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BLOOD FLOW ANALYSIS FROM ANGIOGRAM IMAGE SEQUENCE

MASTER’S THESIS

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Chapter 1

Introduction

Today, in hospitals, clinicians in general and radiologists in particular rely heavily on the medical imaging equipment. By observing the images that these products generate they are able to understand and to assess the patient’s problem more easily and more efficiently.

The primary role of medical imaging so far has been diagnostics. Lately it is more and more also used as an interventional and therapeutic tool in order to achieve minimally invasive procedures. Image-guided therapy is thus a new field that has close relations to interventional radiology, minimally invasive surgery, and robot-assisted surgery.

So far imaging equipment showing only the tissue’s structure was dominant. The radiologists were able to observe tissue deformations and produce a diagnose purely on information on morphology. However, morphology is not the only important indicator for pathology assessment. Diseases and malformations often alter the physiology of the affected tissue as well. Also some pathologies are more evident when observing physiologic changes than morphological ones and physiologic changes may even occur sooner. That is why the demand for visualizing functional aspect in addition to the structural one is on the rise in the last decade.

Functional information is also vital for interventional procedures. It could be used before intervention in order to better plan the operation as well as after the intervention in order to evaluate the success of the operation.

More and more different techniques using different imaging technologies are being developed to tackle this problem of functional representation. Functional image is an image where each pixel instead of the original observed intensity presents the quantity of specific functional parameter. Additionally, results from observing functional aspect can be co-registered with the images showing structure so that both the information about the anatomy and the physiology can be observed at the same time.

1.1 Clinical Background

In this thesis we will focus on the pathologies of the brain area since most of the studies that we worked on are obtained from interventional neuroradiological studies. But it should be stressed that the methods presented here are in general applicable to other areas of the body as well. Especially suitable are liver and kidney regions.
CHAPTER 1. INTRODUCTION

In recent years interventional neuroradiology emerged as an important clinical practice. Interventional neuroradiology is a special branch of medicine which is a combination of neurosurgery and radiology. Methods used are less invasive than those in classical surgery since surgeon enters the affected area by navigating the catheter through vessels instead of entering through the skull. Such treatment which is coming from within the vessel is called endovascular treatment.

Minimally invasive surgery is highly desirable these days since the patient can recover from the operation more quickly and remains in the hospital for fewer days. This also lowers the overall costs of medical treatment.

1.1.1 Common Pathologies

We will now discuss some typical pathologies and corresponding functional parameters which are of interest to clinicians in order to treat these pathologies.

Stroke and Tumour

Two pathologies in the brain that alter the functionality of the surrounding tissues are stroke and tumour. A stroke or "brain attack" occurs when a blood vessel or artery is occluded (ischemic stroke), or when a blood vessel ruptures (hemorrhagic stroke), thereby interrupting blood flow to an area of the brain, and/or contaminating the surrounding cerebral space with blood. On the other hand tumoural process initiates hypervascularization in the growing tissue which eats up a lot of blood carrying oxygen and nutrients away from the healthy region. Such changes can be seen better on functional parametric images.

One way to treat the tumour is by endovascular embolization. This means that the vessels which are supplying the tumour are cut off i.e. blocked so the tumour does not receive the same amount of blood as before. The success of this intervention can be evaluated by observing the blood flow in the organ before and after the intervention. If the intervention was successful then the blood flow to the tumour region should be decreased.

In case of stroke, the blood flow image can provide the clinician with the approximate extent of the stroke. After the intervention the blood flow image should become normalized.

Special procedure known as cerebral parenchymography exists which includes comparison of the blood flow images in two brain hemispheres. Observing both hemispheres at the same time makes it easier to detect areas with abnormal blood supply because that should be roughly the same in both.

Stenosis and Aneurysm

The most common vascular diseases that appears in the brain are due to stenosis and aneurysm. They are shown in Figure 1.1. Both can lead to stroke (ischemic or hemorrhagic). Besides geometric measurements of these pathologies their significance can be revealed by observing the functional point of view.
(a) Stenosis in carotid vessel

(b) Large aneurysm

Figure 1.1: Image of a stenosis and an aneurysm.

Stenosis can be caused by calcification from the inside of vessel hence in effect narrowing the vessel’s diameter. It leads to ischemia and can even cause infarct if the blood flow in this area decreases below the ischemic level.

On the other hand aneurysm is a blood-filled dilatation of a blood vessel. Aneurysms are created on the vessel wall and are the point of potential vessel rupturing thus causing hemorrhage.

Both of these pathologies can be treated by stent implants. Stent can be used to widen the stenotic vessel area. If they are placed at the neck of the aneurysm they limit the blood flow to and from the aneurysm thus creating a stable thrombus within the aneurysm which effectively excludes the aneurysm from the rest of the blood circulation [1]. Image of a stent is shown in Figure 1.2.

Figure 1.2: Stent implant.

For better assessment of these two pathologies as well as to see the effect of the inter-
vention both intra and post operatively, blood velocity and flow parameters in the vessel before, in the middle and after the pathology, are of interest.

**Arterio-Venous Malformation (AVM)**

Cerebral Arteriovenous malformations are masses of abnormal blood vessels which grow in the brain. They consist of a blood vessel nest through which arteries connect directly to veins, instead of through the elaborate collection of capillaries. The location of the connection between the artery and the vein is called the shunt. AVM in the brain is shown in Figure 1.3

![Figure 1.3: Arterio-venous malformation in the brain.](image)

An AVM can be thought of as a "Short Circuit" where the blood, instead of going through the tissue, is pumped through the shunt and back to the heart without ever giving nutrients to the tissue. Problem can also appear when the vessels in the malformation rupture, thus leading to a stroke.

One way to treat this pathology is again by endovascular embolization i.e. filling the malformation with agents which help decrease the blood supply to the malformation. By observing the blood flow in malformation, the success of the embolization treatment can be evaluated.

It is very difficult for clinicians to detect which arteries that enter the malformation contribute to this flow the most. By observing the blood velocity of arteries there is a chance that some arteries are detected as *feeding arteries* hence being more dangerous than the others.

### 1.1.2 Important Functional Parameters

As shown in the previous subsection mostly blood flow and blood velocity are of importance in and around affected regions. We will now explain in more detail these parameters
CHAPTER 1. INTRODUCTION

Blood flow is observed differently in capillary region and in large vessels such as arteries and veins. Since capillaries cannot be seen as a separate vessels using any kind of medical equipment we cannot measure blood velocity in them and can only observe blood flow in a region of capillaries. Blood flow in such a region is then called perfusion. On the other hand in large vessels such as arteries and veins, which are visible in images, we can find both the blood flow and the blood velocity.

Perfusion

Perfusion is generally defined as a blood flow at the capillary level. Presents a measure for the region whether the blood supply is working properly. The part of the tissue which is in a low perfused area (hypoperfused) is in danger of dying out.

Since our studies are oriented toward the brain our main parameter of interest, the perfusion, is called Cerebral Blood Flow (CBF). This and other related parameters are defined below.

- **Cerebral Blood Flow (CBF).** Defined as volume of the arterial blood delivered to the tissue per minute per tissue volume [ml/min/100g].
- **Cerebral Blood Volume (CBV).** Defined as a fraction of the total tissue volume within a voxel occupied by blood [ml/100g].
- **Mean Transit Time (MTT).** Defined as average time it takes a contrast molecule to pass through the tissue studied [min].

These three parameters are mutually related by equation which is called the Central Volume Principle [2].

\[
CBF = \frac{CBV}{MTT} 
\]  

(B.1)

Blood Velocity and Flow

If we observe large vessels it is possible to estimate blood velocity \( \vec{v} \) and flow \( \vec{F} \) in them. They are related through vessel cross-section area \( A \).

\[
\vec{F} = \vec{v}A 
\]

(1.2)  

Blood flow is normally measured in [ml/min] and blood velocity in [cm/s]. Usually first the blood velocity and vessel cross section area are found and then the blood flow calculated using Eq. 1.2.
1.1.3 Medical Imaging Modalities

Unfortunately, few imaging modalities are able to measure functional behavior directly. So most of the imaging equipment come with an additional software portfolio containing algorithms that help clinicians extract such information from the originally produced images. So by designing new tools only software upgrade of the existing equipment is necessary. Sometimes special imaging procedures are required, like injecting contrast material because its propagation and distribution is then easily detected.

Now the most common available imaging modalities will be introduced and their applicability for functional imaging will be discussed.

Nuclear Medicine Imaging

This is the only imaging modality which can produce functional images directly. This is due to the fact that the radionuclides (low-level radioactive chemicals used in nuclear medicine studies) are absorbed by or taken up at varying rates by different tissue types. So a diseased or poorly functioning tissue will emit a different signal than healthy tissue [3].

Two different scanners are used. Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT). PET can be more sensitive than SPECT but is more costly. Drawback of these scanners is that the image resolution they provide is very poor. Also they are much more expensive compared to the other modalities.

