block. The results show a bias smaller than 0.03 s\(^{-1}\) and a standard deviation less than 0.19 s\(^{-1}\) in the strain rate estimate for strain rates in the range -1.5 to 0 s\(^{-1}\).

The strain rate technique is next tested in vivo in a pilot study in 6 pa-
patients with myocardial infarction and 6 normal subjects. Apical cardiac imaging was performed on all subjects, and the results show that reduced strain rates are found in the infarcted muscle segments compared to the normally functioning segments. The method is also tested in imaging of the peristaltic contraction in the stomach muscle, and in imaging of the strain rate in tumors during external compression.

Several methods to improve the real-time strain rate estimate are presented. These include second harmonic imaging and simple clutter filtering. It is shown that both stationary reverberations and clutter filtering introduce a bias in the strain rate estimate, and that a clutter filter therefore only should be used when the reverberation level is high. A method to increase the frame rate by using a sliding window processing technique is also presented.

The angle dependencies of both the strain rate and the strain estimates are described, using a model for the tissue deformation. Furthermore, a method to estimate the strain rate in other directions than along the ultrasound beam is presented. A preliminary test in cardiac short axis imaging indicated that the method could measure simultaneously the transmural and the circumferential strain rates in all parts of the ventricle except where these directions were perpendicular to the beam.
Preface

This dissertation is submitted to the Norwegian University of Science and Technology (NTNU) in partial fulfillment of the requirements for the degree of Doktor ingeniør.

The work has been performed at the Department of Physiology and Biomedical Engineering at the Medical Faculty, NTNU in the period 1995 - 1999. My supervisor has been professor Hans Torp at the Department of Physiology and Biomedical Engineering, while professor Jens Hovem at the Department of Telecommunications, NTNU, has been the administrative supervisor. In the period 1995-1997 the work was supported by the Norwegian Research Council, in 1998 in collaboration between the Norwegian Research Council and GE Vingmed Ultrasound AS and a short period in 1999 by the Medical Faculty. Since early 1999 I have been employed by GE Vingmed Ultrasound AS.

Acknowledgements

I wish to especially thank my supervisor Hans Torp. He introduced me to the exciting subject of Doppler ultrasound imaging, and has been of invaluable help during the preparation of this thesis.

When working on the strain rate imaging technique I had very fruitful collaboration with Asbjørn Stoylen at the Department of Cardiology at the University Hospital of Trondheim. His interest for this topic has been a great motivation for the work, and his clinical examinations using the method have been very valuable.

Also many thanks to Steinar Bjørum, Stein Inge Rabben, Marek Belohlavek, Kai Thommenius, Bjørn Angelsen, Vidar Sørhus, Torgrim Lie, Åge Grønningseter, Stig Slerdahl and Bjørn Olav Haugen for helpful discussions and for review of my work, and to Bjørn Olstad, Jan D’hooge, Tormod Bakke, Sevald Berg, Johan Kirkhorn, Tor Urdalen, Annette Vanvik Lund and Odd Helge Gilja for indispensable help with computer implementations, practical experiments and clinical examinations. All my colleagues at the Department of Physiology and Biomedical Engineering and GE Vingmed Ultrasound during the last years are also thanked for a nice and interesting work environment.

The financial support from the Norwegian Research Council, GE Vingmed Ultrasound AS and the Medical Faculty is greatly appreciated.

Finally, many thanks to Per and Magnar Heimdal for their support and under-
standing during the time I worked with the thesis. In fond memory of my mother Marit Agnete Heimdal who died from breast cancer in 1996. I miss you very much.
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### Nomenclature

#### Symbols

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<th>Definition</th>
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<tr>
<td>$\alpha$</td>
<td>Angle between the ultrasound beam and the u- or v-axis in the cardiac muscle</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Magnitude of the complex autocorrelation coefficient</td>
</tr>
<tr>
<td>$\Delta \phi$</td>
<td>The phase shift of the echo signal from pulse to pulse</td>
</tr>
<tr>
<td>$\Delta r$</td>
<td>Radial distance between two segments or samples</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>Time shift of the RF signal from pulse to pulse</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Finite strain</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Small strain</td>
</tr>
<tr>
<td>$\dot{\varepsilon}$</td>
<td>Small strain rate (velocity gradient)</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Wavelength</td>
</tr>
<tr>
<td>$\omega_0$</td>
<td>Angular center frequency of the transducer</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Autocorrelation coefficient</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Standard deviation (square root of the variance)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>Variance</td>
</tr>
<tr>
<td>$B$</td>
<td>Bandwidth</td>
</tr>
<tr>
<td>$c$</td>
<td>Speed of sound in human tissue (approx. 1540 m/s)</td>
</tr>
<tr>
<td>$C(\tau)$</td>
<td>Cross-correlation function</td>
</tr>
<tr>
<td>$C$</td>
<td>Covariance matrix</td>
</tr>
<tr>
<td>$d(m)$</td>
<td>Displacement of segment number $m$</td>
</tr>
<tr>
<td>$f$</td>
<td>Frequency coordinate</td>
</tr>
<tr>
<td>$f_0$</td>
<td>Center frequency of the transducer</td>
</tr>
<tr>
<td>$G_R(\omega)$</td>
<td>Fourier transform of the autocorrelation estimate $\hat{R}$</td>
</tr>
<tr>
<td>$I_N$</td>
<td>Identity matrix of size $N$ by $N$</td>
</tr>
<tr>
<td>$l$</td>
<td>Frame number</td>
</tr>
<tr>
<td>$L$</td>
<td>Number of frames</td>
</tr>
<tr>
<td>$m$</td>
<td>Radial sample or segment number in a beam</td>
</tr>
<tr>
<td>$M$</td>
<td>Number of radial signal samples or segments in a beam</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Mean value</td>
</tr>
<tr>
<td>$n$</td>
<td>Pulse number, i.e., sample number within a packet</td>
</tr>
<tr>
<td>$N$</td>
<td>Number of samples in a packet, i.e., number of pulses for each sample volume</td>
</tr>
</tbody>
</table>
\( p_x(x) \) Probability density function for the complex vector \( x \)
\( P \) Power
\( Q \) Perfusion or flow per unit volume
\( r \) Spatial coordinate along the ultrasound beam
\( r_s \) Radial sampling distance
\( R(\Delta n) \) Auto-correlation function
\( \hat{R} \) Auto-correlation estimate
\( S(f) \) Doppler spectrum
\( S(k) \) Fourier transform of \( s(r) \)
\( t \) Temporal coordinate within a pulse echo signal
\( T \) Time between pulses, equals \( 1/\text{PRF} \)
\( u \) Circumferential coordinate, clockwise seen from the apex of the heart
\( v \) Meridional coordinate, from apex to base in the heart
\( v \) Velocity
\( w \) Transmural coordinate, from endo- to epicard
\( s(t) \) RF signal, i.e., echo from one pulse
\( x(n) \) Complex IQ signal from one depth and \( N \) pulses, \( n = 1, \ldots, N \)
\( x \) Packet, i.e., complex IQ signal vector
\( x(m,n) \) Complex IQ signal from depth \( m \)

**Abbreviations**

- **DCM** Dilated cardiomyopathy (Abnormally large and thin-walled ventricle)
- **FIR** Finite impulse response
- **HCM** Hypertrophic cardiomyopathy (Abnormally thick ventricle walls)
- **IIR** Infinite impulse response
- **IQ** In-phase and quadrature (real and imaginary parts of the quadrature demodulated signal)
- **LPF** Low pass filter
- **MSDR** Mean to standard deviation ratio
- **MVG** Myocardial velocity gradient
- **PRF** Pulse repetition frequency
- **RF** Radio frequency (received signal before quadrature demodulation)
- **SNR** Signal-to-noise ratio
- **SNR_C** SNR of the calculated strain image
- **SRI** Strain rate imaging
- **TDI** Tissue Doppler imaging

**Definitions**

\( \text{arg} \) Function that returns the argument or phase of a complex variable
argmax  Operation that returns the index that maximizes the submitted function

$\text{cov}$  Covariance function

$E$  Expected value operator

Im  Function that returns the imaginary value of a complex variable

packet  Name used for the vector built up of samples from the same depth in consecutive pulses in the same direction

Re  Function that returns the real value of a complex variable

$T$  Transpose operation

var  Variance function
Part I
Chapter 1

Introduction

This chapter is meant as a short introduction for engineers without background in physiology, and does not go into detail about the clinical issues.

1.1 Tissue viability

Tissue viability is the ability of the tissue to live and grow. In this work, tissue viability is defined by the following three factors:

- **Blood perfusion.** The metabolism in the tissue cells can only take place when enough oxygen and nutrients are available. These substances are supplied by the capillary blood flow.

- **Metabolism.** The tissue cells must be able to absorb and utilize the nutrients and oxygen delivered by the blood. In this factor cell membrane integrity is also included.

- **Function.** The tissue cells must be able to perform some sort of function. A muscle cell must for instance be able to perform contraction and relaxation.

If one or more of these factors are missing, the tissue cannot be fully viable. The clinical interest in tissue viability includes detection of growth in tumors, and cardiac muscle viability.

1.1.1 Viability of cardiac muscle

Left ventricular dysfunction occurs when all or some of the myocardial muscle does not perform normally. This is usually caused by reduced blood perfusion to all or parts of the cardiac muscle. If the muscle is still viable, normal muscle performance can be regained by restoring the blood perfusion to normal levels. The state of the viable muscle with reduced contractile function due to reduced blood perfusion has been termed hibernation.
Several reperfusion procedures exist, but these are normally only justified if viability can be demonstrated. If no viability can be detected, conservative medical therapy or heart transplantation might be the best choice.

1.1.2 Viability in respect to tumors

Viability is not commonly a term used in the description of tumors, but it will be used briefly in this work to describe whether the tumor is growing or not.

Tumors can be divided into benign and malignant types [72]. Benign tumors represent localized growth that usually remains circumscribed, while malignant tumors, cancer, usually invade surrounding tissue. It is of great clinical interest to distinguish these two types of tumors, since malignant tumors need different treatment procedures than benign tumors. Since some of the treatment procedures can be painful and involve some risk, it is important to reduce the number of tumors falsely classified as malignant.

One subtype of benign tumors can be distinguished from malignant tumors by the fact that they are not viable, i.e., that they have stopped growing. An indication of this is that there is no blood flow in the tumor. Without the nutrients supplied by the blood, the tumor cells cannot grow, and will shortly die. There are, on the other hand, other types of tumors that do have blood flow in the tumor, but still are benign.

It is known from breast cancer that most large tumors are palpable masses. This means that the stiffness of a mass can be used as a marker for the disease. Any stiff masses that are not documented in prior examinations are assumed to be malignant tumors until proven otherwise [53].

1.2 Assessment of tissue viability

There are several known techniques to assess viability in tissue. In this work the focus will be on noninvasive ultrasound imaging methods that involve the Doppler technique. Noninvasive means that the techniques do not require entering the body or puncturing the skin. For comparison, some other techniques are presented briefly in this section.

1.2.1 Assessing cardiac muscle viability

Techniques to assess the viability in the cardiac muscle include [7]: positron emission tomography (PET), single photon emission computed tomography (SPECT) and echocardiography during stepwise infusion of dobutamine (Stress echo). Newer techniques are magnetic resonance imaging (MRI) and contrast echocardiography. Table 1.1 shows which factors of the definition of viability these techniques can detect or measure in the cardiac muscle.

With PET, the most common method is to use two different tracers, usually fluorine-18 labeled with deoxyglucose (FDG) and nitrogen-13 labeled with ammonia (N13-ammonia). FDG activity indicates metabolism, while N13-ammonia activity indicates perfusion.
1.2 Assessment of tissue viability

<table>
<thead>
<tr>
<th>Technique</th>
<th>Perfusion</th>
<th>Metabolism</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>SPECT</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Stress echo</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Contrast echo</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MRI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 1.1: The ability of different techniques to detect viability in cardiac muscle tissue. The term function here means muscle thickening or deformation.

With SPECT there are several different tracers and protocols commonly used. Thallium-201 imaging reflects cell membrane integrity. Imaging with technetium-99m labeled compounds reflects perfusion and the uptake is also dependent on cell membrane integrity and mitochondrial function. Radiodinated fatty acids measure metabolism, but this method has still not been validated. Using 511 keV collimators, FDG imaging of metabolism has recently also been possible with SPECT.

Stress echo is usually based on the use of a low-dose dobutamine infusion that enhances the systolic contraction in the regions with reduced function. The contraction can also be enhanced by physically stressing the patient using for instance a treadmill or a stationary exercise bicycle. The increase in contractility is measured by echocardiography as increased wall thickening.

With the MRI technique, methods to detect flow, perfusion, wall motion and cardiac metabolism have been presented. The same dobutamine procedure as with stress echo has been studied, but is only rarely used. Recent developments include myocardial tagging to better quantify the changes in wall motion, and magnetic resonance spectroscopy to assess metabolism.

Contrast echocardiography involves venous or arterial administration of gaseous microbubbles. When insonified by ultrasound pulses these microbubbles produce a high intensity scattering, simplifying the detection of blood. The scattering is also highly nonlinear, allowing detection by harmonic imaging, i.e., receiving the echo at the second or higher harmonic of the transmitted ultrasound frequency. Detection of perfusion is possible using this method, but quantification is yet to be shown.

1.2.2 Assessing the nature of tumors and other lesions

The most common cancer in women is breast cancer. Young female patients (under 30) with breast cancer are usually investigated by grayscale ultrasound, and older by mammography [53]. In young women, the breast is more dense, so the mammographic sensitivity is lower. Tumors are also rare in this age group. Ultrasound is useful to differentiate cystic lesions and solid masses. Cystic lesions are usually considered benign, while solid masses are more uncertain. Mammography is X-ray imaging of the breast. The margins, density and location of a mass is considered in differentiating benign and malignant tumors.
1.3 Aims of study

The technical basis for the work presented in this thesis is the extreme sensitivity to motion of the ultrasound pulsed wave Doppler technique. Miniscule displacements (down to a few microns) in blood and tissue within the human body can be measured. Utilizing this ability of the Doppler technique, the aim of this work is the evaluation and development of Doppler ultrasound methods to detect and quantify two of the tissue viability properties: blood perfusion and tissue deformation.

For blood perfusion, the focus will be mainly on the detection problem. Small blood vessels are often hard to detect, and it is interesting to find the lower limit on the blood velocity that allows detection and measurement. This needs to be evaluated both for pulsed Doppler and for color flow imaging. Also, optimal imaging parameters are important to find.

The Doppler technique can also be used to measure tissue velocities. The deformation (strain and strain rate) of the tissue can be estimated from these velocities, but the variance of such a measurement might be large. Methods to measure the strain and strain rate directly from the Doppler signal is important. To make the method more clinically useful, the estimation should be performed in real-time.

1.4 Publications

References to the papers, posters and abstracts that have been published prior to and during the preparation of this thesis have been included in the References [25, 26, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 77, 85].

1.5 Structure of the thesis

The thesis is divided in two parts. The first part consists of unpublished material, except for two conference papers and one abstract that have been rewritten into the text [31, 32, 37]. The second part consists of three papers. Summaries of these papers are given in Chapter 2.

Chapter 3 reviews several Doppler-based ultrasound imaging methods to detect and measure blood perfusion and tissue deformation. Thematically next in order, Papers 1 and 2 then describe the ability to detect and measure blood flow using pulsed Doppler and color flow imaging.

The strain rate imaging technique to measure tissue deformation is introduced with a technical description in Chapter 4 and a more clinical description in Paper 3. The angle dependency of the method is discussed in Chapter 5. Chapter 6 describes two in vitro experiments performed to validate the strain rate estimates, and Chapter 7 shows several preliminary in vivo results using the method.

Finally, the conclusions and suggestions for future work are presented in Chapter 8. It should be noted that a list of symbols, abbreviations and definitions is included in the beginning of the document for reference purposes.
Chapter 2

Summary of papers

This chapter gives summaries of the three papers that are submitted as part of this thesis.

2.1 Summary of Paper 1

The paper titled "Ultrasound Doppler measurements of low velocity blood flow: Limitations due to clutter signals from vibrating muscles" points at the involuntary vibrations in skeletal muscle cells as an origin for clutter signals of non-zero bandwidth. In the paper, a model of the pulsed wave Doppler signal from vibrating muscles was developed. An experiment with in vivo data was used to estimate the parameters of the model. By comparing this model with previously developed models for the Doppler signal from blood, a theoretical minimum for detectable blood velocity was found. The limit showed a nonlinear relation to the ultrasound frequency. At 6 MHz, and for the measured clutter signal, the limit was 6.4 mm/s.

Using the signal model, it was also possible to estimate the radial component of the muscle vibrations from the phase of the Doppler signal.

2.2 Summary of Paper 2

The paper titled "Detecting small blood vessels in color flow ultrasound imaging: A statistical approach" describes a statistical model for the complex demodulated Doppler signal and a likelihood test for blood detection. In the model, the ultrasound signal was described as a sum of three independent components: tissue clutter, blood and white noise. An approximation of the likelihood test was in the paper shown to involve a clutter filter and a blood enhancement filter.

An experimental in vivo data set of a human arm muscle was used to illustrate how the signal model could be used. The performance of the test was assessed using receiver operating characteristics for different sets of parameters, including the
blood velocity and the PRF. It was also illustrated how the minimum detectable blood velocity could be found.

2.3 Summary of Paper 3

The paper titled "Real-time strain rate imaging of the left ventricle by ultrasound" describes the first clinical pilot study using the strain rate imaging technique. This technique allows real-time imaging of the deformation rate in the cardiac muscle. The strain rate is shown to be equal to the spatial velocity gradient, which is measured using the tissue Doppler technique. The calculation of the gradient along the ultrasound beam is performed in real-time and was presented as color-coded cine-loops and color M-modes.

The method was tested in 6 healthy subjects and 6 patients with recent myocardial infarctions. All the infarcted regions showed up with reduced strain rate, demonstrating the technique to be useful for imaging regional dysfunction.

In this paper, A. Heimdal defined the strain rate concept, the description of the strain rate imaging technique and the discussion on the technical limitations. He also made Figures 1 and 2 and the general revision of the whole paper. A. Støylen performed the patient study and wrote the discussion on the clinical application of the technique. H. Torp and Terje Skjerpe reviewed the technical and clinical parts respectively of the paper. T. Bakke and T. Urdalen implemented the real-time algorithm, A. V. Lund, B. Olstad and S. Berg implemented the post-processing software and M. Belohlavek helped with the review.
Chapter 3

Previous work

In this chapter, Doppler based ultrasound imaging methods for noninvasive assessment of tissue viability and elasticity will be reviewed. The focus will be put on methods to detect perfusion and function.

Perfusion can be detected, and to some extent also measured, with Doppler ultrasound methods. There is, however, a low velocity limit. If the blood flow has a very low velocity, the clutter signal from stationary or slowly moving tissue will overshadow the signal from the blood. This can be overcome by using ultrasound contrast agents that enhance the echo from blood. The contrast agents are usually small gas bubbles, some types also with a shell, that are injected into the blood path. Techniques for detection of contrast agents include the use of non-linear scattering properties or procedures involving destruction of the bubbles using high energy ultrasound. This is a large field of study that is beyond the scope of this thesis and will therefore not be discussed in more detail.

The function of a cell depends on what type of cell it is. The function of a muscle cell is to perform contractions and relaxations. With Doppler-based methods it is possible to measure both the velocity of the muscle motion and the deformation of the muscle.

The deformation or strain measurement can also be used to study the elasticity of tumors. This is done by compressing the tissue around the tumor and investigating how much this compresses the tumor. Hard tumors will not be deformed as much as soft tumors. The stiffness of a tumor is to some extent correlated with its malignancy. Most malignant tumors are described as hard in the literature, while the benign tumors vary in stiffness [13].

3.1 Blood flow detection and velocity estimation

The two most widely used Doppler imaging techniques to detect and measure blood flow are spectral or pulsed Doppler and color flow imaging. Pulsed Doppler can give less variance in the velocity estimate but only gives information for one sample volume at
a time. Color flow imaging reduces the examination time by allowing a simultaneous visualization of a whole two-dimensional region. A pulsed Doppler instrument was developed in 1970 by Baker [6]. In 1976, Anglesen and Brubakk [5] used the pulsed Doppler technique to measure blood flow in the aorta. The same year Holen et al. [41] combined the measured blood velocities with Bernoulli’s equation to measure the pressure gradient in mitral stenosis. Color flow imaging was introduced in the clinical setting in 1984 by Omoto [66]. Hatle and Anglesen published a widely used book on the Doppler techniques in 1982 [27] and 1985 [28]. Ferrara and DeAngelis published a review of the color flow imaging techniques in 1997 [19].

Color flow imaging involves both detection of blood flow and estimation of the blood velocity. The Doppler signal is used for both these purposes, and since the two operations are closely related, both will be reviewed.

Sections 2.1 and 2.2 give summaries of two papers by the author that are presented as part of this thesis and that discuss the detection of low velocity blood flow with pulsed Doppler and color flow imaging, respectively.