Magnetic Resonance Imaging (MRI)

MRI has excellent tissue discrimination between blood vessels, nerves and solid organs even without administration of contrast agents. Also it does not produce ionizing radiation that CT and X-ray do. This very popular modality can be used for finding all kind of functional information but usually not directly.

Blood flow velocity can be found using phase-contrast magnetic resonance imaging. MRI can also be used to find tissue perfusion (scanner called pMRI) as well as water diffusion. pMRI can estimate perfusion either by tracking injected contrast medium or by technique called arterial spin-labeling. Diffusion MRI may be used to measure intravascular and extracellular water diffusion in living tissue [4].

MRI is also used for the visualization of functionally active brain areas. This is called functional MRI (fMRI). Can be used for mapping brain function (e.g. locating visual cortex). Brain function can be considered to encompass not only neuronal activity but also several aspects of cerebral hemodynamics. fMRI is usually based on blood oxygenation level dependent (BOLD) effect which is sensitive to alterations in neuronal activity. In particular, cerebral blood flow, volume and oxygenation are physiological parameters of interest when assessing brain function. All the functional results can easily be mapped to anatomical images.

MRI’s image resolution is better than that of the nuclear medicine equipment. The problem can be with studies that require high frame rate (when contrast is injected) since the resolution can deteriorate quickly as the frame rate is increased.
Ultrasound Imaging (US)

The principle on which US is able to create an image is similar to sonar. The transducer produces a stream of inaudible, high frequency sound waves which penetrate into the body and bounce off the organs inside. The transducer detects sound waves as they bounce off or echo back from the internal structures and contours of the organs. Different tissues reflect these sound waves differently, causing a signature which can be measured and transformed into an image [5].

Perfusion can be calculated by using US as “blood detector”. Blood velocity of a vessel can be calculated with Doppler ultrasound scanners which are capable to work in real-time. When the pulse hits the moving blood, it rebounds back to the probe, however, its frequency is changed which is known as the Doppler shift. This shift is dependant on the angle between moving blood and the probe so the results have to be corrected accordingly.

The drawback of this modality is that the high frequency waves cannot propagate through bone or skull. That is why they are difficult to use for brain imaging but are effective for kidney and heart examination.

X-ray Computed Tomography (CT)

CT enables direct imaging and differentiation of soft tissue structures, such as liver, lung tissue, and fat. It is also a gold standard for perfusion measurement [6].

Computed tomography (CT) perfusion imaging is able to provide a quantitative measurement of regional cerebral blood flow. A perfusion CT study involves sequential acquisition of CT sections during intravenous administration of an iodinated contrast agent. Analysis of the results allows the physician to calculate the regional cerebral blood volume, the blood mean transit time through the cerebral capillaries, and the regional cerebral blood flow.

It is used extensively for acute stroke assessment where it is competing with the use of pMRI. Advantages of CT are that it is more widely available and less expensive than MRI but the problem is that it generates ionizing radiation.

X-ray Angiography

X-ray Angiography is the gold standard for the assessment of the vascular diseases. Additionally, most of the interventions which require stent implants are performed under X-ray guidance. Currently no method(s) for functional analysis exist. It would be of great importance if the success of the intervention on the vessel could be evaluated from the functional effect point of view. Thus additional software tool enabling functional imaging would be desirable.

MRI and CT are 3D imaging modalities while X-ray angiography due to its projection principle provides 2D images. Since X-ray angiograms are generated by projecting 3D structure on the imaging plane some information is lost in the process. On the other hand X-ray equipment is readily available in hospitals in developing as well as developed
The resolution of the produced images is by far greater than with any other modality. Also it is possible to have high frame rate imaging without significantly decreasing the image resolution which is important for observing contrast propagation.

X-ray angiography is invasive due to the substantial dose of ionizing radiation that patients receive. But it is still used more than any other angiography method like Magnetic Resonance Angiography (MRA) and CT Angiography (CTA).

1.2 Objective of the Thesis

Although, there are now many less invasive modalities than X-ray angiography, conventional projective X-ray technology still remains important clinical tool. Conventional angiography also has changed dramatically during the last decade. Digital angiography has replaced film/screen angiography in most applications. In addition, the use and capabilities of endovascular interventional techniques have emerged, and digital angiography has expanded significantly in support of these interventional procedures. Since X-ray angiography is still used so intensely and is to remain the gold standard for quite some time for vessel treatment it proved to be a challenge to try to enhance this modality with functional information thus obtaining quantitative functional x-ray angiography.

As we have seen, blood flow and velocity are of primal importance as functional parameters. Due to its good spatio-temporal resolution, X-ray equipment is suitable for estimating these parameters. However the major problem is its projective nature. This can be avoided to some extent if the imaging angle does not include too many overlapping vessels.

X-ray angiography does not provide us with the functional information directly. This has to be estimated from a sequence of X-ray angiograms with the help of x-ray opaque iodine contrast material. Once injected intra-arterially the propagation of this contrast material can be imaged multiple times per second thus producing dynamic digital X-ray images. Since contrast material is easily visible and has the same properties as the blood, it serves for tracking blood thus enabling estimation of the functional characteristics.

This thesis is basically about developing software tools which enables this estimation of functional parameters (namely blood flow and velocity).

We tackle the problem from two sides. The first one deals with searching the blood flow and velocity in large vessels, namely in arteries. On the other side we have small vessels like capillaries which cannot be seen on the x-ray angiograms, and blood velocity and flow can not be calculated in them but the perfusion parameter becomes important. In that effect we are trying to calculate perfusion of certain capillary regions of the tissue.

We will present applications mostly concerning the brain but other regions are generally also of interest. For example in the kidney region, the perfusion of the tissue that comes from the renal artery is important. This is nowadays performed manually using X-ray angiography by a technique called the renal frame count [7].
1.2.1 Software Design and Development

The software developed was first prototyped using MATLAB® from The Mathworks®. Once the algorithms proved to be effective they were coded in C/C++ using Intel® Integrated Performance Primitives library. This library utilizes Multi-Media Extensions (MMX) and Streaming SIMD Extensions (SSE and SSE2) instruction sets of the Intel processors. These instruction sets enable fast performance by applying vector processing (simultaneous operation on multiple numbers) which is very suitable for signal and image processing.

The final product of this thesis is a program library with functionalities that are discussed in this document.

1.3 Thesis overview

Thesis is composed of two major parts. The first one consists of blood flow and velocity estimation in arteries and the second one of perfusion calculation in the capillary region.

The overview of the thesis by chapters is organized as follows. The basics of X-ray angiography including Digital Subtraction Angiography (DSA) as well as 3D Rotational Angiography (3DRA) are explained in chapter 2. Denoising techniques which are crucial for the estimation of all the parameters are presented in chapter 3. Chapter 4 deals with algorithm steps for blood velocity estimation and chapter 5 discusses problems regarding perfusion estimation. Finally chapter 6 concludes the thesis.
Chapter 2

X-ray Angiography

Angiography is a diagnostic and, increasingly, therapeutic modality concerned with diseases of the circulatory system [8]. In this method, the vessel of interest is opacified by injection of a radiopaque contrast agent so that it can be seen on the radiographic images. It is also possible to take serial angiograms of the contrast material flowing through the vessel.

The equipment consists of C-shaped arm having X-ray source on the one side and detector on the other. It is usually possible to position it around patient to whatever position is the most suitable. The equipment is presented in Figure 2.1.

Figure 2.1: C-arm radiographic system

2.1 X-rays

X-rays are electromagnetic waves and electromagnetic radiation consists of photons. X-rays have very small wavelengths hence it is more common to talk in terms of their energy rather than their wavelength. X-rays have photon energies usually between 5-150 keV.

The X-rays are produced in a region that is nearly a point source and then are directed toward the anatomy that is being imaged. For generating medical images it is important how the X-ray beam reacts with the tissue. While traveling through the material X-rays are
getting attenuated. The formula which relates received intensity $I$ and incident intensity $I_0$ is

$$I = I_0 \exp(-\frac{\mu}{\rho} \rho d) = I_0 \exp(-\mu d)$$

(2.1)

where $\mu/\rho$ is mass attenuation coefficient, $\rho$ is mass density, $\mu$ is called linear attenuation coefficient and $d$ material thickness. As each of these three parameters is getting larger so is the attenuation getting stronger [9].

Linear attenuation parameter $\mu$ depends on the density $\rho$ of the material. So to have a measure of attenuation for a material which is independent of the physical and chemical state of the absorber, mass attenuation coefficient is introduced as $\mu/\rho$. Thus, e.g., the mass attenuation coefficient for water is the same whether present in liquid or vapor form. Each material has its own specific mass attenuation coefficient and attenuates the X-rays differently. Obviously bone has larger $\mu/\rho$ and $\rho$ than that of soft tissue, and thus attenuates much more X-rays than soft tissue does for the same thickness.

It is important to note that the linear attenuation parameter ($\mu$) depends on the energy of the X-ray beam as well. The attenuation decreases as the power of the beam increases as it becomes difficult to absorb such high energy photons. That is why care should be taken to find optimal energy of the X-ray source in order to have good image contrast.

Since blood has attenuation very similar to surrounding soft tissue it is necessary to inject contrast material that attenuates the X-ray significantly. Usually iodinated contrast agent is used for vessel enhancement. Iodine can be incorporated into chemicals that are not toxic and has a linear attenuation coefficient that is different from the most materials in the human body.

### 2.2 X-ray Detectors

Most of the today’s imaging equipment is generating digital images. Digital image processing provides the ability to manipulate the contrast and spatial frequency characteristics of the angiographic image, as well as providing immediate access to the image data during the procedure [8]. Thus the received X-rays have to be transformed into digital information. There are two basic technologies which enable this transformation.

#### 2.2.1 Image Intensifiers with Video Camera

The older one is based on Image Intensifier (II) connected to video camera. First the X-rays strike the phosphor layer at the front of II. This layer turns X-rays into light. Next to the phosphor layer is the photoemitter layer which turns received light into low-energy electrons. This electrons are accelerated and then steered toward output. The electrons strike an output phosphor structure that converts their energy to the final output image made of light which is directed to video camera. This is shown in Figure 2.2 [10]. Video camera consists of an array of charge-coupled device (CCD) sensors which turn light into electric current. Recently, high resolution (1024x1024), high frame rate (30 frames/sec) with 10-bit (1024-level) analog-to-digital convertor, CCD video cameras have become available.
CHAPTER 2. X-RAY ANGIOGRAPHY

Instead of CCD sensors it is possible to have vacuum camera tube. Such tube consists of a “target” plate made of light-sensitive photoconductive materials. Hence, the local electric resistances of the target are changed according to received light. When an electron beam scans the target line by line, the electron beam senses the resistance changes and converts them into electric current changes.

All of the images presented in this thesis were obtained using II based systems.

2.2.2 Direct Radiography

The newer technology is based on Flat panel detector (FD) and is expected that it will replace II based systems in the near future. FD has better dynamic range (12-14 bits per pixel) and spatial resolution. It is also called direct radiography since there is no conversion from X-rays to light and vice-versa. FD uses active matrix thin-film-transistor (TFT) technology. An array of small sensors is grown in hydrogenated amorphous silicon. Each sensor (corresponding later to pixel) has an electrode used for storing of electrical charge. On the top of the array, selenium layer is put which turns X-rays into electrical charge which is collected on the electrode [8]. Electrode is coupled with transistor so it can be isolated during acquisition process and can be connected to circuitry during read-out row by row.

2.2.3 Noise

There are generally three independent sources of noise. The first arises from quantum statistics due to discrete photon count. The second is electronic noise which is generated in the detector. The third is quantization error which occurs when analog signal is being digitized. The overall system noise variance is the sum of the particular noise source variances.

The quantum noise is due to the fact that there is an unavoidable random variation in the number of X-rays reaching a point on an image detector. The quantum noise depends on the average number of X-rays striking the image detector and is a fundamental limit to radiographic image quality [8]. Since X-ray detection is actually a photon counting
process it is governed by the properties of the Poisson process. Meaning that the noise amplitude (standard deviation, $\sigma$) is proportional to the square root of the signal amplitude (the mean, $\mu$).

Electronic noise in the detector depends on the dynamic range $D$ of the camera.

$$\sigma_e = \frac{V_{\text{max}}}{D}$$

Typical dynamic range is between 1000 (60dB) and 2000. It is therefore useful to have object imaged with signal values close to maximum so that electronic noise compared to object presents minimal perturbation.

Variance of the quantization noise of analog to digital converter (ADC) device is usually negligibly small (for a typical 10 bit ADC). If $\delta$ represents the quantization step (value belonging to the least significant bit of ADC) and if we assume that all analog values in the interval are equally likely (having uniform distribution) then the noise variance is

$$\sigma_q^2 = E(x^2) = \int_{-\frac{\delta}{2}}^{\frac{\delta}{2}} x^2 p(x)dx = \frac{1}{\delta} \int_{-\frac{\delta}{2}}^{\frac{\delta}{2}} x^2 dx = \frac{\delta^2}{12}$$

For example the 10 bit ADC gives noise variance that is 10 times smaller than noise variance of the electronic noise for system with dynamic range of 60dB, as evident from

$$\sigma_q^2 = \frac{(1/2^{10})^2}{12} = \frac{(1/1024)^2}{12} = \frac{(1/D)^2}{10} = \frac{\sigma_e^2}{10}$$

It is interesting to observe the signal-to-noise ratio (SNR) of a quantum noise limited system (all other noise sources can be neglected). It is shown to be equal to the square root of the signal amplitude.

$$\text{SNR} = \frac{\mu}{\sigma} = \frac{\mu}{\sqrt{\mu}} = \sqrt{\mu}$$

So keeping the dose as low as possible to minimize the health hazard also decreases the signal to noise ratio.

Angiographic systems require a high-power X-ray generation system in order to produce the short, intense X-ray pulses needed to produce clear images of vessels [8]. That is unlike fluoroscopic studies where patient is under constant exposure and the doses are specially low, making signal to noise ratio much worse. Normally, fluoroscopic images are not used for diagnosis but rather as an aid in performing tasks such as placement of catheters in blood vessels during angiography.

### 2.2.4 Image Contrast

Any medical image can be described in terms of three basic concepts: contrast, spatial resolution, and noise [11]. In this subsection we will discuss the importance of image contrast.
Image contrast, conceptually refers to the difference in brightness or darkness in the image between an area of interest and its surrounding background. It is composed of: radiographic contrast, detector contrast and display contrast \[11\].

Radiographic contrast depends on the subject being imaged (photon attenuation of adjacent regions) as well as the energy of the X-ray beam emitted. It is defined to be fractional difference in photon fluence \(\phi = \text{photons/area}\) between two adjacent areas.

\[
C(\phi) = \frac{|\phi_2 - \phi_1|}{\phi_1}
\]  

For an opaque object \(\phi_2 = 0\) hence contrast equals 1. For a uniform area where \(\phi_2 = \phi_1\), contrast equals 0.

Detector contrast refers to the ability of the detector to convert differences in observed photon count into differences in optical signal amplitude. Today’s electronic detectors have a large linear response region which is an important advantage over e.g. film.

Display contrast is important when the actual image appears on the monitor. Translation from stored digital value to brightness on a monitor is via look-up table (LUT). Operator can control the contents of the LUT. For example only some range of digital values can be spanned across the entire brightness range of display (from black to white), additionally, image level can be adjusted etc. In X-ray imaging, it is important to get good tissue contrast while keeping radiation dose as low as achievable.

### 2.3 Digital Subtraction Angiography

The product of the X-ray angiography imaging device is an image showing both the enhanced vessel as well as the surrounding structure such as e.g. the bones. It is difficult to observe the vessels in such an image. Also the intensity value in the vessel is not proportional just to the amount of the contrast agent but also the structures behind the vessel contribute to the resulting intensity value due to X-ray devices’ projective nature.

To enhance the contrast agent visibility it is first necessary to eliminate background information. This is performed using the digital subtraction from the mask image which is taken prior to the contrast injection and which shows only the non-vessel structure. This technique is called digital subtraction angiography (DSA). Digital subtraction should not be performed as linear but rather as logarithmic as is shown in the next paragraph.

If X-ray beam has intensity \(I_0\) then the intensity that will reach the detector is

\[
I_{\text{mask}} = I_0 e^{-\mu_b x_b}
\]

Where \(x_b\) is the thickness of the body and \(\mu_b\) its attenuation coefficient. When the contrast material with attenuation coefficient \(\mu_c\) is injected into vessel with thickness \(x_c\) (where \(x_c << x_b\)) the observed intensity is

\[
I_{\text{contrast}} = I_0 e^{-(\mu_b x_b + \mu_c x_c)}
\]

Linear subtraction would give

\[
S_{\text{lin}} = I_{\text{mask}} - I_{\text{contrast}} = I_0 e^{-(\mu_b x_b)} - I_0 e^{-(\mu_b x_b + \mu_c x_c)} = I_0 e^{-(\mu_b x_b)} [1 - e^{-(\mu_c x_c)}]
\]
This result is not satisfactory since the thickness of the contrast agent \((x_c)\) is modulated by the patient thickness \(x_b\). But if we perform logarithmic transformation, of the observed intensities, before the subtraction we get

\[
S_{\log} = \ln(I_{mask}) - \ln(I_{contrast}) = (-\mu_b x_b) - (-\mu_b x_b - \mu_c x_c) = \mu_c x_c \tag{2.10}
\]

The thickness of the human body is now eliminated and we have linear dependance on the thickness of the vessel [11]. Logarithmic transformation also serves as a variance stabilizer (variance less dependant on signal’s mean) thus making regions more uniform.

In order to remove the unnecessary anatomy the mask image has to align accurately with the image containing the agent. The alignment can be affected by the motion of the patient, thus motion compensation normally precedes the subtraction. In our test images, motion of the head was negligible so no compensation was performed. Thorough review of motion compensation techniques is presented in [12].