### 3.1.1 Physical basis and data acquisition

The detection and quantification of blood flow velocity with ultrasound is based on the scattered echo from the red blood cells. Detection of blood is based on removing the tissue component of the echo signal by clutter filtering and estimating the power in the remaining signal. The velocity of the detected blood can be found from either the time delay or the phase shift between the echo signals from two or more pulses. It is not possible to detect the Doppler shift using the echo from only one pulse, since the frequency resolution of any spectrum estimator is limited by the inverse of the observation time. To get a reasonable spatial resolution the observation time for each sample volume is usually smaller than a few $\mu$s. This gives a frequency resolution above several 100 kHz, and thus makes it impossible to detect the comparably small Doppler shift of blood (usually a few kHz).

Using the time delay method, the velocity is found as

$$ v = \frac{c \Delta t}{2T}, $$

where $\Delta t$ is the time delay, $c$ is the velocity of sound, and $T$ is the time between the pulses. Using the phase shift method, the velocity is found as

$$ v = \frac{c \Delta \phi}{2f_0 T}, $$

where $\Delta \phi$ is the normalized phase shift ($|\Delta \phi| < 1/2$) and $f_0$ is the center frequency of the received signal. Since $T$ is known and $f_0$ and $c$ do not vary much, the velocity can be estimated from the time delay or the phase shift.

The data acquisition is performed by transmitting and receiving typically between 4 and 16 pulses in each beam direction. The pulse repetition frequency (PRF) must be adjusted according to the velocity of the blood. Using too low PRF makes the time.
delay or the phase shift too large to be estimated without aliasing, and using too high PRF makes it difficult to estimate low velocities since the observation time becomes very small.

### 3.1.2 Signal processing

Figure 3.1 shows a block diagram of a typical color flow imaging system. Electrical pulses are generated in the transmitter and switched to the beamformer. This generates ultrasound pulses that are fired from the transducer array. Echoes received by the same transducer elements are combined in the beam former to an RF signal that is switched to the receiver. The receiver usually consists of complex demodulation, illustrated with the cosine and sine multiplications and the low pass filters (LPF), that produces the in-phase and quadrature (IQ) signals. When RF processing is used, as described on page 13, this stage is not included. Finally, the processing for the gray scale image and the color flow map is performed. This processing can in principle be performed in parallel, but usually different pulses are used for the gray scale image and the flow map.

Analog to digital conversion of the received signal can be performed in different stages of the system. If a digital beam former is used, the signals from each element in the transducer are digitized before they are transferred to the beam former. Other systems use analog delay lines in the beam former, and digitize the signal later in the process.

The velocity estimation is performed as shown in Figure 3.2 by first storing the complex IQ data acquired for each pulse in memory. (I and Q are treated as the real and imaginary part of a complex signal.) The data vector from a single depth, in this

![Figure 3.1: Block diagram of a typical color flow imaging system.](image-url)
thesis termed a packet, is then read from memory and processed to extract a power estimate and a velocity estimate for this position. The processing consists of two steps. First, the strong signal from slowly moving tissue is removed using a clutter filter, then the velocity is estimated. If the time delay method is used, as explained on page 13, the clutter filtered RF signal from several depths is combined for each velocity estimate, while for the phase shift method only the IQ signal from one depth is needed. The velocity is found using (3.1) or (3.2) respectively for the two methods. The power of the signal after clutter filtering is also calculated and is compared to a threshold to detect the presence of blood. The power signal can also be used by itself to generate so-called Power Doppler images [71].

Clutter filter

The clutter filter is a high pass filter to remove the signal from stationary or slowly moving tissue. Since only a few packet samples are available for each depth, the design of these filters is not straightforward. In 1993, Jensen [44] described a clutter filter for use in the time delay method. In 1997, Torp [81] presented a theoretical description of a general class of linear rejection filters for use in the phase shift method. These included finite impulse response (FIR) filters, infinite impulse response (IIR) filters and regression filters.

The output of a FIR filter is a weighted sum of the previous inputs $x(n)$ to the filter:

$$y(n) = \sum_{i=0}^{I} b_i x(n - i),$$

where $n = 1, \ldots, N$, and $N$ is the packet size, and $I$ is the number of zeros in the filter. The output of an IIR filter is on the other hand a weighted combination of both the
previous inputs $x(n)$ and outputs $y(n)$ of the filter:

$$y(n) = \sum_{i=0}^{I} b_i x(n - i) + \sum_{j=1}^{J} a_j y(n - j),$$

(3.4)

where $N$ and $I$ are as in (3.3) and $J$ is the number of poles [70].

Regression filters operate on the assumption that the clutter component of the signal can be approximated with a polynomial of a given order. This polynomial is found by a least-squares regression analysis, and is subtracted from the packet:

$$y(n) = x(n) - \sum_{d=0}^{D} a_d n^d,$$

(3.5)

where $a_d$ are the polynomial coefficients and $D$ is the order of the polynomial.

FIR and IIR filters have a transient that must be removed before further processing. This reduces the number of samples available for velocity estimation and will thus limit the quality of the velocity estimate. FIR filters have in addition been shown by Hoeks et al. [40] to produce a significant bias in the estimates of low velocities. IIR filters can be initialized by providing values to the unavailable inputs and outputs for $n \leq 0$ to reduce the effect of the transient. An evaluation of step-initialized IIR filters have been performed by Kadi and Loupas [45] using simulated signals. They also compared the initialized IIR filter and the regression filter and found that the regression filter had slightly better performance in estimating the correct velocity and power when the clutter component was moving slowly.

**Velocity estimation**

The time delay method was investigated by Bonnefous and Pesque in 1986 [9]. The time delay $\Delta t$ in (3.1) can be found as

$$\Delta t = \arg\max_{\tau} (C(t, \tau)),$$

(3.6)

where $\arg\max$ indicates an operation that returns the time shift $\tau$ that maximizes the cross-correlation function

$$C(t, \tau) = \sum_{n_1} \sum_{n_2} \int_{t-W/2}^{t+W/2} w_{n_1}(t') w_{n_2}(t' + \tau) s_{n_1}(t') s_{n_2}(t' + \tau) dt',$$

(3.7)

where $n_1$ and $n_2$ are pulse indexes, $s_n(t)$ is the clutter filtered RF signal from pulse number $n$, and $w_n(t)$ is a window of length $W$ that is applied to signal number $n$.

In 1985, Kasai et al. [48] presented the use of the autocorrelation technique to estimate blood velocities. This technique had previously been used in radar velocity estimation, and is the one that has been implemented in most current color flow imaging
systems. In this method, the phase shift between the pulses $\Delta \phi$ in (3.2) is found as the phase of the autocorrelation function of the packet with a lag of one sample:

$$\Delta \phi = \arg(R(1)) = \tan^{-1} \frac{R_{Im}(1)}{R_{Re}(1)}, \quad (3.8)$$

where $R_{Re}(\Delta n)$ and $R_{Im}(\Delta n)$ are the real and imaginary values respectively of the autocorrelation function

$$R(\Delta n) = \sum_{n=1}^{N} x(n + \Delta n)x^*(n). \quad (3.9)$$

This technique corresponds to a first order autoregressive (AR) estimate of the mean frequency, as shown for instance in [54].

In 1994, Torp et al. [82] used a parametric model for the autocorrelation function and found the variance of the phase shift estimate to be

$$\sigma^2_{\Delta \phi} \approx \frac{1}{2} \left( \frac{1}{\rho(\Delta m, \Delta n)} - 1 \right) \text{CS}, \quad |\Delta n| > 0, \quad (3.10)$$

where $\rho(\Delta m, \Delta n)$ is the autocorrelation coefficient with radial lag $\Delta m$ along the beam and temporal lag $\Delta n$

$$\rho(\Delta m, \Delta n) = \frac{\sum_{m} \sum_{n} x(m + \Delta m, n + \Delta n)x^*(m, n)}{\sum_{m} \sum_{n} |x(m, n)|^2}, \quad (3.11)$$

and CS is the fractional variance of the signal power estimate. This showed that minimum variance was obtained when the correlation amplitude was maximized. This maximum could occur for $\Delta m \neq 0$, which suggested that using a packet with samples from just one depth could be suboptimal.

**Power estimation, thresholding and Power Doppler**

The power estimation is performed by calculating the remaining power in the signal after the clutter filter. A commonly used estimator for the power is

$$P = R(0) = \frac{1}{N} \sum_{n=1}^{N} |x(n)|^2, \quad (3.12)$$

where $R$ is the autocorrelation function in (3.9) and $x(n)$ here is the IQ signal after clutter filtering.

In color flow imaging the thresholding, i.e., the detection of blood, is performed by comparing the estimated power with a user controlled threshold. If the power is less than this threshold, it means that all the power in the Doppler signal was removed by the clutter filter. This is the case when there is only stationary or slowly moving tissue in the sample volume. As described earlier, only a few samples are available at each
depth, and the slope of the clutter filter will depend on this. By setting the threshold too high, slowly moving blood is not detected, and by setting the threshold too low, fast moving tissue might be detected as blood. To avoid the latter, the intensity of the corresponding sample in the grayscale image is commonly used to separate blood and tissue. Since blood scatters ultrasound much more weakly than tissue, high intensities in the grayscale image indicate tissue, and not blood.

In Power Doppler, the estimated power in (3.12) is commonly averaged over several frames. This reduces the variance of the power estimate and thus increases the sensitivity to low velocity blood flow, but reduces the temporal resolution. Since no mean frequency is calculated, Power Doppler is less sensitive to changes in beam angle than color flow imaging.

### 3.1.3 Specialized methods

#### Alternative velocity estimation techniques

As mentioned earlier, the autocorrelation method corresponds to a first order autoregressive estimation. In 1990, Loupas and McDicken [54] used second order autoregressive estimation by modeling the blood signal with the two poles. In 1991, Ahn and Park [2] used one pole to model the clutter signal and the other for the blood and could thus avoid the clutter filter. Both methods have significantly reduced performance in the presence of white noise.

As an alternative to the cross-correlation technique presented in section 3.1.2, Bohs et al. in 1993 [8] described a sum-absolute-difference method. This method performs a two-dimensional search instead of only a search along the beam. This allows estimation of velocities in other directions than along the ultrasound beam.

In 1991, Ferrari and Algazi [20] presented a wideband maximum likelihood estimator (WMLE) that searched the received echoes for the most likely trajectory caused by moving blood. In 1998, Zagar et al. [93] used the WMLE estimator in combination with a signal alignment procedure, as an alternative to a clutter filter, to measure blood with low flow velocity.

#### Perfusion quantification

In 1991, Eriksson et al. [18] and Dymling et al. [17] described a method to quantify the blood perfusion, rather than the blood velocity. Blood perfusion $Q$ was defined as the net inflow of blood volume to a unit volume of tissue, and was expressed as

$$ Q \sim N_0 E\{|v|\}, \quad (3.13) $$

where $N_0$ is the number of red blood cells in a unit tissue volume, and $E\{|v|\}$ is the mean velocity magnitude of these blood cells. The perfusion was calculated from the estimated one-sided Doppler spectrum $S(f)$ as

$$ Q \sim \int_0^\infty f S(f) df. \quad (3.14) $$
A vascular network where all flow directions were equally probable was assumed. The results of in vivo and in vitro experiments indicated a relation between the estimated perfusion value and the true perfusion, but that large fluctuations in the estimated value occurred by changes in geometry and ultrasound frequency.

In 1995, Adler et al. [1] found that the specific flow $Q/V$ was given by the temporal decorrelation of the Doppler power signal $p(l)$:

$$ R_p(m) = R_p(0)e^{-\frac{m}{T_p}}, $$

where $R_p$ is the frame-to-frame autocorrelation of $p(l)$, and

$$ p(l) = |x(l)|^2 - \frac{1}{L} \sum_{l'=1}^{L} |x(l')|^2. $$

The method was tested in a flow phantom and the velocity found from the specific flow through a sample volume correlated well with the result using a standard Doppler shift technique.

**Harmonic Doppler**

In 1996, Burns et al. [10] described the principles and preliminary results of harmonic Doppler. In this technique, a band pass filter on the RF signal is used to access the second harmonic component of the signal. This second harmonic signal is then processed as before, taking into account the doubled ultrasound frequency, to detect blood. This technique is especially useful combined with the use of contrast agents, since they give a high amount of nonlinear scattering.

### 3.2 Tissue Doppler imaging

The concept of tissue Doppler imaging (TDI) was introduced by McDicken et al. in 1992 [59] and was further developed by Sutherland et al. in 1994 [79]. TDI color maps the tissue velocities rather than the blood velocities, and is mainly used in the cardiac muscle. The velocities in the cardiac tissue is considerably lower (0–15 cm/s) than in the blood, but the amplitude of the echo signal is approximately 40 dB larger than that of blood [62].

The signal processing is much like for color flow imaging in Figure 3.2, only the clutter filter is bypassed or greatly weakened so the signal component from the relatively slowly moving tissue is not removed. Also the velocity map is usually not thresholded, but just superimposed on the grayscale image. The imaging parameters are also optimized differently, the PRF can, for instance, be lower in TDI than in color flow imaging due to the lower velocities in the tissue compared to the blood.
3.3 Strain rate imaging

The term "strain rate" is in this thesis used for the rate of deformation. The rate of deformation is a tensor that describes the rate of change of a length in an object. For small displacements and infinitesimal strains, as the ones occurring from frame to frame in ultrasound imaging, the rate of deformation tensor is approximately equal to the time derivative of the infinitesimal strain tensor, thus explaining the choice of the term "strain rate". The strain and rate of deformation tensors are described in detail in Appendix A. As shown in Appendix A, the rate of deformation is in the one-dimensional case given as the spatial velocity gradient.

Several methods to measure this velocity gradient have been proposed, and these are reviewed in the following sections. The myocardial velocity gradient (MVG) method is a post processing method that uses the TDI velocities found by converting the colors in the digitized TDI image to velocities using the information in the color bar in the same image. The tracking-based strain rate imaging uses a modified cross-correlation technique to track points in the myocardium, while simultaneously measuring their velocity. The real-time strain rate imaging (SRI) method calculates the strain rate directly from the received IQ signals.

3.3.1 Myocardial velocity gradient

In 1994, Fleming et al. [21] suggested using the gradient of the TDI velocity as a measure for the relative change in heart wall thickness:

\[-\frac{dW}{dt} / W = \frac{dv}{dr}.\]  (3.17)

Here, \(W\) is the instantaneous wall thickness and \(dv/dr\) is the velocity gradient across the wall. This gradient was found as the slope of the linear regression of the TDI velocity estimates. Only velocities measured with the ultrasound beam perpendicular to the heart wall were used.

In 1995, Uematsu et al. [84] expanded the method to be used also when the ultrasound beam crossed the heart wall at an angle less than 90 degrees. Short axis views were used, and the motion was assumed to be towards the center of the ventricle. The angle \(\theta\) between the ultrasound beam and the assumed direction of the motion was then used to angle correct the velocity data:

\[v_{\text{corrected}} = \frac{v_{\text{measured}}}{\cos \theta}.\]  (3.18)

The velocity profile between the endocardium and the epicardium was then obtained for each radius from the center of the ventricle. The velocity gradient was finally found as the rate of inclination of each velocity profile by using least squares linear regression.

Using this method on normal volunteers and patients with myocardial infarctions and dilated cardiomyopathy, the peak systolic values in Table 3.1 were found. Significant differences in velocity gradients were found between all the patient groups and the normal volunteers in the affected walls.
Table 3.1: Peak systolic transmural MVG (mean ± standard deviation in s⁻¹) in 11 normal volunteers, 7 patients with old anteroseptal myocardial infarction (Ant MI), 7 patients with old posterior myocardial infarction (Post MI) and 8 patients with dilated cardiomyopathy (DCM) measured by Uematsu et al. [84].

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Ant MI</th>
<th>Post MI</th>
<th>DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroseptal wall</td>
<td>1.69 ± 0.53</td>
<td>0.58 ± 0.41</td>
<td>1.48 ± 0.25</td>
<td>0.72 ± 0.59</td>
</tr>
<tr>
<td>Posterior free wall</td>
<td>3.28 ± 0.67</td>
<td>2.84 ± 0.37</td>
<td>0.17 ± 0.27</td>
<td>0.93 ± 0.67</td>
</tr>
</tbody>
</table>

Table 3.2: Peak transmural MVG (mean ± standard deviation in s⁻¹) in a total of 158 young (30 ± 7 years) and older (58 ± 8 years) normal volunteers, athletes, patients with hypertension, and patients with hypertrophic cardiomyopathy (HCM) measured by Palka et al. [68]. The values were determined for early ventricular ejection (systole), during rapid ventricular filling (early diastole) and during atrial contraction (late diastole). The signs of the values have been changed to conform with the definition of strain rate used in this thesis.

<table>
<thead>
<tr>
<th></th>
<th>Systole</th>
<th>Early diastole</th>
<th>Late diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young normal subjects</td>
<td>4.4 ± 0.8</td>
<td>-9.2 ± 2.0</td>
<td>-1.0 ± 0.9</td>
</tr>
<tr>
<td>Older normal subjects</td>
<td>4.8 ± 0.8</td>
<td>-3.6 ± 1.5</td>
<td>-3.8 ± 0.9</td>
</tr>
<tr>
<td>Athletes</td>
<td>4.6 ± 1.1</td>
<td>-9.9 ± 1.9</td>
<td>-0.9 ± 0.9</td>
</tr>
<tr>
<td>Patients with hypertension</td>
<td>4.2 ± 1.8</td>
<td>-3.3 ± 1.3</td>
<td>-4.3 ± 1.7</td>
</tr>
<tr>
<td>Young patients with HCM</td>
<td>3.2 ± 1.1</td>
<td>-3.7 ± 1.5</td>
<td>-1.3 ± 0.8</td>
</tr>
<tr>
<td>Older patients with HCM</td>
<td>2.9 ± 1.2</td>
<td>-2.6 ± 0.9</td>
<td>-1.4 ± 0.8</td>
</tr>
</tbody>
</table>

Using the same method, Palka et al. [68] in 1997 measured MVG values throughout the cardiac cycle in normals, athletes and patients with hypertension and with hypertrophic cardiomyopathy (HCM). Their results are summarized in Table 3.2. Significant differences in MVG were found between the HCM patients and all the other groups in almost all phases of the cardiac cycle. The exceptions were in early diastole with hypertension and in late diastole with athletes and young normal subjects. The authors concluded that MVG in early diastole was an accurate variable to discriminate between HCM and hypertrophy in athletes.

In 1998, Tsutsui et al. [83] investigated the use of the same MVG method to detect ischemic myocardium during a submaximal two-step dobutamine challenge (10 and 30 μg/kg body weight per min) in 13 patients with and 6 patients without confirmed single-vessel coronary artery disease. Short axis gray scale and tissue Doppler images were obtained, and a visual interpretation of the regional wall motion was done using a four-point scale: 1 = normal, 2 = hypokinesia, 3 = akinesia and 4 = dyskinesia. The measured MVG values are compared to the mean point scores in Table 3.3. In both anteroseptal and posterior segments the MVG values were significantly increasing with the dobutamine in the nonischemic segments. In the ischemic segments there were no
Table 3.3: Mean point scores and peak systolic MVG (mean ± standard deviation in s⁻¹) in nonischemic and ischemic segments during a Dobutamine (μg/kg/min) challenge as measured by Tsutsui et al. [83]

<table>
<thead>
<tr>
<th></th>
<th>Anteroseptal segments</th>
<th>Posterior segments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dobutamine Baseline 10 30</td>
<td>Dobutamine Baseline 10 30</td>
</tr>
<tr>
<td>Point score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>1.08 1.00 1.00</td>
<td>1.00 1.00 1.00</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.14 1.14 1.16</td>
<td>1.16 1.33 1.20</td>
</tr>
<tr>
<td>MVG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>2.6 ± 0.8 4.6 ± 1.2 6.0 ± 1.0</td>
<td>3.9 ± 0.7 6.1 ± 1.5 7.6 ± 1.8</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2.5 ± 0.8 3.1 ± 0.7 2.7 ± 0.7</td>
<td>3.4 ± 1.0 3.5 ± 1.0 4.1 ± 0.9</td>
</tr>
</tbody>
</table>

significant changes in MVG during the dobutamine challenge. The point scores showed normal values throughout the test in all but one patient, which went from normal to hypokinesia during the dobutamine challenge. The endocardial tissue Doppler velocities were also compared, and showed significant changes during the dobutamine challenge only for the nonischemic posterior segments at high dose. The authors concluded that MVG may be more sensitive in detecting subtle wall motion changes than a point score method and TDI.

3.3.2 Tracking-based strain rate imaging

In 1997, Kanai et al. [47] presented an offline strain rate imaging technique based on IQ cross-correlation. Initially, several points along an ultrasound beam perpendicular to the cardiac wall were manually chosen. The velocity $v_i(l)$ of point number $i$ in frame number $l$ was calculated using an IQ cross-correlation technique where the phase of the correlation function at peak magnitude was used to estimate the velocity:

$$v_i(l) = \frac{c}{2\omega_0 T} \arg(C_i(\delta r_{\text{max}})). \hspace{1cm} (3.19)$$

Here, $\delta r_{\text{max}}$ is the radial lag that maximizes $|C_i(\delta r)|$. The IQ cross-correlation function $C_i(\delta r)$ is defined as

$$C_i(\delta r) = \int_{r_{i-W/2}}^{r_{i+W/2}} x^*(r', 1)x(r' + \delta r, 2)dr', \hspace{1cm} (3.20)$$

where $x(r, 1)$ and $x(r, 2)$ were the radial IQ signals derived from pulse numbers 1 and 2, and $W$ corresponded to the length of the pulse. The position $r_i$ of point number $i$ in the next frame was then found as

$$r_i(l + 1) = r_i(l) + T \cdot v_i(l), \hspace{1cm} (3.21)$$
where $T$ is the pulse repetition time. The local strain rate in each frame was finally calculated as

$$
\dot{\varepsilon}_i(l) = \frac{v_{i+1}(l) - v_i(l)}{|r_{i+1}(l) - r_i(l)|}.
$$

(3.22)

The strain rate was color coded and superimposed on a grayscale M-mode image of the same position. The method was limited to areas where the ultrasound beam could be placed perpendicular to the heart wall, and the temporal resolution in the actual system was according to the author not so high since temporal averaging over about 10 received echoes was performed.