The result of DSA operation on an anteroposterior (AP) head image with injected contrast is shown in Figure 2.3. Subtraction allows approximately a factor of 2 reduction in the amount of injected contrast material compared to standard angiography. As a result, DSA studies can be performed with less contrast load and with smaller catheters.

The effective design and use of DSA systems depend greatly on a variety of factors such as contrast material used, amount or concentration of contrast material, rate of injection of the dye, duration of injection, motion artifacts, exposure times, system noise etc.

### 2.3.1 Noise in DSA

Noise is perhaps the single most important limitation to successful DSA. Also, gross patient motion can severely hinder DSA procedures [11]. While there are several ways to
CHAPTER 2. X-RAY ANGIOGRAPHY

quantify noise, the most simple is to determine the standard deviation of the image values about their mean in a uniform region of an image.

Mask Image Averaging

When acquiring the mask image we can use multiple acquisitions before contrast injection and then average them to reduce the noise in the mask image. The SNR of such averaged image increases with $\sqrt{N}$ where N is the number of images averaged.

$$y = \frac{1}{N} \sum_{i=1}^{N} x_i \quad (2.11)$$

Using the variance of the function of random variable theorem [13]

$$\sigma^2_y \approx \sum_{i=1}^{N} \left( \frac{\partial y}{\partial x_i} \right)^2 \sigma^2_{x_i} \quad (2.12)$$

which in our particular case turns into

$$\sigma^2_y \approx \sum_{i=1}^{N} \left( \frac{1}{N} \right)^2 \sigma^2_x = \frac{1}{N} \sigma^2_x \quad (2.13)$$

The standard deviation of noise of averaged image $\sigma_y$ compared to standard deviation of single image $\sigma_x$ in the series is

$$\sigma_y \approx \frac{1}{\sqrt{N}} \sigma_x \quad (2.14)$$

thus the SNR is increasing by $\sqrt{N}$. In our experiments we averaged three images thus increasing the SNR of the mask image almost 2 times.

Signal to Noise Ratio

Although mask and opacification image are obtained with high SNR most of the signal values are contributed by patient anatomy. After subtraction only about 5% of the maximal signal value is left as the remaining signal is contributed only by the contrast material. Additionally subtraction increases the noise variance. If the noise variance in the mask and opacification images equals $\sigma^2$ then the noise variance in the subtracted image is $2\sigma^2$. Thus $SNR_{dsa}$ compared to unsubtracted $SNR$ is

$$SNR_{dsa} \approx 0.05 \frac{SNR}{\sqrt{2}} \quad (2.15)$$

There is a way how to increase the SNR of DSA. As we have seen the signal is equal to $\mu_c x_c$ so increasing the concentration of the injected contrast (thus increasing its linear attenuation coefficient) makes SNR greater. Unfortunately iodine contrast material also presents hazard to the patient, hence it should be kept as low as possible.
2.4 Dynamic Digital Angiography

In order to estimate functional characteristic of the tissue, one needs to view the propagation of blood through that tissue. Blood can be visualized by using contrast agent and DSA. For the brain region, the contrast agent is normally injected into one of the carotids. Now, by using high frame rate, one can get an image sequence showing propagation of the contrast agent. Example is shown in Figure 2.4 where contrast material is injected in one of the carotids so only one brain hemisphere becomes enhanced. This technique is also called Cineangiography since motion of the contrast agent is being imaged with high frame rate.

As the frame rate increases it is difficult for detector to produce clear images on the same spatial grid since sampling rate per pixel is lowered and fewer photons reach CCD sensor thus producing low SNR. For example to have 30 frames per second (FPS) on a 512x512 image matrix, sampling time for each pixel is \( \frac{1}{30} \times \frac{1}{512} \times \frac{1}{512} \), which is around \( 100 \text{ns} \), meaning that sampling rate of 10MHz is required. For that reason images captured with high FPS tend to have lower spatial resolution.

Contrast is usually injected intra-arterially. So it is easier to enhance only some regions which are of interest and contrast gets less dispersed and dissolved which gives better SNR. Unfortunately intra-arterial injection is more dangerous than intravenous one. In case the catheter ruptures the vessel, the blood pressure is much larger in the artery than it would be in the vein.

Our methods which we propose in the later part of the thesis take as input the dynamic sequence of angiograms following injection of iodine contrast material. Iodinated contrast is used because it has the same kinetics as the blood. Usually 25 frames per second are imaged.

![Figure 2.4: DSA contrast propagation.](image-url)
2.5 3D Rotational Angiography

Three dimensional reconstructions have been available using CT or MRI imaging modalities. It is also possible to get 3D data using X-ray equipment. 3D X-ray rotational angiography (3DRA) enables the construction of 3D volumes which is especially suitable for vessel structure inspection.

Reconstruction of three-dimensional objects from 2D X-ray cone-beam projections using circular source path is possible with the algorithm of Feldkamp et al [14]. This algorithm can be adapted to cone-beam projections which are obtained with a C-arm based system as proposed by Grass et al [15].

Imaging procedure goes as follows. Multiple contrast-enhanced images are acquired by rotational projective angiography over an angle of 180°. After acquisition, the 100 contrast-enhanced images are transferred to the workstation. The result is a volume (such as the one shown in Figure 2.5) with isotropic voxels which is an advantage compared to slice-based modalities where usually intra slice pixels are spatially closer to each other than inter slice ones.

![Figure 2.5: vessels in 3D volume reconstructed with 3DRA.](image)

Unsubtracted angiographic images are used. Although obtaining subtracted ones is also theoretically possible, by doing rotational run before contrast injection, this is not necessary since vessels can be fairly easily segmented from the 3D data due to the contrast’s high absorption coefficients.

This is a diagnostic tool. Since this volume is saved in the memory, it enables clinician to explore it as much as they want, without exposing patients to further radiation exposure or contrast injection. It also later leads to decreased time of the clinical intervention.
Chapter 3

Time-Density signals

As we are interested in functional aspect we are using DSA of an image sequence to extract just the propagation of the contrast agent. From the time course of the contrast agent it is possible to derive some functional parameters as will be shown in the next chapters.

We are interested in the time activity of a region (or a single pixel) of the image throughout the image sequence. Typical ideal (noise free) time activity of a region traversed by a contrast agent before and after digital subtraction is shown in Figure 3.1. Only contrast propagation remains on a subtracted sequence.

![Figure 3.1: Time activity of a region belonging to artery.](image)

We are also interested to which physical value does the pixel intensity of the subtracted signal relates. Signal that DSA image measures is

\[ I_{dsa} = d_c \mu_c \]  \hspace{1cm} (3.1)
Where $d_c$ is a distance that x-ray travels through contrast medium and $\mu_c$ a linear attenuation coefficient of the iodine contrast medium. Region of a DSA image (could be a single pixel) has the intensity which corresponds to the integral of DSA signal in the image area.

\[
I_{\text{region}} = \iint_A I_{\text{dsa}} = \iint_A \left[ \int \mu_c(x) dx \right]
\]

\[
\approx \iiint_V \rho_c = m_c
\] (3.2)

Where $\mu_c$ was substituted by a density of a contrast medium $\rho_c$ (since $\mu$ is proportional to it), and $m_c$ is the observed mass of the contrast medium. Since sub-volume that contributes to the intensity of the region is constant throughout the acquisition process, mass will be directly proportional to the density of the contrast medium in that sub-volume.

That is why the signal corresponding to the time course of a region (as shown in Figure 3.1) is most frequently called the Time-Density (TD) signal. However in Figure 3.1 the signals were noise free. This is not the case in practice. Due to low SNR, noise presents a big difficulty in extracting important information from the TD signals. Some real TD signals are shown in Figure 3.2.

![Figure 3.2: Time density signal in the artery ROI (left) and in the capillary ROI (right).](image)

Additional difficulty presents projective nature of X-ray imaging. It is possible that the observed TD signal is actually formed by multiple TD signals merging into one in case of vessel overlapping. Such “noise” is difficult to model and is not related to the quantum or electronic noise.

### 3.1 Denoising of Time-Density Signals

Before TD signals can be used for further processing denoising has to be performed. Two denoising schemes were tried. One is based on Wiener filter and the other one on wavelet-based denoising. We also experimented with some curve fitting procedure but without much success. Curve fitting can in principle be parametric or non-parametric. Non-parametric is just concerned with drawing a smooth curve through the data points (using e.g. smoothing spline) and presume nothing about the underlying process.
CHAPTER 3. TIME-DENSITY SIGNALS

3.1.1 Parametric curve fitting

Parametric fitting is preferred if you know the model describing your data. If the fit is successful then many characteristics of the curve can be easily calculated from the parameters of the model. We first tried with fitting gamma-variate function.

Gamma-variate function is defined as

\[ f(t) = K(t - t_0)^R \exp\left(-\frac{t - t_0}{B}\right) \]  \hspace{1cm} (3.3)

It is presented in Figure 3.3. Gamma variate function was reported to be successfully used in fitting TD signals in perfusion MRI and perfusion CT studies. However we found it difficult to apply to all variety of signals that we came across in observing DSA TD signals. DSA TD signals greatly vary in their width of enhanced interval (which also was influenced by different FPS used). If the image acquisition method becomes standardized then this kind of parametric fitting could provide more success.

Of other parametric fitting methods, polynomial fitting was tried but it was soon abandoned because it was difficult to guess which degree of the polynomial to use for fitting.

3.1.2 Wiener Filtering

The observed TD signal \( w(t) \) is assumed to be composed of an uncorrupted signal \( x(t) \) and additive noise \( n(t) \). Our goal is to obtain an estimate of \( x(t) \) from the observed degraded signal \( w(t) \). Both signals, \( x(t) \) and \( n(t) \), are modeled as a sample functions (realizations) of corresponding random processes \( X(t) \) and \( N(t) \) (with zero mean).

\[ W(t) = X(t) + N(t) \]  \hspace{1cm} (3.4)

Using the theory of Wiener filtering we want to design a linear-time invariant (LTI) system with impulse response \( h(t) \) and transfer function \( H(\omega) \) such that given the input \( W(t) \) it produces the output \( Y(t) \) which is the best estimate of uncorrupted \( X(t) \) in the least-squares sense.

\[ Y(t) = h(t) * W(t) \]
\[ Y(\omega) = H(\omega)W(\omega) \]  \hspace{1cm} (3.5)
CHAPTER 3. TIME-DENSITY SIGNALS

Estimation error is defined as

\[ e(t) = X(t) - Y(t) \]  

(3.6)

So we are seeking a filter for which the expression \( E[e(t)^2] \) will be minimum.

For the Wiener filtering theory to be applicable we must assume that \( X(t) \) and \( N(t) \) are wide-sense stationary processes. Random process is wide-sense stationary if it satisfies:

\[
E[X(t)] = \text{const} \\
E[X(t)X(t + \tau)] = R_{xx}(\tau)
\]  

(3.7)

where \( R \) is the autocorrelation function.

The formula that describes the Wiener filter is

\[ H_{opt}(\omega) = \frac{P_{WX}(\omega)}{P_{WW}(\omega)} \]  

(3.8)

where \( P \) denotes the signal power spectrum [16].

Additionally if we presume that the processes \( X(t) \) and \( N(t) \) (\( N(t) \) having zero mean, \( E[N(t)] = 0 \)) are independent (uncorrelated) we can use the following equalities:

\[
(a) \quad R_{WX}(\tau) = E[W(t)X(t + \tau)] = E[(X(t) + N(t))X(t + \tau)] = E[X(t)X(t + \tau)] + E[N(t)X(t + \tau)] = E[X(t)X(t + \tau)] + E[N(t)]E[X(t)] = E[X(t)X(t + \tau)] = R_{XX}(\tau) \\
\implies P_{WX}(\omega) = P_{XX}(\omega)
\]

(3.9)

(b) \quad P_{WW}(\omega) = P_{XX}(\omega) + P_{NN}(\omega)

(3.10)

Now the formula for the Wiener filter becomes

\[ H_{opt}(\omega) = \frac{P_{XX}(\omega)}{P_{XX}(\omega) + P_{NN}(\omega)} \]  

(3.11)

The effect of this filter can be interpreted as follows. The frequencies where signal is much stronger than noise \( (P_{XX} \gg P_{NN}) \), the filter will leave unchanged since \( H(\omega) \sim 1 \). The frequencies where noise is dominating \( (P_{NN} \gg P_{XX}) \) the filter will attenuate since \( H(\omega) \sim 0 \).

The obtained filter is non-causal. Since we perform the signal processing in off-line mode the resulting filter does not have to be causal. The power spectra are real and non-negative so is \( H(\omega) \) real and non-negative. This means that the filter is a zero-phase filter so there is no delay of obtained \( Y(t) \) with respect to \( W(t) \).

Although Wiener filter is optimally derived, its success in restoring the original signal depends on accurate estimation of power spectrums of the process \( \hat{X}(t) \) and \( N(t) \). The problem is that all we have is the observed degraded signal and its power spectrum.

We have to presume that our processes are ergodic. Ergodic process satisfies the ergodic theorem meaning that time waveform statistics of one realization of the process are
equal to the statistics of the whole process [16]. Although ergodicity is a very restrictive form of stationarity we are forced to make this assumption since we have only one sample function of each random process and otherwise we could not obtain the statistics of the processes.

An alternative, more suitable, representation of Wiener filter can be used

\[ H_{opt}(\omega) = \frac{P_{WW}(\omega) - P_{NN}(\omega)}{P_{WW}(\omega)} \]  \hspace{1cm} (3.12)

Now it is obvious that if we find a good estimate of noise power spectrum we can estimate uncorrupted signal power spectrum since we know the degraded signal power spectrum.

In order to estimate the noise power spectrum we need several assumptions. They are as follows:

- We model noise as an additive, white noise, uncorrelated with the signal i.e. independent and identically distributed (i.i.d.).
- The random process modeling the signal without noise has low-pass nature due to the fact that TD signals are slowly changing functions.

Power spectrum of white noise is constant (uniform) and corresponds to noise variance \( \sigma^2 \). So by knowing the power of noise on any frequency we know the whole power spectrum. The idea is that the high frequency part of degraded signal’s power spectrum should be dominated by noise since TD signals are of low pass nature. Hence we can estimate noise power from this high frequency part. This is visualized in Figure 3.4.

\[ P_{xx} = P_{xx} - P_{nn} \]  \hspace{1cm} (3.13)

Figure 3.4: Subtraction of power spectrums.

We estimate the noise power from the power spectrum samples of the degraded signal. All the samples after the power drops significantly (below 5% of maximum power) are considered to belong to noise and noise variance was taken to be the mean value of these samples. By subtracting the power of noise from the original power spectrum, what remains is the power spectrum of a cleaned version of our original signal. Results of the Wiener filtering of TD signals in two different regions are shown in Figure 3.5. The resulting denoised TD signals turned out to be satisfying.
CHAPTER 3. TIME-DENSITY SIGNALS

Figure 3.5: Denoising results in Artery (a) and Capillary (b) regions.

Implementation details

The filtering was performed in frequency domain so we have a circular convolution in time domain instead of the desired linear one. To alleviate this effect the input signal had boundaries extended by 10% on both sides by constant extrapolation (repetition of the first value on the left and the last value on the right).

Mean signal value was removed at the very beginning and added back at the end so that the power spectrum estimate is not affected by large DC component.

Power spectrum estimate is obtained as a square of amplitude of Discrete Fourier Transform (DFT) of the N-point signal.

\[ P_{WW} = \frac{1}{N} |DFT w(t)|^2 \]  

(3.13)

3.1.3 Wavelet Denoising

The other denoising scheme that we have tried is wavelet based denoising. Denoising is considered to be one of the most successful application of wavelets. Wavelet denoising attempts to remove the noise present in the signal while preserving the signal characteristics, regardless of its frequency content.

Wavelet Theory

Wavelet transform is a linear transform. Each linear transform presents different signal representation. Representation depends on which basis functions of the vector space are used. We would like to have such basis functions that are the most suitable for representing our signal in a sense that the signal can be approximated by only a few basis functions. In that case the contribution of the other basis functions is so small that they can be neglected. If a suitable transformation is used then the energy of the signal will be compressed into a small number of large coefficients in the transformation domain.

Wavelets have turned out to be suitable basis functions for very large variety of signals that commonly occur in practice. Wavelet transform decomposes a signal by performing
inner products with a collection of analysis functions which are scaled and translated version of the wavelet. The amplitude of the wavelet transform tends to be maximum at those scales and locations where the signal most resembles the analysis template [17].

Couple of examples of most commonly used wavelet families, and the ones that we experimented with, are shown in Figure 3.6. All of them form an orthogonal basis. Their properties are displayed in Table 3.1 [18]. The higher the number of vanishing moments the smoother the functions are. Coiflet wavelet and symlet wavelets are near-symmetric while Daubechies wavelets are far from symmetry.

![Wavelet functions: db2 (a), db4 (b), sym8 (c), and coif2 (d).](image)

<table>
<thead>
<tr>
<th>family</th>
<th>filters length</th>
<th>vanishing moments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daubechies N</td>
<td>2N</td>
<td>N</td>
</tr>
<tr>
<td>Symlet N</td>
<td>2N</td>
<td>N</td>
</tr>
<tr>
<td>Coiflet N</td>
<td>6N</td>
<td>2N</td>
</tr>
</tbody>
</table>

Table 3.1: Wavelet families properties.

Wavelet transform is often compared to Fourier transform (FT) since it is common to see it being used in applications where traditionally FT was used. The main difference is that wavelets are localized in scale and in time whereas the standard Fourier transform is only localized in frequency. To have time localization using FT one must use short-time FT. What distinguishes WT from the short-time FT is the multiresolution nature of
the analysis. Also the complexity of calculating fast wavelet transform is $O(N)$ which is more appealing than fast Fourier transform’s $O(N\log N)$.