### 3.3.3 Real-time Doppler strain rate imaging

The strain rate imaging (SRI) method calculates the strain rate in real-time directly from the complex echo signal. This is in contrast to the MVG method described in section 3.3.1 where the tissue velocities first are calculated using the tissue Doppler technique, and the velocity gradient then is calculated offline.

Section 2.3 gives a summary of a paper by the author that is presented as part of this thesis and that gives an clinical introduction to the SRI technique [34]. The technical details and more clinical examples of the method are further described in the following chapters later in this thesis.

### 3.4 Strain imaging

Strain imaging by ultrasound is one of several imaging techniques in the field of sonoelastography, i.e., the use of ultrasound to image tissue elastic parameters. Although these are not all Doppler based methods, some are based on similar physical concepts, and will therefore be reviewed. A review of all the sonoelastography techniques was compiled by Gao et al. in 1996 [24]. The methods can be classified in two main groups. The first consists of methods involving a low frequency vibration that is externally applied. The effect on the imaged tissue is then used to estimate the elasticity in the tissue. The second main group consists of methods involving a static compression of the tissue. By comparing the ultrasound images from before and after the compression, the strain images are generated, and the strain values can be further analyzed to get other tissue elastic parameters. Strain introduced by the tissue itself, like myocardial thickening and cyclic changes in vessel wall thickness, can in principle also be measured using the same techniques.

#### 3.4.1 Vibration amplitude sonoelastography

In 1988, Lerner et al. [52] presented a method where a low-frequency vibration (20–1000 Hz) was externally applied to the tissue. Changes in the stiffness within the tissue caused disturbances in the vibration patterns, which was imaged using Doppler
techniques. In 1990, Lerner et al. [51] presented real-time vibration amplitude images using a modified color Doppler system where vibrations over a threshold were colored.

A mathematical model for the vibration amplitude sonoelastography was presented by Gao et al. in 1995 [23]. The wave field within the tissue was expressed as:

$$\Phi_{\text{total}} = \Phi_i + \Phi_s,$$

(3.23)

where $\Phi_i$ is the incident field and $\Phi_s$ the field scattered by the inhomogeneities in the tissue. These fields satisfied the wave equations

$$(\nabla^2 + k)\Phi_i = 0$$

(3.24)

$$(\nabla^2 + k)\Phi_s = \alpha(r)$$

(3.25)

where $\alpha(r)$ were the inhomogeneity properties. Using a sonoelastic Born approximation, these wave equations could be solved, and the vibration field for an inhomogeneity could be calculated.

### 3.4.2 Strain imaging by speckle tracking

In 1989, Meunier et al. [61] described a method to compute local myocardial deformation from frame-to-frame changes in speckle patterns. In this method, a speckle tracking algorithm [36] was used to compute the frame-to-frame 2D velocity field $(U(x, y), V(x, y))$ for a small region of interest. This velocity field was then decomposed into a translation (T), a rotation (R) and a deformation (D) field:

$$\begin{bmatrix} U \\ V \end{bmatrix} = T + (R + D) \begin{bmatrix} x \\ y \end{bmatrix}.$$  

(3.26)

The deformation field is in fact the strain field, which in this method was further decomposed into the two main directions, perpendicular and parallel to the imaged muscle segment.

In 1998, Meunier [60] expanded the method to three spatial dimensions. He described the deformation through the transformation:

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = M^{-1} \begin{bmatrix} x \\ y \\ z \end{bmatrix} - T,$$

(3.27)

where $T$ is the translation field and $M$ is the combined rotation and deformation field, and then calculated the theoretical limitations of the method. To do this, 3D gray scale images were simulated as the magnitude of the result of convolving an RF point spread function with a tissue object function. Then the cross-correlation coefficient between small volumes of interest in a simulated 3D image transformed using (3.27) and the corresponding 3D image simulated after performing the same transformation on the tissue object function was calculated. The theoretical results showed that lower
ultrasound frequencies and smaller point spread functions were more desirable for a speckle tracking methodology, i.e., higher degrees of rotation and deformation could be allowed without decorrelation. However, these two aims are in conflict. When the ultrasound frequency is reduced, the point spread function becomes larger and vice versa.

In 1999, Maurice and Bertrand [38] studied the speckle-motion artifacts (SMA) arising from tissue shearing. Rotation had previously been shown to result in lateral speckle motion [63, 46], and Maurice and Bertrand showed that shear deformations also produced such artifacts.

3.4.3 Compression RF strain imaging

In 1991, Ophir et al. [67] published a method they called elastography. In this method, the local strain introduced by a small external compression (usually less than 1%) was found by comparing the pre- and post-compression RF echo signals. The authors also estimated the stress field in the tissue from stress measurements close to the transducer surface, and could then calculate the elastic modulus profile in the tissue.

The strain was estimated in the following manner. The RF echo signals were broken into $K$ small, and possibly overlapping, segments of length $T$. Segments number $m$ from the pre- and post-compression RF signals, $s_1(t)$ and $s_2(t)$ respectively, were then cross-correlated. The temporal location of the peak of the cross-correlation function was then used to estimate the time shift, or corresponding displacement $d(m)$, of the segment:

$$d(m) = c \frac{c}{2} \argmax_{\Delta t} \left( C(\Delta t, m) \right),$$

where $\argmax$ indicates an operation that returns the time shift $\Delta t$ that maximizes the cross-correlation function

$$C(\Delta t, m) = \frac{1}{T} \int_{mT}^{(m+1)T} s_1(\tau) s_2(\Delta t + \tau) d\tau.$$  

In the actual implementation, the integral in (3.29) was replaced by a discrete sum, and the peak in the correlation function was found using an interpolation algorithm. The resulting displacements $d(m), m = 0 \ldots M - 1,$ were then used to estimate the strain between two spatially neighboring segments:

$$\varepsilon(m) = \frac{d(m) - d(m - 1)}{r_s},$$

where $r_s$ is the spatial distance between two neighboring segments.

The Cramér-Rao lower bound variance for the strain estimator was in 1995 expressed by Cespedes et al. [12] as

$$\sigma_{CR}^2 = \frac{\sigma_{\varepsilon}^2}{\varepsilon} + \frac{\sigma_{\varepsilon}^2}{\varepsilon} \frac{2\text{cov}(d(m), d(m - 1))}{r_s^2},$$

(3.31)
where $\sigma^2_{CRd(m)}$ is the lower bound variance of the displacement estimate, and $\text{cov}$ is the covariance function. By assuming stationarity of the echo signal, the variance of the displacement estimates was constant, i.e., $\sigma^2_{CRd(m-1)} = \sigma^2_{CRd(m)} = \sigma^2_{CRd}$. This variance is found from the lower bound variance of the time delay estimate, which has been presented by several authors. One commonly used expression is \cite{12}

$$\sigma^2_{CRd} = \frac{c^2}{4} \sigma^2_{CRr} \approx \frac{c^2}{4} \frac{1}{4\pi^2 f_0^2 B T w SNR},$$

(3.32)

where $f_0$ is the center frequency of the ultrasound pulse, $B$ is the signal bandwidth, $T_w$ is the temporal window size used in the estimation of the time delay, and SNR is the signal-to-noise ratio. It was assumed a wide-band band-pass signal with rectangular spectrum, high signal-to-noise ratio (SNR $\gg 1$) and uncorrelated additive white Gaussian noise.

Another expression was presented in 1995 by Walker and Trahey \cite{91}:

$$\sigma^2_{CRd} = \frac{c^2}{4} \sigma^2_{CRr} \approx \frac{c^2}{4} \frac{3}{2\pi^2 T_w (B^3 + 12 f_0^2 B)} \left( \frac{1}{\rho^2} \left( 1 + \frac{1}{SNR} \right)^2 - 1 \right).$$

(3.33)

Here, the effect of partly correlated signal segments was taken into account through the correlation coefficient $\rho$.

Céspedes et al. introduced the following limit for the covariance:

$$\text{cov}(d(m), d(m-1)) \leq \frac{4}{c^2} \sigma^2_{CRd} \left( 1 - \frac{2r_s}{cT_w} \right) \text{ for } r_s \leq \frac{cT_w}{2}$$

$$\text{cov}(d(m), d(m-1)) = 0 \text{ for } r_s > \frac{cT_w}{2}$$

(3.34)

The corresponding Cramér-Rao lower bound variances for the strain estimator then become:

$$\sigma^2_{CRc} \geq \frac{c}{4\pi^2 f_0^2 B T w r_s SNR} \text{ for } r_s \leq \frac{cT_w}{2}$$

$$\sigma^2_{CRc} \geq \frac{c^2}{8\pi^2 f_0^2 B T w r_s^2 SNR} \text{ for } r_s > \frac{cT_w}{2}$$

(3.35)

using (3.32) and

$$\sigma^2_{CRc} \geq \frac{3c}{2\pi^2 T_w r_s (B^3 + 12 f_0^2 B)} \left( \frac{1}{\rho^2} \left( 1 + \frac{1}{SNR} \right)^2 - 1 \right) \text{ for } r_s \leq \frac{cT_w}{2}$$

$$\sigma^2_{CRc} \geq \frac{3c^2}{4\pi^2 T_w r_s^2 (B^3 + 12 f_0^2 B)} \left( \frac{1}{\rho^2} \left( 1 + \frac{1}{SNR} \right)^2 - 1 \right) \text{ for } r_s > \frac{cT_w}{2}$$

(3.36)

using (3.33).
In 1997 Varghese and Ophir [89] presented a modified lower bound variance that was divided into three regions. This combined bound was referred to as the Ziv-Zakai lower bound or the so-called Strain Filter. The three regions were defined by the level of signal-to-noise ratio of the computed strain image (SNR$_C$). This ratio depends both on the SNR in the echo signals and the degree of correlation between the pre- and post-compression signal segments. Since the SNR$_C$ decreases when the strain increases, the regions correspond to regions in strain value also. For low strains, the variance was given by the Cramér-Rao bound (3.36). At strains so large that there are ambiguities in the signal phase, but where the strain still can be estimated by correlating only the signal envelope, the variance was given by the so-called Barankin bound:

\[ \sigma^2_{BB_{\varepsilon}} = 12 \left( \frac{f_0}{B} \right)^2 \sigma^2_{CR_{\varepsilon}}. \]  

Finally, at high strains the variance was expressed as a value independent of the SNR$_C$:

\[ \sigma^2_{CV_{\varepsilon}} = \frac{s^2TC}{12v_s}. \]  

Combining these three bounds, the so-called strain filter or Ziv-Zakai lower bound became:

\[ \sigma^2_{ZZ_{\varepsilon}} \geq \begin{cases} \sigma^2_{CR_{\varepsilon}} & \text{for high SNR}_C \text{ or low strain} \\ \sigma^2_{BB_{\varepsilon}} & \text{for medium SNR}_C \text{ or medium strain} \\ \sigma^2_{CV_{\varepsilon}} & \text{for low SNR}_C \text{ or high strain} \end{cases} \]  

### 3.4.4 Compression IQ strain imaging

Another strain imaging technique based on the phase information of the signal and a multiple step compression was presented by O’Donnell et al. [65] in 1994. Here, a step-wise compression was performed on the imaged object, and for each step the recorded RF signals were quadrature demodulated, resulting in the complex signal segments \( x(t; n) \) for the precompression and \( x(t; n+1) \) for the postcompression. Incremental displacements between neighboring segments were estimated as:

\[ \Delta d_n(m) = \frac{c \left[ \text{arg}(C_n(0, 0)) - \text{arg}(C_n(0, m - 1)) \right]}{2\omega_0}, \]  

where \( c \) is the speed of sound, \( \omega_0 \) is the angular center frequency of the ultrasound pulse and \( C_n(0, m) \) is the base-band cross-correlation function

\[ C_n(t, m) = \frac{1}{T} \int_{mT}^{(m+1)T} x(\tau, n)x^*(t + \tau, n + 1)d\tau, \]  

evaluated at lag zero. Displacements greater than \( \lambda/4 \) will give aliasing of the argument function, but by implementing the phase difference in (3.40) as shown in Figure 3.3, the aliasing will only occur if the differential displacement is greater than \( \lambda/4 \).
3.4 Strain imaging

From this incremental displacement, the strain was calculated in two different ways. In the first, so-called direct procedure, the displacement at depth \(m\) for compression step number \(n\) was found by the summation

\[
d_n(m) = \sum_{i=m_0}^{m} \Delta d_n(i),
\]

(3.42)

where \(i = m_0\) is a stationary point, for instance at the transducer surface. The total displacement after \(N\) compression steps was then found by the sum

\[
d(m) = \sum_{n=0}^{N} d_n(m(n)),
\]

(3.43)

where \(m(n)\) indicates that the position had to be adjusted from step to step in the compression. Finally, the strain was estimated as

\[
\varepsilon(m) = \frac{d(m) - d(m - 1)}{r_s},
\]

(3.44)

where \(r_s\) is the spatial distance between two neighboring segments. Assuming small strains in each compression step, the variance of this estimator is:

\[
\sigma_{\varepsilon}^2 = \frac{C^2 M}{2 \omega_0^2 r_s^2 SNR},
\]

(3.45)

where \(SNR\) is the average signal-to-noise ratio for the chosen location over the \(N\) compression steps.

### Differential procedure

In the second, so-called differential procedure, the differential strain for each step was calculated as:

\[
\Delta \varepsilon_n(m) = \frac{\Delta d_n(m)}{r_s},
\]

(3.46)
where $\Delta d_n(m)$ is defined in (3.40), and $r_s$ is the spatial distance between two neighboring segments. The total strain for depth $m$ was then calculated as:

$$
\varepsilon_m = \sum_{n=0}^{N} \Delta \varepsilon_n(m(n)),
$$

where $m(n)$ indicates that the position had to be adjusted from step to step in the compression. Assuming small strains in each compression step, the variance of this estimator is the same as in (3.45).

### 3.4.5 Spectral strain imaging

In 1994 Talhami et al. [80] presented a spectral strain imaging technique. They modeled the RF signal as a convolution of a random valued object function $g(r)$ and a pulse function $p(r)$:

$$s_0(r) = g(r) \otimes p(r).$$

The corresponding Fourier transform then became:

$$S_0(k) = G(k)P(k),$$

where $k$ is the spatial frequency. By compressing the imaged object with a strain $\varepsilon$, the object function became $g(\varepsilon r)$. Using the Fourier scaling property, the Fourier transform of the RF signal could be written:

$$S(k) = \frac{1}{\varepsilon} G\left(\frac{k}{\varepsilon}\right)P(k).$$

As seen, the object function is frequency scaled with $1/\varepsilon$. Now, since the multiplication with $P(k)$ could be considered as a band pass filter, the strain could be estimated by comparing the spectrum $S(k)$ with the one obtained before the compression, $S_0(k)$.

The strain in an M-mode RF signal $s(r, n)$, where $r$ is the spatial coordinate and $n$ is the temporal pulse to pulse coordinate, was estimated by Talhami et al. as:

$$\hat{\varepsilon} = \frac{\sigma_{\hat{k}}}{\mu_{\hat{k}}},$$

where $\hat{k}(n)$ is a peak spatial frequency estimator over a defined bandwidth K,

$$\hat{k}(n) = \arg\max_{k \in K}(|S(k)|),$$

and $\mu_{\hat{k}}$ and $\sigma_{\hat{k}}$ its mean and standard deviation respectively over a short time window $n = 1, \ldots, N$.

The authors proposed the following understanding of this estimator: If the object function was assumed to be a random but equi-distant train of delta pulses, simulating
the echo from an object with scatterers regularly spaced with a distance $D$, the resulting spectrum $|S(k)|$ would have peaks spaced at $\Delta k = 1/D$. The peak frequency estimator in (3.52), where $K$ was centered on the first peak, would then measure the dominant scatterer spacing. The mean $\mu_k$ would thus estimate the average scatterer spacing over time and the standard deviation $\sigma_k$ would estimate the average change in scatterer spacing. Dividing these then gave the strain estimate in (3.51).

### 3.4.6 Decorrelation

An important quality limiting factor in strain imaging techniques is the decorrelation caused by the compression of the imaged object. Because of the compression, the post-compression signal segments will also be compressed, and thus will not match perfectly with the pre-compression signal segments. Lateral motion will also reduce the correlation. Using simulated RF data, O’Donnell et al. [65] calculated the standard deviation of the strain estimate in (3.28) through (3.30). Their results are given in table 3.4. As seen, the strain error at large strains is reduced when a shorter window is used. At low strains, the decorrelation is less of a problem, and a longer window yields a better result.

Several techniques to reduce the decorrelation have been proposed, including amplitude compression, multicompression, signal stretching and lateral correction, and these will be reviewed in the following sections.

#### Amplitude compression

In 1993, Céspedes and Ophir [14] proposed an amplitude compression technique to reduce the decorrelation noise. The idea of this technique is that the values of the RF cross-correlation function will depend on the signal amplitude. Since the pre- and postcompression signal segments will never match perfectly, a stochastic variations in the signal amplitude might cause a shift of the peak in the cross-correlation function. In effect, this might modulate the strain estimates by the random signal amplitude variations, and cause artifacts in the strain images.

To reduce this artifact, Céspedes and Ophir suggested performing a logarithmic compression of the RF signals prior to calculating the cross-correlation. An experiment was performed using simulated data. The effect on the strain image quality was measured by the mean-to-standard deviation ratio (MSDR):

$$MSDR = \frac{\mu_S}{\sigma_S},$$  \hspace{1cm} (3.53)
No compression  Log compression  Temporal stretching
MSDR  2.1  4.1  3.9

Table 3.5: Average mean-to-standard deviation ratio (MSDR) values of simulated strain images using logarithmic compression or temporal stretching [14].

where \( \mu_S \) and \( \sigma_S \) are respectively the mean and standard deviation of the strain in a region of uniform elasticity. The results are shown in table 3.5. As seen the MSDR is almost doubled when logarithmic compression is used, indicating that the standard deviation is almost halved.

No references to this method have been found in any of the later publications on elastography.

**Multicompression**

In 1996, Varghese [90, 87] used a multiple step compression technique to reduce the decorrelation. The multicompression technique was combined with the signal stretching technique described in the following section. The technique was similar to O’Donnells technique described in Section 3.4.4, only used for RF signals. The idea of the technique was that the decorrelation would be reduced, since the applied strain \( \varepsilon_n \) for each compression step was small. The final strain estimate \( \varepsilon_f \) was in this work found by averaging the strain estimates \( \varepsilon_n \) for all the compression steps:

\[
\varepsilon_f = \frac{1}{N} \sum_{n=1}^{N} \varepsilon_n. \tag{3.54}
\]

The total strain \( \varepsilon_t \) could also be found by accumulating all the strain estimates:

\[
\varepsilon_t = \sum_{n=1}^{N} \varepsilon_n. \tag{3.55}
\]

Assuming that the strain estimates for each step were uncorrelated, the standard deviation of the final or total strain estimate could be reduced by \( \sqrt{N} \), where \( N \) is the number of compression steps:

\[
\sigma_{\varepsilon_f}^2 = \sigma_{\varepsilon_t}^2 = \frac{1}{N} \sigma_{\varepsilon_n}^2. \tag{3.56}
\]

**Signal stretching**

In 1993, Céspedes and Ophir [14] also proposed a signal stretching method to reduce the decorrelation noise. When the imaged object is compressed, the scatterers move closer to each other. For small strains this was modeled as a temporal compression of the RF signal. By stretching the postcompression signal by the same factor, the RF cross-correlation will be improved.
Cespedes and Ophir used a linear interpolation algorithm to stretch the post-compression signal. The stretch factor was chosen equal to the known compression strain. The effect on the strain image quality was measured by the MSDR as defined in (3.53), and the result is shown in the last column in table 3.5. As seen, the MSDR is almost doubled when temporal stretching is used, indicating that the standard deviation is almost halved.

In 1997, Varghese and Ophir [88] presented a theoretical description of this method. The RF signal was described as a convolution of the object function \( g(r) \) and the point spread function \( p(x) \), in addition to uncorrelated random noise \( n_1(r) \):

\[
s_1(r) = g(r) \otimes p(r) + n_1(r).
\] (3.57)

If a strain \( \varepsilon \) was imposed on the object, the measured RF signal would be:

\[
s_2(r) = g\left(\frac{r}{1 + \varepsilon} - r_0\right) \otimes p(r) + n_2(r).
\] (3.58)

The cross-correlation coefficient between these two signals was termed \( \rho_{12} \). The post-compression RF signal was then stretched by the inverse factor \( (1 + \varepsilon) \):

\[
s_3(r) = s_2((1 + \varepsilon)r) = g(r - r_0) \otimes p((1 + \varepsilon)r) + n_3(r).
\] (3.59)

The cross-correlation function between this signal and the pre-compression signal was termed \( \rho_{13} \). By modeling the point spread function as a Gaussian modulated cosine pulse, the following simple relation between the two cross-correlation coefficients was shown:

\[
\rho_{13} = \frac{\rho_{12}}{1 + \varepsilon}.
\] (3.60)

Since \( \varepsilon \leq 0 \) in any compression (in elastography values in the range \(-0.01 < \varepsilon \leq 0 \) are used [67]), \( \rho_{13} \) will always be larger than \( \rho_{12} \), meaning that the stretching operation generally improves the correlation.

Also in 1997, Alam and Ophir [3] showed that the effect of the stretching technique could be described as a low-pass filtering of the pre-compression autocorrelation function \( R_{11}(r) \). The expected value of the cross-correlation estimate was written:

\[
E\{\hat{C}_{13}(\delta r)\} = R_{11}(\delta r) \otimes h(\delta r) \otimes \delta(\delta r - r_0),
\] (3.61)

where \( h(r) \) is the impulse response of the band pass filter and \( r_0 \) is the required shift to get peak cross-correlation. The bandwidth of the low-pass filter was given by the applied strain, the ultrasound frequency and the pulse length. For small strains the filter approached a Dirac delta pulse indicating that the stretching technique approached complete restoration of the correlation. Still the pre-compression signal and the stretched signal were not equal due to the different impulse responses \( p(r) \) and \( p((1 + \varepsilon)r) \) embedded in them, as seen in (3.57) and (3.59). The authors proposed using inverse filtering on the stretched signal to get a further increase in correlation. In the Fourier domain this was described as:

\[
R_3(k)H(k) = \frac{1}{1 + \varepsilon}R_1(k)e^{-j4\pi kr_0/c} + N_3(k)H(k),
\] (3.62)
where the filter $H(k)$ is given by:

$$H(k) = \begin{cases} \frac{P(k)}{R(k)(1+\varepsilon)} & G_3(k) \geq N_3(k) \text{ and } P(k/(1+\varepsilon)) \neq 0 \\ 0 & \text{otherwise} \end{cases}$$  \hspace{1cm} (3.63)

Here $R(k)$, $N(k)$, $P(k)$ and $G(k)$ were the spatial Fourier transforms of $R(r)$, $n(r)$, $p(r)$ and $g(r)$ respectively.

In 1998, Alam et al. [4] described an adaptive strain estimator where the temporal stretching of the post-compression signal was adapted using a binary search method. This adaptiveness was needed since the proper stretching is given by the local strain, an unknown and both spatially and temporally varying parameter. Using a global uniform stretching as in [14] would therefore be suboptimal. The correct local stretching factor will maximize the correlation, so this factor could be found by performing a search over several stretching factors until the peak correlation was found:

$$\hat{\varepsilon} = \arg\max_{\varepsilon} \rho_{13}(\varepsilon),$$  \hspace{1cm} (3.64)

where argmax is a binary search that returns the lag $\varepsilon$ that maximizes the cross-correlation coefficient.

$$\rho_{13}(\varepsilon) = \frac{\int_{-\infty}^{\infty} [g(r) \otimes p(r)] g((1+\varepsilon)r) \otimes p(r) \, dr}{\sqrt{\int_{-\infty}^{\infty} [g(r) \otimes p(r)]^2 \, dr \int_{-\infty}^{\infty} [g((1+\varepsilon)r) \otimes p(r)]^2 \, dr}}.$$  \hspace{1cm} (3.65)

Here $g(r)$ and $p(r)$ are defined in (3.57). The stretching of the point spread function was ignored, i.e., $p((1+\varepsilon)r) \approx p(r)$ was assumed.

**Lateral correction**

In 1998, Konofagou and Ophir [49] presented a method to correct the radial strain measurements for the lateral displacements caused by the compression. These displacements cause a reduction in the correlation between the pre-compression and post-compression signals.

The lateral displacement was found by first laterally interpolating the stretched post-compression signals and then searching among the interpolated signals to find the best match. Using this match as the post-compression signal, an increase in the correlation was observed.

Furthermore, knowing the lateral displacements, the authors were able to calculate the lateral strain, and could by dividing the lateral strain by the radial strain map the local Poisson’s ratio of the tissue:

$$\nu = -\frac{\varepsilon_l}{\varepsilon_r}.$$  \hspace{1cm} (3.66)
3.4 Strain imaging

3.4.7 Dynamic range

In 1997, Konofagou et al. [50] used variable applied strain to expand the dynamic range of the strain measurements. For a certain degree of compression only a limited range of strain values can be found using RF elastography. This range is given by the "band" in the strain filter described in section 3.4.3.

A multiple step compression was performed, but for each step the strain was calculated using the baseline RF data as reference rather than the data from the previous step. Thus, elastograms produced by different amounts of strain were gathered. These elastograms were first normalized by scaling them with the applied strain, then in each elastogram the regions with strains within the strain filter band were chosen, while the rest were disregarded as noise. Finally a composite elastogram was built up by the chosen regions in each step-elastogram.
Chapter 4

One-dimensional strain rate estimation

This chapter describes techniques to estimate the strain rate in one dimension, that is, along the ultrasound beam. In section 4.1, a maximum likelihood strain rate estimator is developed, while section 4.2 describes a real-time implementation of a strain rate estimator.

Section 4.1 was written in collaboration with my supervisor, professor Hans Torp.

4.1 Optimal strain rate estimator

In order to find the optimal strain rate estimator, a statistical model for the IQ-signal is developed in this section. The signal model is general for any packet size $N$, but only the setting with $N = 2$ is considered in the rest of the section. A likelihood function is found from the statistical model, and a maximum likelihood estimator is derived. The lower bound variance is found and compared to the variance presented in the strain imaging field (see Section 3.4). The maximum likelihood estimator is also compared to the linear regression estimator used in the Myocardial Velocity Gradient method (see Section 3.3.1). Finally a closed form expression for the estimator is presented.

4.1.1 Three component Gaussian signal model

Consider the complex demodulated IQ signal $x(m, n), m = 1 \ldots M, n = 1 \ldots N$, consisting of a total of $MN$ samples from $M$ radial positions along each of $N$ consecutive beams in the same direction. This signal is reorganized in a complex signal vector

$$x = [x(1,1), \ldots, x(1,N), x(2,1), \ldots, x(2,N), \ldots, x(M,1), \ldots, x(M,N)]^T.$$  (4.1)
where $T$ is the transpose operation. This signal vector $x$ is modeled as a zero mean complex Gaussian process, with a probability density function described by the covariance matrix $C$:

$$p_x(x) = \frac{1}{\pi^{MN}|C|} e^{-x^TC^{-1}x}$$ (4.2)

where $C = E\{xx^T\}$ can be written out as:

$$C = \{c_{ij}\}_{i=1...MN, j=1...MN}$$

$$c_{ij} = E\{x(m(i), n(i))x^*(m(j), n(j))\}$$

$$m(i) = \left\lceil \frac{i}{N} \right\rceil$$

$$n(i) = [(i-1) \text{ mod } N] + 1$$

and $|C|$ indicates the determinant of $C$, $*$ is complex conjugation, $E\{\cdot\}$ is the expected value operator, $\lceil \cdot \rceil$ is the upwards rounding to the nearest integer, and mod is the modulus operator. The covariance matrix will have a block structure, with $M^2$ blocks of square $N$ by $N$ matrices.

To get a simpler expression for the probability density function, only the situation where there is no correlation between the radial samples is considered. This corresponds to the situation where the radial sampling distance is longer than the radial length of the point spread function, which is approximately equal to the pulse length. The vector $x(m) = [x(m, 1), \ldots, x(m, N)]^T$, i.e., the samples from one range gate, can be defined. By assuming that the signal vectors $x(m)$, $m = 1 \ldots M$, are uncorrelated, the probability density function (pdf) for the long vector $x = [x(1), \ldots, x(M)]^T$ can be found as the product of the pdf for each $x(m)$ (given by setting $M = 1$ in (4.2)), and the logarithmic pdf becomes:

$$\ln p_x(x) = -MN \ln \pi - \sum_{m=1}^{M} \ln |C(m)| - \sum_{m=1}^{M} x(m)^*C(m)^{-1}x(m)$$ (4.3)

where $C(m) = E\{x(m)x(m)^T\}$ and $\ln$ is the natural logarithm.

A three component model for the Doppler signal is used here: a tissue signal $x_t(m, n)$ with varying radial velocity $v(m)$, a stationary clutter signal $x_c(m, n)$, and white noise $x_n(m, n)$. This model is similar to the one used in Paper 2, only with different components. The three components are modeled as independent complex Gaussian stationary processes. The covariance matrices from each of the signal components are added to form the total covariance matrix $C(m)$:

$$C(m) = \sigma_t^2 C_t(m) + \sigma_c^2 C_c(m) + \sigma_n^2 I_N$$ (4.4)
where

\[
\mathbf{C}_t = \{\rho_t(j-i)\}_{i,j} = \begin{bmatrix}
1 & \rho_t(1)^* & \cdots & \rho_t(N-1)^*
\\
\rho_t(1) & 1 & \cdots & \\
\vdots & \vdots & \ddots & \\
\rho_t(N-1) & \cdots & & 1
\end{bmatrix}
\]

\[
\mathbf{C}_c = \{\rho_c(j-i)\}_{i,j}
\]

and the correlation coefficients \(\rho_t(l)\) and \(\rho_c(l)\) are defined as

\[
\rho_t(l) = \frac{E\{x_t(m(i), n(i))x_t^*(m(i-l), n(i-l))\}}{E\{|x_t(m(i), n(i))|^2\}}
\]

and

\[
\rho_c(l) = \frac{E\{x_c(m(i), n(i))x_c^*(m(i-l), n(i-l))\}}{E\{|x_c(m(i), n(i))|^2\}}
\]

The reverberation signal is often a low-pass process, and one can assume that it is temporally constant, resulting in \(\rho_c(l) = 1\) for all \(l\). Reverberations from moving tissue will on the other hand give a reverberation signal with an apparent velocity twice the velocity of the tissue.

4.1.2 Logarithmic likelihood function for \(N = 2\)

In the following, the packet size will be assumed to be \(N = 2\). In this situation it is impossible to reject the reverberation signal, so it will also be assumed that \(\sigma_c = 0\). The expected signal amplitude \(\sigma_t\) is in general a function of \(m\), whereas the white noise amplitude is constant, and is set to 1. The covariance matrix will then take on the form:

\[
\mathbf{C}(m) = \sigma^2(m) \begin{bmatrix}
1 & \rho(m)^* \\
\rho(m) & 1
\end{bmatrix}
\]

where

\[
\sigma^2(m) = \sigma_t^2(m) + 1
\]

and the correlation coefficient is modeled as

\[
\rho(m) = \frac{\sigma_t^2(m) \beta(m)}{\sigma_t^2(m) + 1} e^{j\pi \delta_t v(m)}
\]

The real and positive factor \(\beta(m) = |\rho_t(m)|\) accounts for the decorrelation in the tissue signal, which is caused by transit time effect or velocity gradients, and \(v(m)\) is
the radial velocity component in radial position \( m \) along the beam. In the blood cavity, the tissue signal amplitude is zero, and there is only white noise.

The logarithmic pdf for the signal, given the unknown parameters \( \sigma_t(m) \), \( \beta(m) \) and \( v(m) \) has the general form:

\[
\ln p_x([x(1), \ldots, x(M)]|\sigma_t, \beta, v) = -2M \ln \pi - \sum_{m=1}^{M} \ln \left( \sigma_t^4(m) \left( 1 - |\chi(m)|^2 \right) \right) - \sum_{m=1}^{M} \frac{2}{\sigma_t^2(m) (1 - |\chi(m)|^2)} \left( \hat{P}(m) - \Re \left\{ \chi(m)^* \hat{R}(m) \right\} \right) \tag{4.9}
\]

where

\[
\hat{P}(m) = \frac{1}{2} (|x(m, 1)|^2 + |x(m, 2)|^2) \tag{4.10}
\]

and

\[
\hat{R}(m) = x(m, 1)^* x(m, 2) \tag{4.11}
\]

### 4.1.3 Maximum likelihood estimate

If no restrictions are made for the unknown parameters, maximum likelihood (ML) estimates for \( \beta(m) \), \( \sigma_t(m) \), and \( v(m) \) can be found independently for each radial point \( m \), as the maximum point of (4.9). The tissue signal correlation magnitude \( \beta(m) \) may in general depend on the velocity, but this dependence is in most cases slow compared to the phase shift of \( \rho(m) \). Then, as seen by inspecting (4.9), maximum likelihood is attained when \( \angle \rho = \angle \hat{R} \), so the maximum likelihood estimator for the velocity \( v(m) \) can be found independent of the unknown parameters \( \beta(m) \) and \( \sigma_t(m) \) as:

\[
\hat{v}_{ML}(m) = a \angle \hat{R}(m) \tag{4.12}
\]

where

\[
a = \frac{c}{4\pi f_0 T} \tag{4.13}
\]

This estimator is identical to the well known autocorrelation method [82]. Note that this ML estimator also applies in a situation with several ultrasonic beams. If the beams have no overlap, and there is no variation in the signal parameters transversal to the beam direction, the ML estimate of \( v(m) \) will have the same form as (4.12), where the estimate of \( R \) is averaged over the different beams.

When the number of radial points \( M = 2 \), the ML estimate for \( \{v(1), v(2)\} \) will also give a ML velocity gradient estimator

\[
\hat{\varepsilon}_{ML} = \frac{\hat{v}_{ML}(1) - \hat{v}_{ML}(2)}{\Delta r} \tag{4.14}
\]
where $\Delta r$ is the spatial distance between two samples in the radial direction. The velocity is here defined positive towards the transducer, while the index $m$ increases away from the transducer. If $M > 2$, a linear model for the velocity $v(r)$ might be inserted in (4.9) to give a likelihood function for the strain rate. To do this, the tissue signal amplitude, $\sigma_r$ and correlation magnitude $\rho$ are assumed to be constant for all the $M$ radial ranges are considered. The logarithmic pdf can then be written:

$$
\ln p_x(x|v(m), \sigma, |\rho|) = -M \ln \left( \frac{\pi^2 \sigma^2}{2} (1 - |\rho|^2) \right) - \frac{2M}{\sigma^2 (1 - |\rho|^2)} \left( \hat{P} - \text{Re} \left\{ \frac{1}{M} \sum_{m=1}^{M} \rho(m)^* \hat{R}(m) \right\} \right)
$$

(4.15)

where $\hat{R}(m)$ is given in (4.11) and

$$
\hat{P} = \frac{1}{2M} \sum_{m=1}^{M} (|x(m, 1)|^2 + |x(m, 2)|^2)
$$

The linear velocity profile is given by the start velocity $v_1$, and the strain rate $\dot{\varepsilon}$, as

$$
v(m) = v_1 - (m - 1)\dot{\varepsilon} r_s, \quad m = 1, \ldots, M, \quad (4.16)
$$

where $r_s$ is the radial sampling distance. When (4.15) is combined with (4.16) and (4.7), the likelihood function for $\{v_1, \dot{\varepsilon}\}$ takes on the simple form:

$$
\ln p_x(x|v_1, \dot{\varepsilon}) = -M \ln \left( \frac{\pi^2 \sigma^2}{2b} \right) - \frac{2M}{b} \hat{P} + \frac{2}{b} |\rho| \text{Re} \left\{ e^{-i\frac{\pi}{4} \hat{G}_R(-\frac{r_s}{a} \dot{\varepsilon})} \right\}
$$

(4.17)

where $a$ is given in (4.13) and

$$
b = \sigma^2 (1 - |\rho|^2)
$$

$$
\hat{G}_R(\omega) = \sum_{m=1}^{M} \hat{R}(m) e^{-i(m-1)\omega}
$$

Maximum of (4.17) occurs when the real value function in the last term is maximized. If $\dot{\varepsilon}$ is chosen to maximize the magnitude of the Fourier transform $G_R(\omega)$, the start velocity $v_1$ can be chosen so the phase angle of the product in the real value function becomes zero. The ML estimate of $\{v_1, \dot{\varepsilon}\}$ is thus:

$$
\hat{v}_{1ML} = a \hat{G}_R(\omega_{\text{max}}) \quad (4.18)
$$

$$
\hat{\dot{\varepsilon}}_{ML} = -\frac{a}{r_s} \omega_{\text{max}} \quad (4.19)
$$

where $a$ is given in (4.13) and

$$
\omega_{\text{max}} = \arg\max_{\omega} |\hat{G}_R(\omega)|
$$

(4.20)
4.1.4 Cramér-Rao bound

The Cramér-Rao lower variance bounds for the velocity and the strain rate when \( N = 2 \) are now found by inverting the Fisher information matrix \[86, \text{p.79}\] as shown in Appendix B:

\[
\var(\hat{v}_1) \geq \frac{a^2(1 - |\rho|^2)}{|\rho|^2} \frac{2M - 1}{M(M + 1)} \tag{4.21}
\]

and

\[
\var(\hat{\varepsilon}) \geq \frac{a^2}{(r_s)^2} \frac{(1 - |\rho|^2)}{|\rho|^2} \frac{6}{M(M^2 - 1)} \tag{4.22}
\]

In the following, the radial distance between the sampling points \( r_s \) is chosen to be equal to the pulse length \( \Delta \), the smallest value for which there is no correlation between adjacent signals. From (4.8) one can see that the correlation magnitude is given by the signal amplitude and the decorrelation factor \( \beta \). In 1994, Torp \[82\] presented a parametric model for the decorrelation factor that was given by the signal to noise ratio, the pulse length \( \Delta \), and the beam opening angle \( \Theta \):

\[
\beta = e^{-\frac{3}{2}(\frac{v_r}{v_t})^2 - \frac{3}{2}(\frac{v_t}{v_t})^2} \tag{4.23}
\]

where \( v_r \) was the radial velocity component, and \( v_t \) was the transversal component, which for simplicity will be chosen equal to zero for the rest of this chapter. As seen from (4.8), the correlation magnitude can be written

\[
|\rho| = \frac{1}{1 + \sigma_t^2} \beta. \tag{4.24}
\]

The Cramér-Rao bound in (4.22) can be rewritten

\[
\var(\hat{\varepsilon}) \geq \left( \frac{\frac{1}{2\pi N_b T}}{2\pi N_b T} \right)^2 \frac{(1 - |\rho|^2)}{|\rho|^2} \frac{6}{M(M^2 - 1)} \tag{4.25}
\]

where

\[
N_b = \frac{2f_0\Delta}{c} \tag{4.26}
\]

is the number of half periods used in the ultrasound pulse. Figure 4.1 shows a plot of the Cramér-Rao bound as a function of PRF found using (4.23), (4.24), and (4.25). The transversal velocity component was set to zero and the radial velocity component was chosen to 6 cm/s in this example. Since the noise power was set to 1, the signal to noise ratio is \( SNR = \sigma_t^2 \).

For high SNR (and \( PRF \gg v_r/\Delta \)) the Cramér-Rao bound approximates to

\[
\var(\hat{\varepsilon}) \geq \left( \frac{\sqrt{3}v_r}{\pi N_b^2} \right)^2 \frac{6}{M(M^2 - 1)} \approx \frac{9\lambda}{4\pi^2 N_b L^3 v_r^2} \tag{4.27}
\]
4.1 Optimal strain rate estimator

Figure 4.1: Lower Cramér-Rao bound on the strain rate standard deviation (SD) as a function of the pulse repetition frequency (PRF). The following values were used in this example: \(c = 1540 \text{ m/s}, \ f_0 = 4 \text{ MHz}, \ N_b = 3, v_r = 6 \text{ cm/s}, v_t = 0 \text{ cm/s}, \ M \Delta = 10 \text{ mm}\). Curves for SNR = 5, 10, 15, 20, 25, and 30 dB are shown.
where the last approximation applies when \( M^2 \gg 1 \). The constant \( L \) is the spatial size of the sample vector:

\[
L = \frac{MN_b\lambda}{2}
\]  
(4.28)

From (4.27) one can see that for high signal to noise ratios the Cramér-Rao bound is independent of the PRF (assuming \( PRF \gg \frac{v_r}{\Delta} \)) and inversely proportional to the center frequency \( f_0 \) and the pulse length \( \Delta \), as long as the radial resolution (given by \( N_b \)) is kept constant. The variance decreases with the third power of the total radial sample volume length \( L \).