Wavelet denoising should not be considered a smoothing method because smoothing always eliminates the high frequency part and keeps the low frequency one. By observing the signal at different scales wavelets are able to remove the noise without destroying all the high frequency information.

**Wavelet Shrinkage**

Denoising via wavelet shrinkage method was first suggested in article [19]. The problem is the same as with Wiener filtering. We would like to find the estimate $\hat{y}$ of uncorrupted signal $x(t)$ from the noisy observation $y(t)$. Noise $n(t)$ is assumed to be additive i.i.d.

$$y(t) = x(t) + n(t) \quad (3.14)$$

We are searching for estimation with small mean square error. The wavelet denoising gives near minimax optimal results [20].

$$MSE(\hat{y}, y) = E[(y - \hat{y})^2]$$

$$\text{Minimax}(\hat{y}, y) = \inf_{\hat{y}} \sup_y MSE(\hat{y}, y) \quad (3.15)$$

Minimax criteria means that the maximum error should be minimal. So if two equal mean square errors exist one with small number of large errors or the other with larger number of smaller errors the later one would be preferred.

The denoising procedure involves three steps: a linear forward wavelet transform, nonlinear shrinkage of the wavelet coefficients in the wavelet domain and a linear inverse wavelet transform.

The shrinkage is performed because of the following. Wavelet transform has a nice property of de-correlating the signal. Meaning that due to its compact base the signal will be presented by only few large coefficients in the wavelet domain. On the other hand noise which is not correlated will be distributed throughout the wavelet domain in every scale and the corresponding wavelet coefficients will be small because orthogonal wavelet transform preserves the energy of the signal. Gaussian white noise in any one orthogonal basis is again a white noise in any other (and with the same amplitude).

The wavelet coefficients of a noisy signal are also noisy and if we could eliminate the noise in the wavelet domain, we would also eliminate it in the time domain. Since wavelet coefficients corresponding to noise are small in value and coefficients corresponding to the signal are large therefore the thresholding has the effect that it kills the noise while not killing the signal [21].

There are a couple of questions one needs to answer before successfully applying wavelet denoising. Which wavelet transform (family) to use? How to find the threshold value? Which thresholding technique to apply?

**Choice of Wavelet Family**

We have experimented with Daubechies, coiflet and symlet wavelet families. Their properties were shown in Table 3.1. All of them are orthogonal. Usually symmetry property
Threshold Value

Threshold value selection is vital to good denoising. If threshold is too small it is likely that the result will still be noisy. A large threshold on the other hand, produces a large number of zero coefficients which corresponds to signal which is smooth. Thus numerous methods for threshold selection are being used and not one is considered to be the best.

We decided to use universal threshold as proposed by Donoho [21]. It is called universal because the threshold is globally applied meaning that the same threshold is used for every decomposition level (subband). They expect the noise to be modeled as Gaussian i.i.d with zero mean and variance $\sigma^2$. The threshold is defined as

$$ t = \sigma \sqrt{2 \log(N)} $$

(3.16)

where $N$ is the signal length. It was proved by Donoho [20] that the probability that the maximum noise value will be smaller than this universal threshold is approaching 1 as the signal length goes to infinity. Thus this thresholding scheme exhibits near optimal minimax error performance.

In our images noise is likely to have a Poisson distributed values. Since for high photon count Poisson distribution can be approximated by Gaussian we consider that the difference should be negligible.

We still have to estimate noise standard deviation $\sigma$. The best place to estimate noise is from the detail coefficients of the first decomposition level ($cD_1$). Since the first level is corresponding to the smallest scale (highest frequency) most of the coefficients there will be due to noise. So the idea that is commonly used is to estimate standard deviation as the median value of these mostly noisy coefficients.

$$ \sigma = \frac{\text{median}(|cD1|)}{0.6745} $$

(3.17)

The median value is additionally divided by the number 0.6745 which is the median value of Gaussian noise with $\mu = 0, \sigma = 1$, so it presents calibration (tuning) step for noise with normal distribution.

Usually universal threshold gives values which are bit too large and the resulting signals are hence too smooth. So other thresholding schemes which are subband adaptive exist. We have also experimented with one such threshold estimator called SURE (Stein’s Unbiased Risk Estimator) but due to relatively small signal sizes, by which this estimator is influenced, the results were not useful.

Thresholding Technique

As stated earlier only the detail coefficients of all performed decomposition levels are being thresholded (shrunked). Approximation coefficients remain unaltered. Two thresholding techniques are being used. The first one is called hard thresholding. The function...
can be defined as
\[ F_{\text{hard}}(x, \text{thr}) = \begin{cases} 0 & \text{if } |x| < \text{thr} \\ x & \text{otherwise} \end{cases} \quad (3.18) \]

The second one is called soft thresholding. Soft thresholding was introduced by Donoho in [22]. It is mathematically defined as
\[ F_{\text{soft}}(x, \text{thr}) = \text{sgn}(x) \max(|x| - \text{thr}, 0) \quad (3.19) \]

Both of these non-linear thresholding techniques are visualized in Figure 3.7. We have experimentally found soft thresholding to be the preferred method. Hard thresholding has discontinuous characteristic which can leave some abrupt artifacts.

**Implementation details**

The implementation was based on standard two channel filter bank for each decomposition and reconstruction step (Figure 3.8). We are aware of existence of lifting technique which performs twice as fast than filter bank implementation. But problem of that technique is that it requires a new implementation if different wavelet transform (different
family) wants to be used. This is not the case with filter bank implementation so we opted for generality over the speed. Additionally since we used optimized library which utilizes SIMD instruction set we doubt that our lifting implementation would be faster than library’s filter bank implementation.

The number of decompositions and the filter size used were based on the length of the input data which was around 150 samples long. So we performed three levels of decomposition and used Daubechies 4 filters (8-tap). Daubechies family is the most popular although other families have a priori better suitability but experimentally all of the families produced similar results.

Since only half of coefficients from one decomposition level are transferred to the next decomposition level, for making implementation easier the length of the signal should be dividable by \(2^{\text{NoDecompLevels}}\). Otherwise we may end up splitting odd number of coefficients. We extended the signal beforehand to meet this criteria by constant extrapolation.

**Boundary conditions.** The wavelet theory assumes that all the signals are infinite in length. But in practice we are dealing with finite length signals. Since implementation is composed of convolution the problem is what to do when sample outside the signal is required. One way to make signals infinite is by defining some boundary conditions.

One approach is to assume zero padding. The problem with this boundary condition is that after convolution we end up with larger sequence than the input’s signal length. So as the number of decompositions rises, the number of coefficients in the wavelet domain is much larger then the length of the input signal. It is not possible to eliminate some of them since all of the coefficients are needed to preserve perfect reconstruction (PR) property \[23\]. This was not desirable for our implementation.

If periodic boundary condition is used then the convolution turns into a circular one and the result of transformation is the same length as the input. Unfortunately the periodization leads to discontinuity at the point of continuation. These singularities then show up in the wavelet analysis as large coefficients \[23\]. We used this boundary condition and the discontinuity effect was alleviated by constant extrapolation of our signal before the start of the decomposition. The result was then truncated to pre-extended signal length thus avoiding the issues at periodic continuation point. Symmetric boundary condition can also be used. But this will only work for symmetric wavelets since convolution of two symmetric functions is also symmetric \[17\].

**Results**

Now the wavelet denoising results will be shown. Unfortunately no ground truth exists for our TD signals so we can only visually assess the quality of the denoised signals. The result of denoising one TD signal is shown in Figure 3.9.

Effect of different thresholding techniques is shown in Figure 3.10. As evident the soft thresholding gives visually more appealing results.

**Shift-Invariant Wavelet Transform**

The property of discrete wavelet transform (DWT) is that it is not shift-invariant. Meaning that DWT of a translated version of a signal X is not, in general, the translated version
of the DWT of $X$. There is no simple connection between coefficients in wavelet domain between two shifted versions of the signal.

This presents the problem as the denoising performance can change depending on the shift of the signal. Sometimes some artifacts appear, sometimes not, depending on the alignment between features of a signal and features of basis functions.

That is why the need for designing shift-invariant discrete wavelet transform (SIDWT) emerged. This transform is also known under the names: stationary, redundant, and non-decimated wavelet transform.

Shift-variance of standard DWT comes from downsampling steps. Thus one way to get shift-invariant transform is by eliminating these steps. Hence the name “non-decimated”. Such transform will be composing the signal to functions of over-complete basis. Meaning that some basis functions are not linearly independent from the others.
Such functions are said to form frame not basis since they form redundant set. That is why it is also called redundant wavelet transform. This redundant wavelet transform lies between standard dyadic wavelet transform and continuous wavelet transform regarding the amount of steps the wavelet functions are being shifted or scaled.

The redundancy can help to reduce the sensitivity to noise and better results are accomplish especially for denoising applications. New methods substitute in denoising algorithm DWT with SIDWT. Such method is also referred to as second generation denoising. SIDWT requires larger storage, and more computation is involved ($O(N \log N)$).

**Implementation of Shift-Invariant DWT.** There are several ways how to achieve shift-invariance. One way would be to try to estimate the denoising results for all the shifts of the input signal and then average these results [24]. It was soon discovered by Beylkin [25] that not all shifts are necessary. The shift by any odd number will give the same coefficients as the shift by one. The similar is true for any even number. So it is enough to use two different shifts per decomposition to obtain all possible wavelet coefficients.

The equivalent view at the same problem is through observing the decimators (downsamplers). They present the problem as they eliminate odd or even indexed samples. Different results would appear if we use odd-indexing decimators or even-indexing ones. So we could save the denoising results for all different combinations of decimator type and then average these results. At each step of the decomposition we can choose odd or even indexed decimators. There are $2^J$ different decompositions with $J$ being the number of decomposition steps. Transform resulting from each such different combination is called $\epsilon$-decimated DWT.

The other way to get rid of decimators is by using the noble identities (Figure 3.11) which define how to perform interchanging of decimation/upsampling and filtering elements. Then we could put all the decimators at the end following by all the upsamplers at the front of the inverse step which cancel each other. The effect of noble identities is that filters need to be upsampled (zeros inserted). The filter at level $J$ needs to be upsampled $J - 1$ times. We used this technique in our studies through MATLAB® swt and iswt functions from the wavelet toolbox [18].

Obviously the number of coefficients in each decomposition level is not $N$ any more. If all the decompositions are performed there are $N \log_2 N$ detail coefficients. Each detail and approximation level now has the same number of coefficients as the input signal. Such non-decimated transform also called stationary wavelet transform within its coefficients.
contains the coefficients of all $\epsilon$-decimated DWTs. So all three implementation techniques discussed are equivalent versions of one another.

Result comparing the use of standard DWT and shift-invariant DWT is shown in Figure 3.12.

![Figure 3.12: Denoising using decimated (a) and non-decimated (b) DWT. Dabuechies 4 filterd, soft thresholding, 3 levels of decomposition.](image)

The result of wavelet shrinkage by subband for the Figure 3.12b is shown in Figure 3.13. Dashed lines present universal threshold. Shift-invariant transform gives a bit smoother results. It is evident that as the decomposition goes deeper there are more large coefficients which are not part of noise.

Since wavelet-based denoising is not a classical smoothing method it can have problems if the signal contains sharp strong features which are actually due to noise but the technique considers them as part of the signal and only gradually attenuates them. This can be seen in the example shown in Figure 3.14. In that example wavelet coefficients which present sharp feature are above the shrinkage threshold.

### 3.1.4 Wiener vs. Wavelet denoising

Wiener filtering is a linear filtering method which relies on the statistical data obtained from the entire signal. So it is optimal but in average error sense. On the other hand Wavelet denoising observes the signal at multiple resolutions and different features can be better seen on different resolutions. It also uses a non-linear shrinkage method which usually gives it an edge over the linear wiener filtering. Wavelet transform is local in nature so changing one coefficient only affects the small area around the signal.

Comparison of the results for wiener and wavelet denoising is shown in Figure 3.15. The result using wavelet denoising gives visually preferred results although wiener denoised results are also satisfying.
Figure 3.13: Wavelet shrinkage by decomposition levels.
Figure 3.14: Problem with wavelet denoising.

Figure 3.15: Wiener denoising (left) compared to the corresponding SIDWT (right) denoising.
Chapter 4

Blood Flow and Velocity in Arteries

The idea how to estimate blood flow and velocity in arteries is to use two sets of data. One is the 3D volume of the arterial tree and other 2D sequence of DSA images showing contrast propagation through these arteries. These two datasets can be co-registered mechanically since the imaging setting is known. So 3D volume can be accurately projected onto the 2D image. The 3D volume will give us the structure and flow should be calculated from DSA images for different vessels. With the help of the 3D volume and by knowing the imaging settings vessel overlap can be detected which is otherwise impossible just by observing 2D images.

The first set is obtained by 3D Rotational Angiography run. The output of this run is a 3D cube of voxels. In this cube the vessel arterial tree is hidden and needs to be segmented (extracted) out first. This should not be a very difficult problem since the voxels corresponding to arteries have high intensity values due to the contrast material which was injected before the rotational run.

The other data set is obtained from a typical DSA run obtained with another contrast injection. On this run contrast propagation should be clearly visible. It is desirable to image with high number of frames per second (at least 25fps) so that the contrast does not move much between consecutive frames. Otherwise flow from the short vessels will be difficult to estimate. Since the contrast flows through the arteries of the brain for about 3-4 seconds imaging with 25 fps acquires around 150-200 images.

The problem of patient motion between 3D-RA run and DSA run is not considered. For brain studies the patient’s head is usually tightly fixed so this should not present a problem for registering these two runs.

If assuming laminar (non-turbulent) blood flow there are two common possibilities of the cross-section velocity profile. If plug flow is in effect then the velocity is the same along the cross-section. If the flow is of Poiseuille type than the velocity profile is parabolic. These two flow types are shown in Figure 4.1. Unfortunately the simpler plug flow is not normally found in human circulation, except in large vessels such as aorta.

In reality due to all sorts of problems the flow calculation is highly complex. List of physical effects that present a particular problem is given below [26].

- Blood is a non-newtonian fluid. The viscosity changes, it drops as the velocity rises.
- Tortuosity (bending) of blood vessels as well as vessel overlap
• Pulsatile blood flow

• The radial velocity profile is not constant during the cardiac cycle and varies between the extremes of plug and laminar flow.

• Usually cross-sectional area of an artery is not constant but is slowly decreasing with distance. Arteries are elastic and undergo cross-sectional area changes due to pulsatile pressure variations within their lumen.

• Contrast medium undergoes diffusion as it propagates along the vessel but fortunately this is minimal for the period of angiographic study.

• Contrast medium does not mix uniformly with blood. It is injected into a small cross-sectional region of the blood due to the fact that the catheter tip is smaller than the blood vessel. It is denser than blood and undergoes a degree of settling [26].

• Short vessel lengths are common in practice and this is a difficulty for all the algorithms.

4.1 Overview of Previous Work

A relatively recent review of blood velocity techniques using X-ray angiography was presented in [27]. All of the techniques first estimate the blood velocity in a vessel and then calculate flow using equation 1.2. Blood flow in a vessel (no bifurcations) is constant (mass conservation law) and velocity changes depending on the vessel cross-section area.

Algorithms that were so far proposed by authors can be divided into the following categories:

• Techniques based on injection of contrast as a sequence of short pulses

• Techniques based on measuring the transit time of contrast medium from one region of the vessel to the other
• Techniques based on measuring the distance contrast medium travels between two frames.

• Techniques based on 2D time-distance-density parametric images

• Optical flow based methods

Numerous simplifying assumptions had to be used by all the authors in order to simplify the problem and be able to estimate the velocity but this limits their applicability to phantoms or very narrow class of blood vessels. Usually the following assumptions are used.

• Contrast is incompressible fluid, with zero-diffusion. Zero diffusion means there is no loss of contrast material through the vessel wall while it is traveling.

• Flow is axi-symmetric (symmetry around axis). This is invalid in large asymmetric objects such as aneurysm.

• Flow is laminar. Turbulent flows are generally not considered.

• Arteries are static objects which do not move and are not elastic.

• Dilution effect of contrast mixing with blood is ignored.

When observing a vessel on an image it is presented as a 2D object which intensity values, due to projective nature of X-ray equipment, are already integrated in the imaging direction. If the flow is axisymmetric then it makes sense to present a vessel as single-dimensional object by integrating intensity values across the vessel. So we get intensity distribution as a 1D function of vessel centerline axial distance. This reasonable assumption greatly simplifies the algorithms and almost all of the methods make use of this. This is shown in Figure 4.2. Dotted lines are the direction of integration.

Figure 4.2: Turning 2D vessel into 1D object.

When transforming vessel into 1D signal it is not possible to recover its radial velocity distribution. However this is usually not that important and it also requires high magnification of vessel since more pixels are required at the cross-section.

The selection of flow measurement algorithms for any application are dependant on the specific requirements of that application. It depends on what is the studied object: a
vessel, perfusion bed with inlet and outlet vessels, or an aneurysm. Is the flow pulsatile or steady, is it axisymmetric (how close), what is the extent of contrast diffusion. Do we want the entire flow of the vessel or the axial distribution of velocities [27].

4.1.1 Contrast Injection by a Series of Pulses

Injection of contrast is performed by a sequence of short pulses instead of normally one long injection. Then by knowing the injection time frequency (f) and if the length $\Delta s$ between two pulses can be estimated (spatial frequency) from the image sequence, then velocity is calculated simply as $v = \Delta s \cdot f$. Results are reported to have accuracy around 10%. This method was successfully used in [28]. However the problem is the inability of the most of the current contrast injectors to provide such injection profile.