### 4.1.5 Comparing to previous work

In Section 3.4.3 the Cramér-Rao lower bound for estimating the small strain \( \varepsilon \) using the elastography technique was presented. To compare this with the Cramér-Rao bound for strain rate presented above, a relation between the small strain and the strain rate must be defined. Since only two pulses were used in the elastography method, the relation is given as

\[
\dot{\varepsilon} = \frac{\varepsilon}{T},
\]  
(4.29)

where \( T \) is the time between the two pulses. The variance of the strain rate estimator can then be related to the variance of the strain estimator as

\[
\text{var}(\dot{\varepsilon}) \approx \frac{1}{T^2} \text{var}(\varepsilon).
\]  
(4.30)

The Cramér-Rao bounds presented for the strain estimates in Section 3.4 can then be compared to the Cramér-Rao bound for the strain rate estimator. Setting the number of radial samples to \( M = 2 \) (4.22) is rewritten:

\[
\text{var}(\dot{\varepsilon}) \geq \frac{\varepsilon^2}{16\pi^2 f_0^2 T^2 r_s^2} (|\rho|^{-2} - 1).
\]  
(4.31)

Combining with (4.24) and (4.30) and writing \( \sigma_t^{-2} = \sigma_n^2 / \sigma_i^2 = 1 / SNR \) the following strain variance is found:

\[
\text{var}(\varepsilon) \approx \frac{\varepsilon^2}{16\pi^2 f_0^2 r_s^2} \left( \frac{1}{\beta^2} \left( 1 + \frac{1}{SNR} \right)^2 - 1 \right).
\]  
(4.32)

Comparing this with the strain Cramér-Rao bound in (3.36) one can see that they are equal if \( r_s > \frac{\beta}{2\sqrt{12}} \), i.e., the samples are separated by at least one pulse length, if \( T_w = 1 / B \) and if \( B^2 < 12 f_0^2 \), i.e., the pulse is longer than \( 1 / \sqrt{12} \approx 0.3 \) periods. Notice that the correlation coefficient magnitude \( \beta \) is written \( \rho \) in (3.36). When the samples are closer than one pulse length, as they can be in the elastography technique, the Cramér-Rao bound in (3.36) becomes smaller than the one in (4.32).
### 4.1 Optimal strain rate estimator

#### 4.1.6 Comparing to linear regression

The maximum likelihood (ML) strain rate estimator can be compared to the one obtained by linear regression applied to the ML velocity estimates from individual ranges \{\hat{v}_{ML}(m), m = 1, \ldots, M\}. The ML estimate of \(v(m)\) is given by the phase angle of \(\hat{R}(m)\) as shown in (4.12) in the previous section. This means the autocorrelation estimate can be written

\[
\hat{R}(m) = |\hat{R}(m)| e^{i \hat{\theta}_{ML}}.
\]  

(4.33)

Using the model in (4.16) for the velocity, the phase angle error of the autocorrelation estimate is

\[
\Delta \theta = \frac{\hat{v}_{ML}(m) - v_1 + (m - 1) \hat{\varepsilon}_r s}{a}.
\]  

(4.34)

Assuming that the ML estimates of \(v(m)\) are close to the linear model, \(i.e.,\) small errors \(|\Delta \theta| \ll 1\), the exponential function of the phase angle error can be approximated to the second order Taylor expansion:

\[
\text{Re} \left\{ e^{-i \Delta \theta} \right\} \approx 1 - \frac{1}{2} (\Delta \theta)^2.
\]  

(4.35)

By inserting this in (4.17) one gets the following approximate form of the logarithmic likelihood function

\[
\ln p(x | v_1, \hat{\varepsilon}) = c_1 + \frac{2}{b} |\rho| \text{Re} \left\{ \sum_{m=1}^{M} |\hat{R}(m)| e^{-i \hat{\theta}} \right\}
\]

\[
\approx c_1 + \frac{2}{b} |\rho| \sum_{m=1}^{M} |\hat{R}(m)| \left(1 - \frac{1}{2} (\Delta \theta)^2\right)
\]

\[
= c_2 + \frac{|\rho|}{a b} \sum_{m=1}^{M} |\hat{R}(m)| (\hat{v}_{ML}(m) - v_1 + (m - 1) \hat{\varepsilon}_r s)^2
\]  

(4.36)

where \(c_1\) and \(c_2\) are constants. The linear mean square error (MSE) functional for \(\hat{v}_{ML}\) has the form

\[
MSE = \sum_{m=1}^{M} (\hat{v}_{ML}(m) - v_1 + (m - 1) \hat{\varepsilon}_r s)^2.
\]  

(4.37)

By comparing (4.36) and (4.37) one can recognize that the ML estimate of \(\{v_1, \hat{\varepsilon}\}\) is a linear *weighted* mean square fit to the model, where the weights are the magnitude of the corresponding correlation estimates. By inspecting the joint probability of the phase and magnitude of the autocorrelation estimator (see Figure 4.2), one can observe that the phase angle has decreasing variance for increasing magnitude of \(R\). This means that the likelihood function in (4.36) gives increased weight to the velocity estimates.
which have lowest variance. In contrast, the linear regression method in (4.37) gives uniform weight to all the velocity estimates.

Figure 4.2 was generated by simulating the complex data vector in (4.1) for $M = 1$ and $N = 2$ and calculating the autocorrelation as in (4.11). This was repeated 1000 times to generate the scatter plot.

The two estimation methods have been compared by computer simulations. Signals including noise were generated, with a velocity gradient of 1.0 m/s/m. The velocity in each depth range was estimated, and the regression line was found by the two methods. A typical outcome is shown in Figure 4.3. Note that the two outlayer points give a large error in the linear regression line, while the effect on the weighted regression line is much less since the weights associated with these points are lower.

In Figure 4.4, strain rates estimated by the two methods are compared for 50 independent simulations, showing less variance for the ML method.
Figure 4.3: Linear regression fit (dashed line) and weighted linear regression fit (solid line) to simulated velocity estimates (circles). The following values were used in this simulation: $c = 1540\,\text{m/s}$, $f_0 = 4\,\text{MHz}$, $N_0 = 3$, $SNR = 20\,\text{dB}$, $PRF = 300\,\text{Hz}$, $v_1 = 1.0\,\text{cm/s}$, $\dot{\mathbf{v}} = 1.0\,\text{s}^{-1}$.
Figure 4.4: Strain rates found by linear regression (stars) and weighted linear regression (circles) in 50 independent simulations. The following values were used in the simulations: $c = 1540\, \text{m/s}$, $f_0 = 4\, \text{MHz}$, $N_b = 3$, $SNR = 20\, \text{dB}$, $PRF = 300\, \text{Hz}$, $v_1 = 1.0\, \text{cm/s}$, $\dot{e} = 1.0\, \text{s}^{-1}$
4.1.7 A closed form approximation

In Section 4.1.3 it was shown that the maximum likelihood (ML) estimate of the strain rate was found by maximizing the magnitude of the Fourier transform of the autocorrelation estimate. An alternative form of the likelihood function will now be developed from the magnitude square of the Fourier transform:

\[
\left| \hat{G}_R(\omega) \right|^2 = M \hat{S}(0) + 2M \text{Re} \left\{ \sum_{m=1}^{M-1} (1 - \frac{m}{M}) \hat{S}(m)e^{-im\omega} \right\} \tag{4.38}
\]

where

\[
\hat{S}(m) = \frac{1}{M - m} \sum_{k=1}^{M-m} \hat{R}(k)^* \hat{R}(k + m) \tag{4.39}
\]

By doing this, the number of statistics is reduced by one, since \( \hat{S}(0) \) is independent of the unknown strain rate. Note that the expected values of the strain correlation estimates \( \hat{S}(m), m = 1, \ldots, M - 1 \) have the following properties:

\[
E \left\{ \hat{S}(m) \right\} = \frac{1}{M - m} \sum_{k=1}^{M-m} E \left\{ \hat{R}(k)^* \hat{R}(k + m) \right\}
\]

\[
= \frac{1}{M - m} \sum_{k=1}^{M-m} E \left\{ \hat{R}(k)^* \right\} E \left\{ \hat{R}(k + m) \right\}
\]

\[
= |R|^2 e^{im\omega_s} \tag{4.40}
\]

where

\[
\omega_s \equiv -\frac{4\pi f_0 T_r}{c}. \tag{4.41}
\]

The strain correlation estimates can also be written:

\[
\hat{S}(m) = |\hat{S}(m)| e^{im\hat{\omega}_s(m)} \tag{4.42}
\]

where

\[
\hat{\omega}_s(m) \equiv \frac{1}{m} \angle \hat{S}(m). \tag{4.43}
\]

As explained in section 4.1.3, the maximum likelihood estimate for the strain rate is found from the frequency that maximizes the magnitude of \( \hat{G}_R(\omega) \). To find the maximum, (4.38) is differentiated. By combining with (4.42) this can be written:

\[
\frac{\partial}{\partial \omega} \left| \hat{G}_R(\omega) \right|^2 = -2M \sum_{m=1}^{M-1} m(1 - \frac{m}{M})|\hat{S}(m)| \sin(m(\hat{\omega}_s(m) - \omega))
\]

\[
\approx -2M \sum_{m=1}^{M-1} m^2 (1 - \frac{m}{M})|\hat{S}(m)| (\hat{\omega}_s(m) - \omega) \tag{4.44}
\]
where the last approximation is valid when the estimation error for all the phase angle estimates $\hat{\omega}_s(m)$ are small. By setting (4.44) equal to zero and combining with (4.19) one gets the following explicit form of the maximum likelihood estimator for strain rate:

$$
\hat{\varepsilon}_{ML} = -\frac{c}{4\pi f_0 T_s} \frac{\sum_{m=1}^{M-1} a_m |\hat{S}(m)| \hat{\omega}_s(m)}{\sum_{m=1}^{M-1} a_m |\hat{S}(m)|}
$$

(4.45)

where

$$
a_m \equiv m^2 \left(1 - \frac{m}{M}\right).
$$

(4.46)

Note that the ML estimator in this form is a weighted average of the strain correlation angle estimates $\hat{\omega}_s(m)$ with radial lags $m = 1, \ldots, M-1$. The weights are the products of the correlation magnitudes and lag-dependent constants $a_m$. As seen in (4.40), the strain correlation magnitudes all have the same expected value, and since they all are calculated by sums of products from the set $\{R(1), \ldots, R(m)\}$, they will probably not differ much in magnitude. The weighting function $a_m$ is plotted in Figure 4.5, and show a peak at $m/M = 2/3$, which means that this lag has the highest weight in the likelihood function. In order to save computations in a real-time implementation, it will probably be a good idea to simplify the ML estimator by just calculating $\hat{S}(m)$ for one, or maybe a few $m$-values close to the peak of $a_m$.

### 4.1.8 Conclusions

Under certain assumptions, the maximum likelihood estimate for strain rate can be found as the peak of the Fourier transform of a vector of complex valued temporal correlation estimates. An analytical expression for the Cramér-Rao bound was found. Simulation results indicate that the ML estimator is unbiased, but the criterion for estimator efficiency has not been demonstrated, so the Cramér-Rao bound is not necessarily attained by the ML estimator. Comparison with linear regression methods showed that the ML estimator gave higher weights to the velocity estimates with lowest variance, which explained the significant improvement compared to simple linear regression.

The closed form approximation to the ML estimator developed in the last section showed a close relationship to a simpler algorithm which is suitable for real-time implementation. The algorithm extracts the phase shift of the autocorrelation estimates in the radial direction by a radial correlation operation. The closed form ML estimator expression indicates an optimum value for the radial lag to be used in the simplified estimator, which should equal $2/3$ of the total radial sampling volume.

### 4.2 Real-time strain rate estimator

The principles of a real-time implementation of the strain rate estimation is described in this section. This imaging technique is for simplicity termed Strain Rate Imaging (SRI).
Figure 4.5: The weight function used in the maximum likelihood estimator for strain rate. $M = 30$ in this example.
Table 4.1: Color map used for strain rate imaging. The interpretations when the ultrasound beam is along the muscle, as in the apical views, and perpendicular to the muscle, as in the parasternal long axis view (PLAX), are described. In the parasternal short axis view (SAX) the angle between the beam and the muscle varies, and thus also the interpretation.

<table>
<thead>
<tr>
<th>Color</th>
<th>Strain rate</th>
<th>Apical views</th>
<th>PLAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark blue</td>
<td>Large positive</td>
<td>Rapid lengthening</td>
<td>Rapid thickening</td>
</tr>
<tr>
<td>Cyan</td>
<td>Medium positive</td>
<td>Slow lengthening</td>
<td>Slow thickening</td>
</tr>
<tr>
<td>Green</td>
<td>Near zero</td>
<td>No length change</td>
<td>No thickness change</td>
</tr>
<tr>
<td>Yellow</td>
<td>Medium negative</td>
<td>Slow shortening</td>
<td>Slow thinning</td>
</tr>
<tr>
<td>Red</td>
<td>Large negative</td>
<td>Rapid shortening</td>
<td>Rapid thinning</td>
</tr>
</tbody>
</table>

4.2.1 Basic implementation

A simplified implementation of the strain rate estimation in (4.45) involves calculating $S(m)$ only for the $m$-value that maximizes $a(m)$ in (4.46), $m' = 2M/3$. The simple estimator then becomes:

\[
\hat{\varepsilon}_{\text{SRI}} = -\frac{c}{4\pi f_0 T r_s} \frac{a_{m'}|\hat{S}(m')|}{a_{m'}|\hat{S}(m')|} = -\frac{c}{4\pi f_0 T (m'r_s) \frac{M - m' M}{M}} \left( \sum_{k=1}^{M-m'} \hat{R}(k)^* \hat{R}(k + m') \right)
\]

A constant offset of $2M/3$ samples (equivalent to a spatial distance of $\Delta r = 2M r_s/3$) is used in the multiplication of the correlation functions. The result is averaged over the remaining $M/3$ samples.

The visualization can be performed in the same fashion as in tissue Doppler, by coloring the gray scale image according to the estimated strain rate. In the strain rate images presented in this thesis, the color map described in Table 4.1 has been used. A difference from tissue Doppler is the smooth transition at strain rates near zero as opposed to the sharp transition from negative to positive velocities in tissue Doppler. The reason for this smooth transition is to suppress the apparent noise caused by the estimator variance.

4.2.2 High frame rate

To achieve high frame rate in color Doppler applications, two techniques are commonly used: multi line acquisition (MLA) and interleaving. These two techniques make it possible to acquire more data than in the basic mode. The time to acquire one frame
of Doppler data is in the basic mode

\[ t_{D0} = N_b NT, \]  

(4.48)

where \( N_b \) is the number of beams in the image, \( N \) is the number of pulses in each direction and \( T \) is the pulse repetition time. The relatively small extra delay related to the change in setup of the transmitter and beamformer between pulses is ignored here.

In the MLA method, a broad beam is transmitted. When receiving the echo, the signals from all the transducer elements are processed in parallel in two or more beamformers. Each beamformer time delays the element signals differently to generate different receive beams. This way, two or more beams can be acquired during the time for one pulse-echo cycle, and the frame rate can be increased correspondingly. Using MLA, the time to acquire a frame of Doppler data is

\[ t_{DMLA} = \frac{N_b}{N_{MLA}} NT, \]  

(4.49)

where \( N_{MLA} \) is the number of beams that are processed in parallel.

In the interleaving technique, the waiting time \( T \) from one pulse to the next in the same direction is utilized to send pulses in other directions, as illustrated in Figure 4.6. There is however a minimum waiting time \( T_0 \) where no other pulses can be fired in any direction. This is given by the time for the pulse to travel to the maximum depth and back: \( T_0 > 2d/c \). The number of directions that pulses are fired during the time \( T \) is called the interleave group size, \( N_{int} \). This obviously has to be an integer number, and \( T = N_{int} T_0 \). Using interleaving, the time to acquire a frame of Doppler data becomes

\[ t_{Dint} = \frac{N_b}{N_{int} N_{MLA}} NT. \]  

(4.50)

A typical scanning procedure for a tissue Doppler application is illustrated in Figure 4.7. A tissue frame is first captured, using high beam density. The PRF used for tissue Doppler is usually so low that only one interleave group is necessary. So \( N \) Doppler
One-dimensional strain rate estimation

Figure 4.7: Illustration of the scanning procedure for a tissue Doppler application. The packet size $N = 3$ and the interleave group size $N_{int} = N_b$ in this example. $T$ is the pulse repetition time, $T_T$ and $T_D$ are the times needed to acquire a tissue frame and a Doppler frame respectively, and $T_F$ is the total acquisition time for one tissue Doppler frame.

Figure 4.8: Illustration of the scanning procedure for a high frame rate SRI application. The packet size $N = 3$ and the interleave group size $N_{int} = N_b$ in this example. $T$ is the pulse repetition time, $t_T$ and $t_D$ are the times needed to acquire a tissue frame and a Doppler frame respectively, and $t_F$ is the total acquisition time for one SRI frame.

Subframes are captured separately, usually using fewer beams than in the tissue frame. The velocity is calculated from the $N$ subframes, is color coded and mapped onto the tissue frame. The time to acquire a tissue Doppler frame then becomes

$$t_F = t_T + \frac{N_b}{N_{MLA}} NT,$$

where $t_T$ is the time required to acquire the tissue frame.

The same scanning procedure can be used for strain rate imaging, but since even lower PRF is optimal for SRI, as illustrated by Figure 4.1 earlier in this Chapter, a different procedure can be used. Instead of collecting a tissue frame, the number of beams in the Doppler subframes can be increased to allow tissue visualization based on only these frames. As illustrated in Figure 4.8, the Doppler frame is still generated from $N$ subframes, but a sliding window technique can be used, so the time for one frame will be only

$$t_{FSRI} = t_T,$$
assuming that the time to acquire one Doppler subframe is equal to the time to acquire one tissue frame. Comparing (4.51) and (4.52) one can see that the time for one frame is greatly reduced and thus allowing a high frame rate.

If the same method were to be tried in color flow imaging or tissue Doppler imaging, the low PRF would lead to a lot of aliasing and make clutter filtering impossible, thus making the interpretation of the measured velocities very difficult.

4.2.3 Second harmonic imaging

Second harmonic imaging has recently been shown by many authors to produce much better image quality in gray scale images [11, 64, 75]. The technique involves using a band-pass filter for the second harmonic component of the received signal before further processing of the data.

This technique can also be used in strain rate imaging. First of all the background gray scale image can be generated using second harmonic imaging, but also the strain rate can be estimated using the second harmonic part of the signal. When using second harmonic data for Doppler applications the center frequency parameter $f_0$ in the estimators for velocity or strain rate must be replaced by $2f_0$. Except from this the estimators are as before.

The benefit by doing this is a strain rate estimate with less bias and smaller variance, since there are less reverberations in the second harmonic signal. The $2f_0$ factor will also double the phase shift of each of the correlation function estimates in 4.47, and thus also the phase shift of the product. Since stationary reverberations have a phase shift of zero, using second harmonic causes the tissue signal to be separated more from the stationary clutter.

A drawback is that the Nyquist limit for strain rate

$$\dot{\varepsilon}_{Nyq} = \frac{c}{4f_0 T \Delta f}$$

will be halved when $2f_0$ is used rather than $f_0$. However, when using second harmonic imaging, $f_0$ is usually reduced. So in effect, the Nyquist strain rate might not be affected very much.

4.3 Estimating strain from strain rate

As explained in Section 3.3, the estimated strain rate is in fact a velocity gradient. The strain rate is equal to the temporal derivative of the strain only for infinitesimal strains. It will be shown that the calculation of a possible large accumulated strain after a certain time from the strain rate data must take this into account.

The relation between the finite strain and the strain rate can be developed by way of an example. Consider an infinitesimal one-dimensional object of length $L(t)$ that experiences a strain rate $\dot{\varepsilon}(t)$. 
Figure 4.9: Example of an object that changes length $L(t)$ as a function of time.
The change in length over a small time step $\Delta t$ can then be estimated as

$$L(t + \Delta t) - L(t) \approx \Delta t \dot{\varepsilon}(t)L(t). \quad (4.54)$$

Letting $\Delta t \to 0$ one gets the temporal derivative of the length:

$$\ddot{L}(t) = \lim_{\Delta t \to 0} \frac{L(t + \Delta t) - L(t)}{\Delta t} = \dot{\varepsilon}(t)L(t). \quad (4.55)$$

The solution to this differential equation is

$$L(t) = L_0 \exp \left( \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau \right) \quad (4.56)$$

where $L_0 = L(t_0)$. The accumulated finite strain is finally found as

$$\epsilon(t) = \frac{L(t) - L_0}{L_0} = \exp \left( \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau \right) - 1. \quad (4.57)$$

Just integrating the strain rate values would in comparison give a strain

$$\ddot{\epsilon}(t) = \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau. \quad (4.58)$$

This is in fact the first order Taylor expansion of the expression in (4.57):

$$\exp \left( \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau \right) - 1 = \sum_{n=0}^{\infty} \frac{\left( \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau \right)^n}{n!} - 1 \approx \sum_{n=0}^{1} \frac{\left( \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau \right)^n}{n!} - 1 = \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau. \quad (4.59)$$

This approximation is only good when $\left| \int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau \right| \ll 1$, which might not always be the case. Figure 4.10 shows a comparison of the two methods to calculate the strain. As seen, just integrating the strain rates overestimates the strain. The effect is clearly visible at strains in the range found in the cardiac muscle.
Figure 4.10: The estimated strain of the object in Figure 4.9. The start time was chosen to $t_0 = 0$. The solid line shows the strain estimated using (4.57) while the dashed line shows the approximated strain estimated using (4.58).
Chapter 5

Angle dependence of strain rate

The concepts of strain and strain rate in principle relate to deformation of three-dimensional objects. Appendix A gives an introduction to the strain and strain rate tensors suitable for describing such deformations. We will in this chapter not go further into the tensor description, but instead describe the angle dependence of the one-dimensional strain rate and strain estimates and how to calculate the strain rate in directions other than along the ultrasound beam.

5.1 Angle dependence of the strain rate and strain estimates

As all other Doppler based imaging methods, strain rate imaging as described in the previous chapter is also angle dependent. The method measures the strain rate as the gradient of the velocity component along the ultrasound beam. If the desired strain rate is in another direction, the measured strain rate, and the calculated strain, will depend on the angle between the beam and the direction of the desired strain.

In this section we give a theoretical description of the angle dependence of systolic strain measurements. We base this on a simplified model of how the muscle deforms.

5.1.1 Coordinate definitions

Locally for each muscle segment, we define the coordinates:

- \( r \) - along the ultrasound beam, positive away from the transducer
- \( u \) - circumferential, clockwise seen from the apex
- \( v \) - meridional (longitudinal), from apex to base
- \( w \) - transmural, from endocardium to epicardium
where $u$, $v$ and $w$ will be approximately perpendicular, as shown in Figure 5.1. The origin $(u,v,w) = (0,0,0)$ does not need to be defined in relation to the macroscopic ventricle geometry, and can be chosen anywhere in the imaged muscle segment.

Furthermore we define $\alpha$ as the angle between the $v$-axis and the $r$-axis, so that zero degrees corresponds to measuring along the muscle in the meridional direction. We assume that the angle is in the $v$-$w$-plane (long axis or apical views), so the problem becomes two-dimensional. Notice that the angle is negative in Figure 5.1.

### 5.1.2 Assumed relation between strain and strain rate

As shown in section 4.3, the strain $\varepsilon$ after a time $t$ can be estimated from the measured strain rate as

$$\varepsilon(t_0,t) = \exp\left(\int_{t_0}^{t} \dot{\varepsilon}(\tau)d\tau\right) - 1. \quad (5.1)$$

The starting time $t_0$ is here specified separately. The inverse relation becomes

$$\dot{\varepsilon}(t) = \frac{d\ln(\varepsilon(t_0,t) + 1)}{dt}. \quad (5.2)$$
For small strains \(|\epsilon(t_0, t)| \ll 1\) one can use the approximate formulas:

\[
\epsilon(t_0, t) = \int_{t_0}^{t} \dot{\epsilon}(\tau) d\tau
\]

(5.3)

and

\[
\dot{\epsilon}(t) = \frac{d\epsilon(t_0, t)}{dt} \approx \frac{\epsilon(t_0, t + \Delta t) - \epsilon(t_0, t)}{\Delta t} = \frac{\epsilon(t, \Delta t)}{\Delta t}
\]

(5.4)

where the approximation is valid for \(\Delta t \ll 1\).

### 5.1.3 Strain rate angle dependence

Without losing generality, we can assume that the point \((v, w) = (0, 0)\) is not moving. If the strain rate is spatially homogeneous in the muscle segment, the muscle point \((v, w)\) will then move with the velocity components:

\[
v_v = v \dot{v}_v
\]

(5.5)

and

\[
v_w = w \dot{w}_w
\]

(5.6)

These velocity components are shown in Figure 5.2.

We want to find the strain rate along the ultrasound beam

\[
\dot{\epsilon}_r = \frac{dv_r}{dr}
\]

(5.7)

Notice that, for simplicity, the velocity \(v_r\) is defined as being positive away from the transducer, i.e., in positive \(r\)-direction. This is opposite of the usual definition for the velocity sign in Doppler imaging. Since the center of the muscle is not moving, the velocity derivative can be simplified to

\[
\dot{\epsilon}_r = \frac{v_r}{\Delta r}
\]

(5.8)

where \(\Delta r\) is the distance over which the strain rate is measured. Since the beam has the angle \(\alpha\) to the \(v\)-axis, the velocity along the ultrasound beam in position \((v, w)\) becomes

\[
v_r = v \dot{v}_v \cos \alpha + w \dot{w}_w \sin \alpha
\]

(5.9)
The coordinates can also be written

\[ v = \Delta r \cos \alpha \] (5.10)

and

\[ w = \Delta r \sin \alpha \] (5.11)

so the measured strain rate becomes:

\[ \dot{\varepsilon}_r = \dot{\varepsilon}_v \cos^2 \alpha + \dot{\varepsilon}_w \sin^2 \alpha \] (5.12)

Notice that when imaging from the apex, the angle \( \alpha \) will be close to zero for most of the ventricle.

The same formulas will apply if one is imaging in the u-w-plane (short axis view) by interchanging u and v, and redefining \( \alpha \) as the angle between the u-axis and the r-axis. In that case \( \alpha \) will have values from \(-\pi\) to \(\pi\).

### 5.1.4 Assuming incompressible material

Since the cardiac muscle tissue can be considered incompressible, the following relation holds if \( u, v \) and \( w \) are the principal strain direction (see Appendix A):

\[ (\varepsilon_u + 1)(\varepsilon_v + 1)(\varepsilon_w + 1) = 1 \] (5.13)
### 5.1 Angle dependence of the strain rate and strain estimates

<table>
<thead>
<tr>
<th>Method</th>
<th>Value derived from</th>
<th>Reference</th>
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<td>MR tagging</td>
<td>Local Lagrangian strains</td>
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<td>Long axis FS</td>
<td>[16]</td>
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<table>
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<td>Wall thickening</td>
<td>[69]</td>
</tr>
</tbody>
</table>

Table 5.1: Normal values for systolic strain in the human myocardium. SD: Standard deviation. FS: Fractional shortening.

By using 5.4 we can derive the corresponding relation for strain rate:

\[ \dot{\varepsilon}_u + \dot{\varepsilon}_v + \dot{\varepsilon}_w = 0. \]  \hspace{1cm} (5.14)

This relation is also given in the literature in [57, p. 337] and [22, p. 232]. There are unlimited solutions that satisfy these equations, but each parameter has only a small range that is clinically relevant.

Normal systolic strain values can be found in the literature. \( \varepsilon_u \) has been measured directly using MR tagging, but since the circumference of the ventricle has an approximately linear relationship to the radius, the systolic midwall fractional shortening of the minor axis in the left ventricle can also be used. \( \varepsilon_v \) has also been measured directly using MR tagging, but the fractional shortening of the major axis can also be used as an indication. \( \varepsilon_w \) is systolic wall thickening, and has been measured in numerous studies. The values and references are given in Table 5.1. In some publications, the strain was given as the Greens strain tensor \( E \) (see Appendix A). The strains in Table 5.1 were then converted from the diagonal components of \( E \) using:

\[ \varepsilon_x = \sqrt{2E_{xx} + 1} - 1 \]  \hspace{1cm} (5.15)

Several studies have showed that there is a difference between \( \varepsilon_w \) in the different walls [73, 76], which can explain the large standard deviation of this value in Table 5.1.

These normal values do not exactly satisfy the incompressibility equation, but by introducing a small offset in each value the relation holds. One solution is for example \( \varepsilon_u = -0.19, \varepsilon_v = -0.17, \varepsilon_w = 0.48 \). These are all values at a distance of 0.2 standard deviations from the normal mean value.

Normal values for strain rate have not been found in the literature.

#### 5.1.5 Relative errors caused by angle mismatch

One might propose that there is a linear relationship between \( \dot{\varepsilon}_u \) and \( \dot{\varepsilon}_v \):

\[ \dot{\varepsilon}_u(t) = k_{uv} \dot{\varepsilon}_v(t). \]  \hspace{1cm} (5.16)

Using the incompressibility equation (5.14) we then get the relation

\[ \dot{\varepsilon}_w(t) = -k_{wv} \dot{\varepsilon}_v(t), \]  \hspace{1cm} (5.17)
Figure 5.3: Relative strain rate error caused by the angle $\alpha$. The parameter $k_{wv}$ is the linearity constant in the assumed linear relationship between $\dot{\varepsilon}_w$ and $\dot{\varepsilon}_v$.

where $k_{wv} = 1 + k_{uv}$.

The relation between the measured strain rate $\dot{\varepsilon}_r(t)$ and the desired strain rate $\dot{\varepsilon}_v(t)$ in (5.12) can then be rewritten

$$\dot{\varepsilon}_r(t) = \dot{\varepsilon}_v(t) \left( \cos^2 \alpha - k_{wv} \sin^2 \alpha \right)$$
$$= \dot{\varepsilon}_v(t) \left( 1 + \Delta_\varepsilon(\alpha, k_{wv}) \right),$$

(5.18)

where

$$\Delta_\varepsilon(\alpha, k_{wv}) = \frac{\dot{\varepsilon}_r(t) - \dot{\varepsilon}_v(t)}{\dot{\varepsilon}_v(t)}$$
$$= \cos^2 \alpha - k_{wv} \sin^2 \alpha - 1$$

(5.19)
is the relative strain rate error caused by the angle $\alpha$ when assuming the linearity constant $k_{wv}$. Figure 5.3 shows the relation for $k_{uv} = 0, 1$ and 2, or correspondingly $k_{wv} = 1, 2$ and 3.

A relative error for accumulated strain measurements can also be derived. Inserting (5.18) into (5.1) one gets

$$\varepsilon_\tau(t) = \left( \int_0^t \dot{\varepsilon}_v(\tau) d\tau \right)^{1+\Delta_\varepsilon(\alpha, k_{wv})} - 1$$
$$= (\varepsilon_\tau(t) + 1)^{1+\Delta_\varepsilon(\alpha, k_{wv})} - 1.$$ 

(5.20)
Figure 5.4: Relative accumulated strain error caused by the angle $\alpha$ for different values for the meridional systolic shortening $\varepsilon_v$. The parameter $k_{wv}$ is the linearity constant in the assumed linear relationship between $\dot{\varepsilon}_v$ and $\dot{\varepsilon}_v$.

By rearranging this equation the relative strain error is found as

$$
\Delta \varepsilon(\alpha, k_{wv}) = \frac{\varepsilon_v(t) - \varepsilon_v(t)}{\varepsilon_v(t)} = \frac{(\varepsilon_v(t) + 1)^{1+\Delta \varepsilon(\alpha, k_{wv})} - 1}{\varepsilon_v(t)} - 1.
$$

Figure 5.4 shows this relationship for different values of $\varepsilon_v$ for $k_{wv} = 1$, 2 and 3. As seen, the shape of $\Delta \varepsilon(\alpha, k_{wv})$ is very similar to $\Delta \varepsilon(\alpha, k_{wv})$, and a first order Taylor expansion of (5.21) assuming small $\varepsilon_v(t)$ can be shown to be equal to $\Delta \varepsilon(\alpha, k_{wv})$.

5.1.6 Discussion and conclusions

Several assumptions have been made in the calculations, and these have to be taken into account when discussing the results: A constant linear relationship between two of the strain rate components has been assumed. Combined with the assumption of incompressibility and no shear strains, a linear relationship will exist between any two of the three strain rate components. To be able to get simple expressions we have also assumed that the strain rate is spatially homogeneous.
The formula for incompressibility assumes that \( u, v \) and \( w \) are the principal strain directions. This is not necessarily true, especially since the ventricle is known to have about 15 degrees rotation from the base to the apex around the major axis during the systole. When we insert values from the literature, we see that the formula is not perfectly fulfilled. Therefore the relations between \( S_w \) and \( S_v \) are probably somewhat different than what we have used, and thus the curves will be different. These uncertainties make it difficult to exactly predict the angle dependence, but still the curves give an impression of the behaviour.

5.2 Estimation of more components of the strain rate tensor

Using velocity-information from more than one beam at the time it is possible to calculate the strain rate in other directions than along the beam. Using the same coordinate definitions as in Section 5.1.1, but also including the lateral direction \( l \) perpendicular to the beams in the image plane. The beams are assumed to be parallel in the region of interest.

The \( vw \)-axis system is then a rotation of the \( lr \)-axis system by an angle of \( (\alpha - \pi/2) \), and one can write

\[
\begin{align*}
  v &= r \cos \alpha + l \sin \alpha \\
  w &= r \sin \alpha - l \cos \alpha.
\end{align*}
\]

Substituting this in (5.9) one gets

\[
\dot{v}_r = \dot{\epsilon}_v (r \cos \alpha + l \sin \alpha) \cos \alpha + \dot{\epsilon}_w (r \sin \alpha - l \cos \alpha) \sin \alpha.
\]

Taking the derivatives in the two directions \( r \) and \( l \), one gets the two equations

\[
\begin{align*}
  \frac{\partial \dot{v}_r}{\partial r} &= \dot{\epsilon}_v \cos^2 \alpha + \dot{\epsilon}_w \sin^2 \alpha \\
  \frac{\partial \dot{v}_r}{\partial l} &= \dot{\epsilon}_v \sin \alpha \cos \alpha - \dot{\epsilon}_w \sin \alpha \cos \alpha.
\end{align*}
\]

Solving for \( \dot{\epsilon}_v \) and \( \dot{\epsilon}_w \) gives

\[
\begin{align*}
  \dot{\epsilon}_v &= \frac{\partial \dot{v}_r}{\partial r} + \frac{\partial \dot{v}_r}{\partial l} \tan \alpha \\
  \dot{\epsilon}_w &= \frac{\partial \dot{v}_r}{\partial r} - \frac{\partial \dot{v}_r}{\partial l} \cot \alpha.
\end{align*}
\]

This means the strain rates in the anatomical directions \( v \) (meridional) and \( w \) (transmural) can be found from the radial and lateral gradients of the measured radial velocity, as long as the angle \( \alpha \) is known. The image plane \( lr \) must coincide with the \( vw \) plane, which is the case for all apical views and the parasternal long axis view (PLAX).
5.3 Discussion of other angle dependencies

The same formulas apply if one substitutes $v$ with $u$, so the strain rate in the $u$-direction (circumferential) can also be found. The image plane $lr$ must then coincide with the $uw$ plane, which is the case for the short axis view (SAX).

There will be some angles where the strain rates are unavailable, though. For the $u$ or the $v$ directions these are the angles where $\tan \alpha$ approaches infinite values. For the $w$-direction these are the angles where $\cot \alpha$ approaches infinite values.

In the SAX view and using a sector scan, an approximation of $\alpha$ can automatically be found if the user defines the centre of the ventricle. By assuming that the SAX cross section of the ventricle is circular, $\alpha$ at a particular location is given as

$$\alpha = \frac{3\pi}{2} - \theta_b + \theta_c$$

(5.29)

where $\theta_b$ is the angle of the ultrasound beam that intersects the point ($\theta_b = 0$ is defined as the center beam), and $\theta_c$ is the angle between the center ultrasound beam and an imaginary beam from the centre of the ventricle through the point.

A preliminary test has been performed using this method. A velocity data set from a healthy volunteer was obtained using tissue Doppler imaging with high beam density. The short axis view was used. Figure 5.5 shows the estimated circumferential and transmural strain rate components in three phases of the cardiac cycle. The myocardium was segmented manually.

As expected, the radial strain rate is equal to the transmural strain rate at twelve and six o’clock in the images, and the circumferential strain rate at two and ten o’clock. Except from where the $\cot \alpha$ or $\tan \alpha$ approach infinity, the apparent noise in the images does not seem to be increased by this procedure.

5.3 Discussion of other angle dependencies

Both skeletal and cardiac muscles are highly anisotropic due to the ordered arrangement of the muscle fibers. An in vitro study on bovine tendon, which also is anisotropic, by Holland et al. [42] has shown that the ultrasonic backscatter intensity is reduced $24.6 \pm 1.1$ dB when imaged parallel to the tendon compared to imaging perpendicular to it.

In the cardiac muscle the fiber orientation angle changes up to 180 degrees from endocardium to epicardium [78], so the angle dependency will be more complex. In vivo short-axis imaging on healthy subjects has been shown by Holland et al. [43] to give differences in integrated backscatter values in different parts of the muscle. Their results showed that the intensity was highest in the anterior septum and was decreased by $15.9 \pm 3.5$ dB in the lateral wall, by $17.7 \pm 3.5$ dB in the inferior septum and by $8.1 \pm 3.8$ dB in the posterior wall.

A reduction in the backscattered intensity will increase the variance in the strain rate estimate, since other signal components, like white noise and reverberation noise, will become more dominant. This must be kept in mind when analyzing the strain rates measured in different parts of the muscle.
Figure 5.5: Color coded images of the radial strain rate $\dot{e}_r$ (top row), the circumferential strain rate $\dot{e}_u$ (mid row) and the transmural strain rate $\dot{e}_w$ (bottom row) from (a) mid systole, (b) early diastolic relaxation and (c) mid diastole. Positive strain rate (thickening/lengthening) is colored blue and negative strain rate (thinning/shortening) red. The noisy areas at twelve and six o’clock in the mid row and at two and ten o’clock in the bottom row are caused by the tan $\alpha$ and the cot $\alpha$ factors respectively.
Chapter 6

In vitro experiments

In this chapter, two strain rate validation experiments are described. The collected IQ-data from one of the experiments was also used to study the effect of stationary reverberations and clutter filtering on the strain rate imaging.

6.1 Validation tests for the strain rate estimator

When a new imaging technique is introduced it is always interesting to know if it really measures the correct value. The real-time strain rate imaging technique has therefore been tested in two experiments. First, the relatively simple test for zero strain rate was performed. This was done in collaboration with A. V. Lund, MS, and was part of her Master’s thesis [55]. The second test was for more clinically relevant strain rates up to -1.5 s\(^{-1}\), and was performed by compressing a gel block. This experiment was performed in collaboration with J. D’Hooge, MS, B. Bijnens, PhD, and G. Sutherland, PhD, at the University Hospital Gasthuisberg in Leuven, Belgium. A similar experiment was later performed by M. Belohlavek, PhD, at the Mayo Clinic in Rochester, Minnesota, USA, and some of his results are included for comparison.

6.1.1 Zero strain rate test

To test what effect a pure motion without deformation of an object would give on the estimated strain rate, the following experiment was performed: A 5×5×5 cm block of floral foam (Smithers-Oasis Company, Cuyahoga Falls, Ohio, USA) was drenched in water and boiled under vacuum to remove all air bubbles. The block was fastened to a movable rod as shown in Figure 6.1 and imaged using a 2.5 MHz phased array probe and a specially programmed System Five digital ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway). Both IQ-data and real-time estimated strain rate data were gathered. The setup parameters used in the experiment are listed in Table 6.1.
In vitro experiments

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<thead>
<tr>
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<th>Value</th>
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<td>Transmit frequency</td>
<td>f₀</td>
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<tr>
<td>Pulse repetition time</td>
<td>T</td>
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<td>N_r</td>
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<tr>
<td>Lateral averaging</td>
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Table 6.1: Parameters used in the experiment.

![Figure 6.1: Illustration of the experiment setup showing how a foam block was moved up and down in a water bath [55].](image)

Three different motion patterns were used: Motion towards the probe, motion laterally in the image and motion perpendicular to the image plane. In one experiment a thin plastic plate was put between the probe and the foam block to create stationary reverberations inside the block. The speed of the block was measured with pulsed Doppler to be 58 mm/s. This is higher than the normal tissue velocities in the heart (22–25 mm/s). Second harmonic strain rate imaging was also performed in some of the experiments.

Figure 6.2 shows SRI images in the fundamental and second harmonic mode, and also shows the effect of stationary reverberations.

The collected strain rate images were processed in Matlab. Here, the mean value and standard deviation of the measured strain rate values within the foam block were calculated. Values were taken at distances larger than the size of the point spread function to get statistically independent measures. Since the expected strain rate was
6.1 Validation tests for the strain rate estimator

Figure 6.2: Strain rate imaging (SRI) of a block that is moving but not deforming [55]. The yellow rectangle indicates the position of the block in the image. (a) Fundamental SRI. (b) Fundamental SRI when reverberations were introduced. (c) Second harmonic SRI with no reverberations. (d) Color map used for the strain rate values. A low Nyquist strain rate has been used to better visualize the variance.
Table 6.2: Mean bias and standard deviation of the measured strain rates within a non-deforming foam block moving at a speed of 58 mm/s. Both fundamental strain rate imaging (SRI) and second harmonic (Octave) SRI was used. $\Delta r$ was 1 cm in all cases.

<table>
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<th>Standard deviation $s^{-1}$</th>
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<td></td>
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<tr>
<td>SRI, no reverberations</td>
<td>$-0.012$</td>
<td>$0.19$</td>
</tr>
<tr>
<td>Octave SRI, no reverberations</td>
<td>$-0.0041$</td>
<td>$0.088$</td>
</tr>
<tr>
<td>SRI, with reverberations</td>
<td>$-0.15$</td>
<td>$0.46$</td>
</tr>
<tr>
<td>Octave SRI, with reverberations</td>
<td>$-0.013$</td>
<td>$0.19$</td>
</tr>
<tr>
<td>Motion perpendicular through image plane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRI</td>
<td>$-0.028$</td>
<td>$0.18$</td>
</tr>
<tr>
<td>Octave SRI</td>
<td>$-0.0090$</td>
<td>$0.14$</td>
</tr>
<tr>
<td>Motion laterally in image</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octave SRI</td>
<td>$-0.0089$</td>
<td>$0.17$</td>
</tr>
</tbody>
</table>

The estimated variances (square of the standard deviations) are not directly comparable with the Cramér-Rao variance lower bound in Section 4.1.4, since the packet size was assumed to be $N = 2$ in the development of the lower bound, while $N = 3$ in the experiment. The Cramér-Rao for $N = 2$ is found by inserting the parameters in Table 6.1 in (4.22). The correlation coefficient magnitude $|\rho|$ for the experiment with motion towards the probe was estimated from the IQ-data using spatial averaging of (3.11) to be 0.994, and the number of estimation samples was set as $M = N_{\Delta r} + N_r$.

$$\sigma^2 \geq \sqrt{\frac{c^2}{16\pi^2 f_0^2 T_s^2 T_r^2} (|\rho|^2 - 1)} \frac{6}{M(M^2 - 1)} = 0.112 \, s^{-1}. \quad (6.1)$$

The bound in (6.1) was further divided by $\sqrt{N_l}$ to account for the lateral averaging, assuming non-overlapping beams. To account for the increase in packet size from $N = 2$ to $N = 3$, the bound was further divided by $\sqrt{2}$, assuming independent signal in the additional echo. These two assumptions are not realistic but give a limit for the lowest possible variance. The standard deviation lower bound was this way calculated to:

$$\sigma^2 \geq \sqrt{\frac{c^2}{32\pi^2 f_0^2 T_s^2 T_r^2 N_l} (|\rho|^2 - 1)} \frac{6}{M(M^2 - 1)} = 0.0459 \, s^{-1}. \quad (6.2)$$

The correct lower bound would be between the values in (6.1) and (6.2).

As seen in Table 6.2, the standard deviation was increased when a stationary reverberation was introduced, but reduced when second harmonic strain rate imaging was used. There seemed to be little dependence on the direction of the motion, and
the bias was always less than 0.03 \( s^{-1} \) in magnitude when there were no reverberations. Both the biases and the standard deviations were small compared to the normal peak magnitude strain rates found in cardiac imaging (up to 10 \( s^{-1} \) in Table 3.2 in Section 3.3.1), so even if the standard deviations were almost twice as large as the Cramér-Rao bound, the effect of reducing the variance would be small.

### 6.1.2 Gel block compression test

To test whether the strain rate imaging technique measured correct strain rates in the range that is found in the cardiac muscle, the following experiment was performed.

A specially programmed System Five digital ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway) was used to collect IQ-data and real-time strain rate data from a dynamic in vitro model of myocardial tissue. The model consisted of a 10\( \times \)10\( \times \)10 cm homogeneous gel block [15], that was exposed to 10 % cyclic compression with a frequency of 5 Hz. This simulated the systolic phase of the cardiac contraction. The model was imaged in the direction of the compression, as shown in Figure 6.3. Both surfaces were oiled with ultrasound gel to avoid shear forces in the gel block. Because of this and the homogeneity of the phantom, a spatially constant strain rate could be assumed throughout the phantom. The scanning parameters that were used are listed in Table 6.3.

Strain rate images from peak compression rate and peak relaxation rate are shown in Figure 6.4.

The distance \( L(t) \) to the back plate was continuously measured by tracking the peak intensity from the compressing plate in a reconstructed M-mode from the middle
In vitro experiments

Figure 6.4: Strain rate images of the gel being released in (a) and being compressed in (b). The compressing plate and its direction of motion is drawn in for clarity. Notice the spatially uniform strain rate along the middle beam in the images.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of sound</td>
<td>$c$</td>
<td>1560 m/s</td>
</tr>
<tr>
<td>Transmit frequency</td>
<td>$f_0$</td>
<td>2.5, 3.3, and 4.0 MHz</td>
</tr>
<tr>
<td>Pulse repetition time</td>
<td>$T$</td>
<td>1/350 s</td>
</tr>
<tr>
<td>Packet size</td>
<td>$N$</td>
<td>3</td>
</tr>
<tr>
<td>Sample distance</td>
<td>$\Delta r$</td>
<td>11 mm</td>
</tr>
<tr>
<td>Sample distance</td>
<td>$N_{\Delta r}$</td>
<td>12 samples</td>
</tr>
<tr>
<td>Radial averaging</td>
<td>$N_{r}$</td>
<td>3 samples</td>
</tr>
<tr>
<td>Lateral averaging</td>
<td>$N_{l}$</td>
<td>3 beams</td>
</tr>
</tbody>
</table>

Table 6.3: Parameters used in the experiment.
beam. Figure 6.5 shows this M-mode.

The instantaneous strain imposed on the gel was then estimated as

\[
\dot{\varepsilon}(t) = \frac{L(t) - L_0}{L_0}
\]

where \(L_0\) was the maximum distance from the probe to the back plate. The assumed strain rate along the middle beam in the gel was then estimated as

\[
\dot{\varepsilon}_a = \frac{d\dot{\varepsilon}(t)}{dt} 
= \frac{\dot{\varepsilon}(t + \Delta t) - \dot{\varepsilon}(t)}{\Delta t}
\]

where \(\Delta t\) here was the time from frame to frame. This strain rate was then compared to the one measured by real time SRI. Figure 6.6 shows a comparison of the assumed strain rate and the mean strain rate found by SRI. A scatter plot of all the values found by SRI is also included to illustrate the variance.

The peak negative assumed strain rate was then compared to the strain rate measured with SRI at the same time in the compression cycle. The peak negative strain
Figure 6.6: Comparison of the assumed strain rate (dashed line) and the mean strain rate measured using real time SRI (solid line). A scatter plot of all the strain rate values along the beam is also included to give an impression of the variance.
rate for this experiment was estimated to \(-1.5 \text{ s}^{-1}\). Table 6.4 shows the bias and standard deviation of the SRI values in percentage of this strain rate value.

As in the previous section, the Cramér-Rao bound for \(N = 2\) was found by inserting the parameters in Table 6.3 in (4.22). The correlation coefficient magnitude \(|\rho|\) for the 4.4 MHz experiment was estimated from the IQ-data using spatial averaging of (3.11). In the area of highest motion, i.e., near the back plate at peak strain rate, \(|\rho|\) was found to be 0.966. The number of estimation samples was again set as \(M = N_{\Delta r} + N_r\).

\[
\sigma_\varepsilon^2 \geq \sqrt{\frac{c^2}{16\pi^2 f_0^2 T^2 r_s^2} (|\rho|^2 - 1) \frac{6}{M(M^2 - 1)}} = 0.0501 \text{ s}^{-1}. \quad (6.5)
\]

The bound in (6.5) was further divided by \(\sqrt{2N_l}\) to account for the lateral averaging and the increase in packet size. The standard deviation lower bound was this way calculated to:

\[
\sigma_\varepsilon \geq \sqrt{\frac{c^2}{32\pi^2 f_0^2 T^2 r_s^2 N_l} (|\rho|^2 - 1) \frac{6}{M(M^2 - 1)}} = 0.0205 \text{ s}^{-1}. \quad (6.6)
\]

The correct lower bound would be between the values in (6.5) and (6.6). The 7.4% relative standard deviation for the 4.4 MHz experiment corresponds to a standard deviation of 0.111 \(\text{ s}^{-1}\) for comparison.

From the results one can conclude that the implemented strain rate imaging technique measured the strain rate in real time with a bias less than 2 percent of the normal peak negative systolic strain rate value. The standard deviation of the strain rate value was 11 percent or less. This is several times higher than the Cramér-Rao bound, indicating that further improvements in the strain estimation are possible.

The same experiment was performed for lower strain rates by Marek Belohlavek at the Mayo Clinic. His results are shown in Figure 6.7 for comparison. Notice that the sign of the strain rate has been reversed in his presentation.

### 6.2 Effects of stationary reverberations and clutter filtering

Stationary reverberations are often present in clinical ultrasound imaging. In Doppler imaging stationary reverberations give a bias towards zero and an increased variance in
Compression Phase

Figure 6.7: Comparison of measured strain rate and assumed (calculated) strain rate. The correlation \( r \), the regression line \( y \) and the t-test p-value are given. This figure was made by Marek Belohovek.
the velocity magnitude estimates. Since SRI is an extension of the tissue Doppler technique [39], it will thereby be affected by the stationary reverberations. The stationary reverberations can be removed using a clutter filter on the Doppler signal. For low blood velocities the filter introduces a bias and an increased variance in the velocity estimate [45, 81]. In this section, the effect of stationary reverberations and polynomial regression type clutter filtering on SRI is studied in an in vitro experiment, to find out whether the clutter filter used in Doppler imaging is useful also in SRI.

6.2.1 Theory

First, $v$ is defined as the velocity component and $r$ as the position along the ultrasound beam axis. Both are in this section defined positive away from the transducer. In the ideal case of a velocity field linearly dependent on spatial position the strain rate $\dot{\epsilon}$ is found from two point velocities $v_1$ and $v_2$ at a radial distance $\Delta r$ from each other as

$$\dot{\epsilon} = \frac{v_1 - v_2}{\Delta r}$$ (6.7)

If there are velocity dependent biases $b_v(v)$ for the velocity estimates

$$\hat{v} = v + b_v(v),$$ (6.8)

the estimated strain rate, $\hat{\epsilon}$, will be

$$\hat{\epsilon} = \frac{v_1 - v_2 + b_v(v_1) - b_v(v_2)}{\Delta r} \approx \dot{\epsilon} \left(1 + \frac{\partial b_v(v_1)}{\partial v}\right)$$ (6.9)

resulting in a strain rate bias

$$b_\epsilon(v) = \dot{\epsilon} \frac{\partial b_v(v)}{\partial v}.$$ (6.10)

If in an experimental setup, the velocity is linearly dependent on the distance from the transducer, $r$, the strain rate will be

$$\dot{\epsilon}(v) = \frac{v}{r}$$ (6.11)

which is a spatially constant value. The strain rate bias is then

$$b_\epsilon(v) = \frac{v}{r} \frac{\partial b_v(v)}{\partial v}.$$ (6.12)

6.2.2 Methods

The same experiment setup of a cyclically compressed gel block as described in Section 6.1 was used, only IQ-data were gathered rather than real time processed strain rate
data. The IQ-data were collected for 1000 ms and transferred to Matlab for post-processing. The way the experiment was set up, the local strain rate and velocity in the gel block were as described in (6.11).

Stationary reverberations were simulated by adding a white Gaussian noise vector to each of the beams in the IQ-data before processing. The signal-to-clutter ratio (SCR), defined as the power of the IQ-data divided by the power of the Gaussian noise, was varied in different simulations. The resulting IQ-data beams were bandpass filtered to a bandwidth of 0.74 MHz to make them more suitable for the autocorrelation method. The velocity in each sample was estimated using the autocorrelation method [48] on data from 3 consecutive pulses. The strain rate was then estimated from the velocity difference over 1 cm along the ultrasound beam. The estimated strain rate data were finally smoothed by averaging over 1 cm along the ultrasound beam. This way \( N_e = 3710 \) strain rate samples with and without added reverberation noise were generated. The samples were collected in vectors called \( e_{\text{rev}} \) and \( e \) respectively. By plotting the elements in these vectors against each other in a scatter plot, one gets an impression of the variance and bias caused by the reverberations. Increased strain rate estimate variance when introducing stationary reverberations could then be indicated by a reduced correlation coefficient (\( \rho_e \)) between \( e_{\text{rev}} \) and \( e \):

\[
\rho_e = \frac{\sum_{n_1=1}^{N_e} e(n_1)e_{\text{rev}}(n_1)}{\sqrt{\sum_{n_2=1}^{N_e} e^2(n_2)\sum_{n_3=1}^{N_e} e_{\text{rev}}^2(n_3)}}.
\]  

(6.13)

The regression curve of \( e_{\text{rev}} \) on \( e \) was found as

\[
e_{\text{rev}} = \alpha e + \beta
\]  

(6.14)

and least squares estimators for the slope \( \alpha \) and the offset \( \beta \) were found as

\[
\hat{\alpha} = \frac{\sum_{n_1=1}^{N_e} (e_{\text{rev}}(n_1) - \bar{e_{\text{rev}}})(e(n_1) - \bar{e})}{\sum_{n_2=1}^{N_e} (e(n_2) - \bar{e})}
\]  

(6.15)

and

\[
\hat{\beta} = \bar{e_{\text{rev}}} - \hat{\alpha}\bar{e}
\]  

(6.16)

where \( \bar{e_{\text{rev}}} \) and \( \bar{e} \) are the mean values of \( e_{\text{rev}} \) and \( e \) respectively. The regression curve could give an impression of the bias in the strain rate estimate caused by the reverberations. If \( \beta \neq 0 \) there was a bias independent of the strain rate value, and if \( \alpha \neq 1 \) there was a fractional bias, i.e., a bias that depends on the strain rate.

Later, the same IQ-data were passed through a zero order polynomial regression clutter filter before the velocity and strain rate were calculated. This filter involved simply to subtract the mean of the complex signal in each sample. The velocities and strain rates found from the clutter filtered data were presented in the same fashion as earlier. Since the clutter filter removes all the stationary clutter, the result is independent of the SCR.
6.2 Effects of stationary reverberations and clutter filtering

<table>
<thead>
<tr>
<th>SCR</th>
<th>( \rho_e )</th>
<th>( \alpha )</th>
<th>( \beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 dB</td>
<td>1.0 ± 0.00019</td>
<td>0.99 ± 0.0045</td>
<td>-0.0021 ± 0.012</td>
</tr>
<tr>
<td>10 dB</td>
<td>0.98 ± 0.0046</td>
<td>0.90 ± 0.041</td>
<td>-0.015 ± 0.030</td>
</tr>
<tr>
<td>0 dB</td>
<td>0.21 ± 0.16</td>
<td>0.13 ± 0.095</td>
<td>0.045 ± 0.036</td>
</tr>
</tbody>
</table>

**Table 6.5:** Correlation coefficient \( \rho_e \), regression line slope \( \alpha \) and offset \( \beta \) (mean value ± standard deviation) for different signal to clutter ratios (SCR) when clutter filtering was not used.

<table>
<thead>
<tr>
<th>SCR</th>
<th>( \rho_e )</th>
<th>( \alpha )</th>
<th>( \beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20 dB</td>
<td>0.30</td>
<td>0.32</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

**Table 6.6:** Correlation coefficient \( \rho_e \), regression line slope \( \alpha \) and offset \( \beta \) (mean value), equal for all signal to clutter ratios (SCR) when clutter filtering was used.

To reduce the variance in the estimates of \( \rho_e \), \( \alpha \) and \( \beta \), the same calculations were performed 10 times with different realizations of the white Gaussian noise each time. The presented values for \( \rho_e \), \( \alpha \) and \( \beta \), are the mean values and standard deviations from these 10 calculations.

### 6.2.3 Results

Figure 6.8 shows the effect of stationary reverberations and a zero order polynomial regression clutter filter on the measured velocity. Notice that the reverberations cause the velocity magnitude to be under-estimated, while the clutter filtering causes overestimation. The theoretical bias according to [81] is included in panel (b) for comparison.

Figure 6.9 shows scatter plots of \( \epsilon_{rev} \) versus \( \epsilon \) for three different SCRs, when no clutter filtering was performed. The correlation coefficient and the mean fractional bias are presented in Table 6.5. Notice that the correlation coefficient is reduced as the SCR is reduced, indicating that the estimate variance is increasing. Also notice that the mean fractional bias is increasing as the SCR is reduced.

Figure 6.10 shows a scatter plot of \( \epsilon_{rev} \) versus \( \epsilon \) when the IQ-data was clutter filtered before further processing. Notice the large estimation error for strain rates near zero. The correlation coefficient and the mean fractional bias are presented in Table 6.6. The results were independent of the SCR and had zero standard deviation.

Notice that for 0 dB SCR, the correlation coefficient is larger with clutter filtering than without. At 10 and 20 dB SCR, though, the correlation coefficient is largest when no clutter filter is used. Similarly, for 0 dB SCR the regression line slope \( \alpha \) is closer to unity with clutter filtering than without, while at 10 and 20 dB the slope is closest to unity when clutter filtering is used. The correlation line offset \( \beta \) was close to zero in all the settings.
Figure 6.8: Scatter plots of the measured velocity after introducing stationary reverberations at SCR = 0 dB in (a) and after clutter filtering in (b) versus the actual velocity. The velocities are measured relative to the Nyquist limit. The solid line is the theoretical response.
Figure 6.9: Scatter plots of $e_{rev}$ (SR$_{rev}$) versus $e$ (SR) for (a) SCR = 20 dB, (b) SCR = 10 dB and (c) SCR = 0 dB when no clutter filtering was performed. The solid line is a linear regression of the data, and the dashed line is a line with unity slope for comparison.
Figure 6.10: Scatter plot of $e_{rev}$ (SR$_{rev}$) versus $e$ (SR) when a zero order chatter filter was used. The solid line is a linear regression of the data, and the dashed line is a line with unity slope for comparison. Notice the vertical axis gaps included to show the large variance around zero strain rate.
6.2 Effects of stationary reverberations and clutter filtering

6.2.4 Discussion and conclusions

Since stationary reverberations introduce an increased variance in the velocity estimates, it seems reasonable that the variance of the velocity gradient, i.e., the strain rate, is also increased. Stationary reverberations also introduce a velocity bias with a negative slope, as seen in Figure 6.8 (a). Equation (6.12) then shows that this results in a bias towards zero in the strain rate estimate as seen in Figure 6.9.

For velocities that differ from zero, clutter filtering reduces the variance of the velocity estimates caused by stationary reverberations, and thereby also improves the strain rate estimate as seen by comparing Figure 6.9 (c) and Figure 6.10. If the actual velocity is zero, the clutter filter removes everything except the white noise. The velocity estimate, and thus also the velocity gradient, will then be randomly distributed. In our experiment zero velocity corresponds to zero strain rate as in (6.11), so this explains the large variance for zero strain rate in Figure 6.10.

In itself, however, clutter filtering gives a velocity bias with a negative slope, especially for low velocity magnitudes, as seen in Figure 6.8 (b). Thus, from (6.12) one can see that clutter filtering results in a bias towards zero in the strain rate estimate, as seen in Figure 6.10.

The sign of the velocity bias slope, and thereby the sign of the strain rate bias, will depend on the type of clutter filter and the number of pulses, N. In this work only the setting with a zero order clutter filter and a signal of N = 3 has been investigated.

In conclusion, when there are high clutter levels and velocities differing from zero, a zero order clutter filter could be used to lower the variance and fractional bias of the strain rate estimate, while at low clutter levels, this type of clutter filtering should not be performed.
In vitro experiments
Chapter 7

In vivo examples of strain rate imaging

In this chapter some preliminary clinical strain rate images are presented. The technique has been tested on healthy and infarcted hearts, and on breast and liver with tumors and cysts. Asbjørn Steylen, M.D., at the University Hospital of Trondheim and Odd Helge Gilja, M.D., Ph.D., at Haukeland University Hospital in Bergen have acquired most of the data presented in this chapter.

7.1 Cardiac muscle function

Strain rate imaging from the apical view gives an estimate of the local meridional (longitudinal) strain rate in the muscle. This is because the beam is parallel or close to parallel to the meridional axis in most of the ventricle. In the apex other angles are present, but the basal parts of the apical segments are usually accessible without too large an angle.

The measured strain rate has been found to be most easy to interpret by using curved M-mode analysis.

7.1.1 Normal findings

Figure 7.1 shows the result of a curved M-mode along a normal interventricular septum for one full heart beat at a relaxed heart rate. The figure also illustrates the normal findings in the left ventricle walls:

1. A shortening (yellow) in the systole that propagates from the base to the apex.
2. A quick lengthening (blue) in the early diastole.
3. When the heart rate is low, a period of no length change (green).
Figure 7.1: (a) Real-time strain rate image from mid systole of a normal left ventricle. (b) Curved M-mode through the septum for one heart cycle. The yellow curve in (a) indicates where the curved M-mode in (b) is taken. The numbers correspond to the normal findings in section 7.1.1. The data was acquired by Asbjörn Støylen.

4. A lengthening (blue) during the atrial contraction.

5. Some recoiling (yellow) after the quick lengthening (blue) occurrences.

The amount of systolic shortening and early diastolic relaxation strain rates in a muscle segment might give information on the viability of the segment. The lengthening during atrial contraction is not expected to give much information on the performance of the left ventricle, since it is only an effect of the atrium pumping blood into the left ventricle cavity.

7.1.2 Infarction examples

In recent myocardial infarctions, parts of the left ventricle do not contract normally. This can show up as reduced or delayed systolic strain rate. Examples from recent apical infarction, recent inferior infarction and recent lateral infarction are shown in Figures 7.2-7.4

7.2 Stomach muscle function

The peristaltic motion of the stomach can be visualized with strain rate imaging. Figure 7.5 shows a 2D view with little information, while Figures 7.6 and 7.7 show the timing and position of the peristaltic motion. Figure 7.6 shows curved anatomical M-modes along the upper and lower walls in Figure 7.5. The curves were adjusted for each time step so they always stayed inside the muscle. Figure 7.7 shows four M-modes perpendicular to both walls. The walls have been manually segmented out.
Figure 7.2: (a) A 4-chamber view 2D frame from mid systole of a patient with apical infarction. Notice only contraction (yellow) in the healthy basal parts of the walls. (b) A curved M-mode through the septal wall with apical infarction. Notice akinesia (green) in the apical part of the wall during systole. The data was acquired by Asbjørn Støylen.

Figure 7.3: (a) A 2-chamber view 2D frame from mid systole of a patient with basal inferior infarction. Notice only contraction (yellow) in the healthy apical part of the wall. (b) A curved M-mode through the inferior wall with basal infarction. Notice akinesia (green) in the basal part of the wall during systole. The data was acquired by Asbjørn Støylen.
Figure 7.4: (a) A 4-chamber view 2D frame from mid systole of a patient with lateral infarction. Notice only contraction (yellow) in the septum and the healthy apical part of the lateral wall. (b) A curved M-mode through a lateral wall with basal infarction. Notice akinesia (green) or hypokinesia (mottled yellow and green) in the basal part of the wall during systole. The data was acquired by Asbjørn Stoylen.

Figure 7.5: Strain rate image of the stomach at the beginning of a peristaltic motion. The walls are manually sketched. The inward peristaltic bulging at position A moves distally down to D in 8 seconds. The lines A, B, C and D indicate where the corresponding anatomical M-Modes in Figure 7.7 are taken. The data was acquired by Odd Helge Gilja.
Figure 7.6: Curved anatomical M-modes along the upper (upper panel) and lower (bottom panel) stomach walls in Figure 7.5. Notice how the contraction (blue) starts at position A and propagates to position D. A wave of relaxation (yellow) follows. The vertical lines are probably caused by the nearby pulsating aorta. The color gain has been increased compared to Figure 7.5.

7.3 Tumors and cysts

Strain rate imaging can perhaps be used in a way similar to elastography, which is described in Section 3.4. The idea is to detect differences in stiffness within the tissue by measuring the strain rate during external compression. This procedure was tested in three preliminary studies, one involving a breast tumor, one involving a liver metastasis and one involving a liver cyst.

7.3.1 Breast tumor

The strain rate imaging technique was tried out on a young healthy volunteer and an old patient that had discovered a lump in the breast. In x-ray mammography, the lump was clearly visible, as seen in Figure 7.8. A biopsy was later performed that showed the lump to be a malignant tumor.

Both persons were imaged using the strain rate imaging technique. The probe was positioned on the skin surface, in the patient directly above the tumor, and pushed inwards to compress the breast. The probe was pushed approximately 5 mm, and then the pressure was released.

Strain rate images from mid-compression, and M-modes during compression and relaxation are shown in Figure 7.9 for the breast with the tumor, and Figure 7.10 for the healthy breast. Notice that the strain rate is spatially homogeneous in the healthy breast, while in the breast with a tumor the strain rate is lower within the tumor than in the surroundings, indicating that it resisted the compression.
In vivo examples of strain rate imaging

**Figure 7.7:** Anatomical M-Modes through the stomach. The walls are manually segmented out. The color gain has been increased compared to Figure 7.5 to see the color in the walls. Notice that the contraction happens later in the more distal M-modes, and that the walls are greenish (not changing) before the contraction, blue (thickening) during the contraction, and yellow (thinning) after the contraction.
7.3 Tumors and cysts

**Figure 7.8:** X-ray mammography of a breast with a tumor.

**Figure 7.9:** Strain rate image during compression (left) and M-mode during compression and relaxation (right) of a breast with a tumor. The M-mode is taken through the center of the tumor. The vertical axes are scaled in cm, and the color map shows strain rate in s$^{-1}$. 
In vivo examples of strain rate imaging

Figure 7.10: Strain rate image during compression (left) and M-mode during compression and relaxation (right) of a normal breast. Vertical axis is scaled in cm, and color map shows strain rate in s\(^{-1}\).

7.3.2 Liver cyst and tumor

Since tumors are usually more stiff than the surrounding tissue while cysts usually are less stiff than the surrounding tissue, their appearances in compression strain rate images will be different. During compression, a stiff object might resist the compression and have lower strain rate than the surroundings. This is to some degree seen in the compression strain rate image of a liver tumor in Figure 7.11.

A soft object might be compressed more than its surroundings during external compression. This can be seen in the compression strain rate image of a liver cyst in Figure 7.12.
Figure 7.11: Tissue (left) and strain rate (right) images during compression of a liver with a tumor. Data was acquired by Odd Helge Gilja.

Figure 7.12: Tissue (left) and strain rate (right) images during compression of a liver with a cyst. Data was acquired by Odd Helge Gilja.
In vivo examples of strain rate imaging
Chapter 8

Conclusions and future directions

8.1 Concluding remarks

The goal of this thesis was to develop and evaluate Doppler based methods to detect and quantify two of the tissue viability properties.

The first property was blood perfusion. The detection of blood using pulsed Doppler and color flow Doppler was investigated in Papers 1 and 2. In Paper 1 it was found that involuntary skeletal muscle vibrations in the hand of the operator or in the patient itself produce low frequency side bands in the Doppler signal and thus limit the possibility of detecting the low velocity blood flow. An in vivo measurement of a normally vibrating muscle was performed, and used to model the Doppler clutter signal. For this measurement and a model for the Doppler signal from blood, it was found that capillary blood flow was not detectable with any Doppler method, regardless of observation time. In Paper 2, the color flow imaging technique with limited observation time was considered. The demodulated Doppler signal used in color flow imaging was modeled as a complex Gaussian signal, and a likelihood test for the presence of blood was developed. An approximation of the likelihood function was shown to describe clutter filtering and blood enhancement. Using an in vivo measured clutter signal, it was illustrated how this model could be used to optimize the detection.

The second viability property was the tissue function. This was limited to the self-induced deformation of muscle tissue and the response in tumors to externally introduced deformation. To measure the deformation, a strain rate imaging technique was developed.

A maximum likelihood estimator for the strain rate was developed for packet size \( N = 2 \), together with an analytical expression for the lower bound variance. The variance was shown to depend on both the velocity and the velocity gradient in the tissue. It was shown that the maximum likelihood estimator gave improved strain rate
estimates as compared to the linear regression method used in the Myocardial Velocity Gradient method, published by other authors. A simplified estimator was implemented for real-time performance in an ultrasound scanner, and was tested in \textit{in vitro} and \textit{in vivo} experiments.

The \textit{in vitro} experiments involved cyclic compression of a gel block, and was performed to validate the method. Strain rates in the range $-1.5 - 0 \text{ s}^{-1}$ were tested. The results showed a bias smaller than $0.03 \text{ s}^{-1}$ in magnitude and a standard deviation less than $0.19 \text{ s}^{-1}$ for all the experiments. This standard deviation was almost twice the Cramér-Rao lower bound for the same settings, but still small compared to the normal peak strain rates found in a normally contracting cardiac muscle, which has been reported as high as $10 \text{ s}^{-1}$ in magnitude, depending on the position and direction.

Paper 3 describes a pilot study, where the strain rate imaging technique was used \textit{in vivo} to image 6 patients with myocardial infarction and 6 normals. All the affected regions in the patients showed up with reduced strain rate, demonstrating the technique to be useful for imaging regional dysfunction.

Other \textit{in vivo} experiments presented in Section 7 showed some of the potentials of the method. In cardiac imaging, regions of myocardial infarction showed up as delayed or reduced systolic strain rate. In imaging of the stomach muscle, the normal peristaltic contraction was measurable. In tumor imaging, the resistance to external pressure, indicated by reduced strain rate compared to the surroundings, was demonstrated for a breast tumor and a liver tumor. A liver cyst showed increased strain rate compared to the surrounding tissue.

Methods to increase the frame rate and to improve the strain rate estimator quality through the use of second harmonic imaging, have been presented. The effect of stationary reverberations and a simple clutter filter have been investigated. It was shown that both the reverberations and the clutter filter introduced a bias in the strain rate estimate, and that a clutter filter therefore only should be used when the reverberation level is high.

It has been shown that, in one dimension, the accumulated strain can be estimated from the instantaneous strain rate, and the two-dimensional angle dependencies of both the strain rate and the strain measurements have been described. Furthermore, a method to estimate the strain rate in directions in the image not necessarily along the ultrasound beam was developed. The method involved the calculation of the velocity gradient both along the ultrasound beam, and from beam to beam laterally in the image. From these gradients, the strain rate in any direction except perpendicular to the beam could be found. A preliminary test in cardiac short axis imaging indicated that the method could measure simultaneously the transmural and the circumferential strain rates in all parts of the ventricle except where these directions were perpendicular to the beam.
8.2 Suggestions for future work

Detecting and quantifying capillary blood perfusion by ultrasound seems to be a difficult task. Still, using ultrasound contrast agents, this might be possible. The echo from the contrast agent in the blood will then be increased, and might be detectable even in the presence of clutter signal from sources like vibrating muscles.

Paper 1 also showed that it was possible to measure the muscle vibration pattern. This opens for the possibility of using adaptive clutter filters that might be more narrow than ordinary clutter filters. Blood of lower velocity might then be detectable.

For the strain rate imaging technique, the real-time estimation can be improved using an estimator closer to the optimal. This might be possible given increased signal processing capabilities and data transfer speeds in the ultrasound scanner. Implementing the high frame rate and second harmonic methods described in Sections 4.2.2 and 4.2.3 will probably also improve the estimator quality and thus the clinical usefulness of this method.

The use of strain rate imaging in the clinical setting needs further studies. Other suggestions for the strain rate imaging technique are to acquire 3D data sets to allow a fast quantification of the strain rate in all parts of the left ventricle. The angle dependency and correction in 3D would then need to be investigated.

A method to detect the third viability property, metabolism, might be to use specially designed contrast agents which can bind to either viable or non-viable tissue.
Appendix A

The strain, strain rate and rate-of-deformation tensors

This appendix contains some basic definitions from continuum mechanics, based on a textbook by L. E. Malvern [57].

A.1 Elementary definitions

If an object of initial length $L_0$ changes length to $L$, the conventional strain can be measured as

$$\epsilon = \frac{L - L_0}{L_0}. \quad (A.1)$$

The change in angle, $\alpha$, between two line segments that originally were perpendicular describes the shear strain. A common measure for the shear strain is

$$\gamma = \frac{1}{2} \tan \alpha. \quad (A.2)$$

Also, the change in volume can be measured by the volume strain

$$\epsilon_V = \frac{V - V_0}{V_0}. \quad (A.3)$$

where $V_0$ is the initial volume and $V$ is the volume after deformation. An incompressible material will thus have a volume strain of zero.

A.2 Strain tensors

The strain definitions in the previous section are impractical for describing deformations in more than one direction. A tensor formalism is commonly used to describe
The strain, strain rate and rate-of-deformation tensors

multi-dimensional deformations. This tensor defines a quadratic form that describes the change in quadratic length of a material segment:

\[ |dx|^2 - |dX|^2 = 2dX \cdot E \cdot dX, \]  

(A.4)

in Lagrangian formulation and

\[ |dx|^2 - |dX|^2 = 2dx \cdot e \cdot dx, \]  

(A.5)

in Eulerian formulation. Here \( dX \) is an initial material vector that is displaced, stretched and rotated to a new position \( dx \), as shown in Figure A.1, and \( E \) and \( e \) are two definitions of the strain tensor. The Green’s strain tensor or Lagrangian strain tensor \( E_{ij} \) can be written

\[ E_{ij} = \frac{1}{2} \left( \frac{\partial u_j}{\partial X_i} + \frac{\partial u_i}{\partial X_j} + \frac{\partial u_k}{\partial X_i} \frac{\partial u_k}{\partial X_j} \right), \]  

(A.6)

while the Almansi’s strain tensor or Eulerian strain tensor \( e_{ij} \) can be written

\[ e_{ij} = \frac{1}{2} \left( \frac{\partial u_j}{\partial x_i} + \frac{\partial u_i}{\partial x_j} + \frac{\partial u_k}{\partial x_i} \frac{\partial u_k}{\partial x_j} \right), \]  

(A.7)

where \( u_k \) is the displacement, \( X_k \) is the original material position, and \( x_k \) is the material position after the deformation, for the spatial directions \( k = 1, 2, 3 \). In these equations and the rest of the section the summation convention which states that in Cartesian coordinates whenever the same letter subscript occurs twice in a term, that subscript is to be given all possible values and the results added together, is adopted.

The two tensors are symmetric, i.e.,

\[ E_{ij} = E_{ji}, \quad e_{ij} = e_{ji}. \]  

(A.8)

Because of this, there always exist three orthogonal principal strain directions where only principal strains and no shear strains are present. This property applies to all the tensors described in this appendix.

In one dimension the two strain tensors reduce to the strains

\[ \varepsilon_X = E_{11} = \frac{\partial u_1}{\partial X_1} + \frac{1}{2} \left( \frac{\partial u_1}{\partial X_1} \right)^2 \]  

(A.9)
and
\[ \varepsilon_x = \varepsilon_{11} = \frac{1}{2} \left( \frac{\partial u_1}{\partial x_1} + \frac{\partial u_1}{\partial x_1} \right)^2. \] (A.10)

For small strains both tensors in (A.6) and (A.7) reduce to the Cauchy’s infinitesimal strain tensor:
\[ \varepsilon_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right). \] (A.11)

This can be written out as
\[ \varepsilon_{xx} = \frac{\partial u_1}{\partial x_1}, \quad \varepsilon_{xy} = \frac{1}{2} \left( \frac{\partial u_1}{\partial y} + \frac{\partial u_2}{\partial x} \right) = \varepsilon_{yx}, \]
\[ \varepsilon_{yy} = \frac{\partial u_1}{\partial y}, \quad \varepsilon_{xz} = \frac{1}{2} \left( \frac{\partial u_1}{\partial z} + \frac{\partial u_3}{\partial x} \right) = \varepsilon_{zx}, \]
\[ \varepsilon_{zz} = \frac{\partial u_1}{\partial z}, \quad \varepsilon_{yz} = \frac{1}{2} \left( \frac{\partial u_1}{\partial y} + \frac{\partial u_3}{\partial y} \right) = \varepsilon_{zy}. \] (A.12)

The expressions in the first column represent strains and the expressions in the last column, if doubled, represent shear strains. In one dimension, the small strain tensor reduces to the small strain:
\[ \varepsilon = \varepsilon_{xx} = \frac{\partial u_x}{\partial x}. \] (A.13)

### A.3 Strain rate and rate-of-deformation tensors

The strain rate tensor is the time derivative of the strain tensor
\[ \dot{\varepsilon} = \frac{d\varepsilon}{dt}, \quad \dot{\varepsilon} = \frac{d\varepsilon}{dt}. \] (A.14)

Notice that the derivative operator is defined as
\[ \frac{d}{dt} = \left( \frac{\partial}{\partial t} + \mathbf{v} \cdot \text{grad} \right), \] (A.15)

where \( \mathbf{v} \) is the velocity field, so both the strain and the strain rate tensors depend on the initial configuration of the object through the displacement \( \mathbf{u} \) in (A.6) and (A.7).

To describe motion in linear viscosity theory [57] the rate-of-deformation tensor is commonly used
\[ D_{ij} = \frac{1}{2} \left( \frac{\partial v_j}{\partial x_i} + \frac{\partial v_i}{\partial x_j} \right) \] (A.16)

where \( v_k \) is the velocity and \( x_k \) is the spatial direction number \( k = 1, 2, 3 \). Note that this tensor is given by the instantaneous velocity field, which can be measured by ultrasound Doppler techniques.
The strain rate tensors can then be written:

\[ \mathbf{E} = \mathbf{F}^T \cdot \mathbf{D} \cdot \mathbf{F}, \]  

(A.17)

and

\[ \dot{\mathbf{e}} = \mathbf{D} - (\mathbf{e} \cdot \mathbf{L} + \mathbf{L}^T \cdot \mathbf{e}), \]  

(A.18)

where \( \mathbf{F} \) is the deformation gradient tensor given by

\[ F_{ij} = \frac{\partial x_i}{\partial X_j}, \]  

(A.19)

and \( \mathbf{L} \) is the spatial velocity gradient tensor given by

\[ L_{ij} = \frac{\partial v_i}{\partial x_j}. \]  

(A.20)

From this one can see that it generally is not possible to derive the strain tensor \( \mathbf{E} \) or \( \mathbf{e} \) from the rate-of-deformation \( \mathbf{D} \) only.

As seen by using (A.11), the strain rate tensor is approximately equal to the rate-of-deformation tensor when the displacements and displacement gradients are small, i.e., for small strains:

\[ \hat{E}_{ij} \approx \dot{e}_{ij} \approx \dot{e}_{ij} \approx \frac{1}{2} \left( \frac{\partial \hat{u}_j}{\partial x_i} + \frac{\partial \hat{u}_i}{\partial x_j} \right) \]

\[ = \frac{1}{2} \left( \frac{\partial v_j}{\partial x_i} + \frac{\partial v_i}{\partial x_j} \right) = D_{ij} \]  

(A.21)

In one dimension the small strain rate or rate-of-deformation becomes the spatial velocity gradient:

\[ \dot{\varepsilon} = \frac{\partial v_x}{\partial x}. \]  

(A.22)

The temporal integral of the small strain rate

\[ \varepsilon = \int_{t_0}^{t} \frac{\partial v_x}{\partial x} \, dt. \]  

(A.23)

only has a physical significance if the strain rate is small, or if a material integration is used, i.e., evaluating the integral by following each point through its motion. The latter case is often a formidable problem, but an approximation can be achieved by assuming spatially constant strain rate. The conventional strain \( \varepsilon \) in (A.1) can be found as [57, p 151]

\[ \varepsilon = e^\varepsilon - 1. \]  

(A.24)
Appendix B

Fisher information matrix and Cramér-Rao bound

The Cramér-Rao bound is found as the diagonal elements of the inverted Fisher matrix $F$ \cite[p. 79]{86}:

$$F = -E \left\{ \begin{array}{c}
\frac{\partial^2}{\partial \theta^2} \ln p_x(x|\theta_1, \theta) \\
\frac{\partial^2}{\partial \theta^2} \ln p_x(x|\theta_1, \theta)
\end{array} \right\}.$$

First the partial derivatives found in $F$ are calculated:

$$\frac{\partial}{\partial \theta_1} \ln p_x(x|\theta_1, \theta) = \frac{2|\rho|}{ab} \text{Im} \left\{ \sum_{m=1}^{M} \hat{R}(m) e^{-i \frac{\theta_1 + (m-1) \Delta \theta}{2}} \right\}$$

$$\frac{\partial}{\partial \theta_2} \ln p_x(x|\theta_1, \theta) = \frac{2|\rho|\Delta r}{ab} \text{Im} \left\{ \sum_{m=1}^{M} (m-1) \hat{R}(m) e^{-i \frac{\theta_1 + (m-1) \Delta \theta}{2}} \right\}$$

$$E \left\{ \frac{\partial^2}{\partial \theta_1^2} \ln p_x(x|\theta_1, \theta) \right\} = -\frac{2|\rho|^2}{a^2(1-|\rho|^2)} \text{Re} \left\{ \sum_{m=1}^{M} \hat{R}(m) e^{-i \frac{\theta_1 + (m-1) \Delta \theta}{2}} \right\}$$

$$= \frac{2|\rho|^2}{a^2(1-|\rho|^2)} M$$

$$E \left\{ \frac{\partial^2}{\partial \theta_1 \partial \theta_2} \ln p_x(x|\theta_1, \theta) \right\} = -\frac{2|\rho|^2(\Delta r)^2}{a^2(1-|\rho|^2)} \sum_{m=1}^{M} (m-1)^2$$

$$= \frac{2|\rho|^2(\Delta r)^2}{a^2(1-|\rho|^2)} \frac{(M-1)M(2M-1)}{6}$$
\[
E \left\{ \frac{\partial^2}{\partial v_1 \partial \xi} \ln p_x(x|v_1, \xi) \right\} = - \frac{2|\rho|^2 \Delta r}{a^2(1-|\rho|^2)} \sum_{m=1}^{M}(m-1) \\
= \frac{2|\rho|^2 \Delta r}{a^2(1-|\rho|^2)} \frac{(M-1)M}{2}
\]  
(B.6)

In these calculations it has been utilized that
\[
E \{ \phi(m) \} = \sigma^2 \rho(m) = \sigma^2 |\rho| e^{\frac{(v_1 + (m-1)\Delta \varphi)}{a}}.
\]  
(B.7)

Thus the Fisher information matrix is
\[
F = \begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix} = \frac{2M|\rho|^2}{a^2(1-|\rho|^2)} \left[ \frac{M-1}{2} \Delta r \frac{(M-1)(2M-1)}{6}(\Delta r)^2 \right].
\]  
(B.8)

The inverse of \( F \) is found as
\[
F^{-1} = \frac{1}{|F|} \begin{bmatrix} F_{22} & -F_{12} \\ -F_{21} & F_{11} \end{bmatrix}
\]  
(B.9)

where the determinant \( |F| \) is
\[
|F| = \left( \frac{2M|\rho|^2}{a^2(1-|\rho|^2)} \right)^2 (\Delta r)^2 \frac{M^2 - 1}{12}.
\]  
(B.10)

The Cramér-Rao bounds are then finally found as
\[
\text{var}(v_1) \geq \frac{F_{22}}{|F|} = \frac{a^2(1-|\rho|^2)}{|\rho|^2} \frac{2M - 1}{M(M+1)}
\]  
(B.11)

and
\[
\text{var}(\xi) \geq \frac{F_{11}}{|F|} = \frac{a^2(1-|\rho|^2)}{(\Delta r)^2|\rho|^2} \frac{6}{M(M^2 - 1)}
\]  
(B.12)
References


Part II

Papers