4.1.2 Vessel Transit Time Estimation

These techniques are based on the measurement of the Time-Density signals at the two regions of interest (ROI) on the target vessel. ROI are usually on the opposite ends of the vessel. If the distance between the two ROI is known than by estimating the time it takes for the contrast agent to travel from one ROI to the other it is possible to estimate average velocity of the contrast agent. This is shown in Figure 4.3. Second TD signal is shown as being diluted during the traversal which is usually the case.  

![Figure 4.3: Transit time between two ROI.](image)

The problem is how to estimate the exact time of arrival from TD signals. The most common features of TD signals used are peak, half-peak and maximum inclination point of the uptake interval. This technique in general fails in the condition of pulsatile flow. Such flow will not be characterized well since it is not known what is happening to the contrast agent between two ROI.

4.1.3 Contrast Traversal Distance Estimation

The idea of these techniques is to find the distance that contrast agent has traversed between two frames of a sequence. Very desirable feature of this technique is that it produces velocity as a function of position. Then the velocity distribution along the vessel can be
observed which is closer to the original idea of estimating instantaneous blood flow and velocity. They also work well for the condition of pulsatile flow.

Distance-Density (DD) signals are constructed showing contrast distribution along the vessel. Usually cross-correlation is calculated to find the best match between these two signals and the translation point of the best match is the distance being traveled. Or similarly one signal is being shifted and sum of square errors (SSE) is being calculated between these two signals. The shift corresponding to minimal SSE error is used as the distance traveled. This is shown in figure 4.4. This technique was applied successfully in [29]. The problem can be short vessels and low fps value because than contrast agent moves too much between the frames.

Density value is obtained by integrating the pixel intensities across the vessel lumen perpendicular to centerline. This is valid if the vessel cross section area is constant and correction has been done for angulation [26]. Otherwise the density profile along the vessel can be misleading as shown in Figure 4.5. Requirement of constant cross-section makes these methods unsuitable for stenosis detection which could otherwise be detected as velocity increase within the vessel.
4.1.4 Time-Distance-Density Images

It is possible to combine Time-Density and Distance-Density signals into 2D parametric image called Time-Distance-Density (TDD) image. This technique was proposed in [30]. Such image can be formed by aligning DD signals column-wise or aligning TD signals row-wise. Additionally every row is normalized by dividing with the maximum value of the row. This normalization step assumes that the vessel cross-sectional area at each point does not vary with time.

For synthetic case of Gaussian profile of the both TD and DD signals the TDD image is shown in Figure 4.6. Every row is a TD signal (horizontal gray bar) and every column DD (vertical bar).

![Figure 4.6: Time-Distance-Density parametric image.](image)

By observing iso-density lines and by calculating the gradient of that line, velocity can be estimated. In the above image all iso-density lines have the same angle since the velocity of propagation was made constant.

Normally spatial resolution of the contrast is much better than temporal one. By observing one TD signal (Figure 4.7 (a)) and one DD signal (Figure 4.7 (b)) from the above image (Figure 4.6) we can see that the number of samples describing the contrast profile in DD signal is significantly higher than the number of samples in TD signal. That is also one advantage of DD based techniques over TD based ones.

4.1.5 Optical Flow Based Methods

This method also relies on distance-density signals. Two consecutive DD signals are considered. They are separated in time by one sampling interval $\Delta t$, $I(x, t)$ and $I(x, t+1)$. The name of optical flow comes from the main assumption that the intensity outlook of the signal does not change during the motion. So in fact we are tracking intensity levels. In our case that means that the contrast agent preserves its shape between the two frames. The shape is only translated by $\Delta s$ then:

$$ I(s, t + \Delta t) = I(s - v\Delta t, t) $$

(4.1)
where \( v \) is the contrast medium velocity. Using the first order Taylor series:

\[
I(s - v \Delta t, t) \approx I(s, t) - v \Delta t I'(s, t)
\]  

(4.2)

We can extract velocity \( v \):

\[
v = \frac{I(s - v \Delta t, t) - I(s, t)}{\Delta t} = \frac{I(s, t + \Delta t) - I(s, t)}{\Delta t}
\]  

(4.3)

In the limit \( \Delta t \to 0 \)

\[
v = \frac{\partial I(s, t)}{\partial t}
\]  

(4.4)

This is also visualized in Figure 4.8.

Figure 4.8: Velocity estimation using Optical Flow method.

Differential optical flow method as presented above is local by nature. Since at the point of interest the first order approximation of the signal neighborhood is used, this method can run into problems if that part of the signal cannot be approximated well by a linear function. Neighborhood needs to be larger as the motion increases hence optical
flow techniques prefer small motions. If due to motion, linear approximation gets violated, then the estimated distance traveled between two frames would be over- or underestimated.

Additionally the results are heavily dependant on the magnitudes of the derivatives. Hence if the spatial gradient of the signal is low (whole vessel is filled with contrast) no velocity can be calculated. That is why traversal of the leading and trailing edge of the contrast material are of interest since then the spatial gradient is usually sufficiently strong. In [26] it is proposed to use the weighted optical flow method. In this method the initial velocity estimates are weighted depending on the magnitude of the spatial derivative. This technique was successfully used in [31], [26] and [32]. However since it relies on DD signals it has the same problems as all the other DD based methods.

4.2 Proposed Algorithm Outline

In order to use any of the above mentioned methods contrast propagation in vessel of interest should be extracted. Thus vessel itself should first be segmented.

Ideally for flow estimation we should observe contrast propagation in 3D not in 2D. One attempt of reconstructing such 3D flow, from 3D volume and a sequence of DSA images, and subsequently visualizing it, was done by [33]. Vessel overlapping as always presented a problem and extremely high frame rates imaging (∼ 100 fps) are required.

The algorithm for estimating the blood velocity and flow, using 3D volume of arteries and sequence of 2D DSA images, that we used and performed tests on, can be summarized into these steps:

1. From 3D cube, vessel tree should first be segmented.

2. Every vessel of the vessel tree should be detected and labeled. Vessels are segments with no bifurcations. For each of these vessels we are interested in blood flow value.

3. 3D centerline together with distance transform of vessels should be computed. From the distance transform cross-section area of the vessel can be found. Centerline is required to find the actual length of the vessel in 3D.

4. Each 3D vessel can be projected onto 2D image thus automatically segmenting vessel in 2D image sequence. This would otherwise be very difficult task to do by just observing 2D images. Also overlapping vessels can be detected.

5. Contrast propagation in each vessel can now be recovered from 2D sequence.

6. Once we have contrast propagation one of the methods for velocity estimation presented in the previous section can be used. We relied on vessel transit time methods hence actual vessel length was of importance.

7. Finally flow for each vessel is found by multiplying velocity and cross-section area.
4.3 3D Vessel Segmentation

Vessel tree has to be segmented from a 3D cube of voxels. The volumes that we had access to were of size 256x256x256 with 16 bits per pixel. 2D Slice through the volume typically looks like in Figure 4.9.

![Figure 4.9: Slice through volume.](image)

Voxels that belong to vessels have high gray level intensity (shown white in the image) because contrast medium was injected prior to rotational run. This gray level is proportional to linear attenuation coefficient of the contrast medium. That value is usually higher than attenuation coefficient of any other tissue with the attenuation of bones being the closest.

4.3.1 Global Thresholding

Since the voxels belonging to vessels are supposed to have the highest gray level values in the volume the most intuitive approach to segmenting the vessel tree would be to use global thresholding.

In global thresholding we set all the voxels having value above the threshold to foreground label and all the voxels having value below the threshold to background label. Thus we have turned gray scale volume into binary one having only foreground and background objects denoted with values 1 and 0 respectively.

\[ F_{th}(v) = \begin{cases} 1 & \text{if } F(v) \geq thr \\ 0 & \text{if } F(v) < thr \end{cases} \]  \hspace{1cm} (4.5)

where \( v \) is voxel and \( F(v) \) corresponding gray value.
The problem left is how to find the global threshold value. Usually this can be estimated from volume histogram which should hopefully be bimodal and then threshold would have a value between the two peaks. The typical histogram for our volumes is shown in Figure 4.10.

Unfortunately this histogram is unimodal, having only one peak. The histogram is not bimodal because vessels occupy only a small portion of the entire volume (about 1%) and additionally they do not have exactly the same gray level since the gray levels are dispersed around some mean value. So they do not accumulate much to be noticeable in the histogram.

The optimal threshold used for vessel segmentation which is experimentally found is also shown. It is difficult to estimate this threshold from such histogram. Results using the optimal threshold level as well as lower than optimal threshold level is shown in Figure 4.11. Volumes were visualized using surface rendering.

One method of finding global threshold level is called \textit{p-tile} segmentation and is based on \textit{a priori} knowledge about the imaging area. If we expect that our vessels occupy e.g. 0.5\% of the volume then we can adjust our threshold level so that after thresholding exactly 0.5\% of voxels are given foreground label. This threshold value does not have to be iteratively computed, rather it can easily be found from cumulative histogram. Cumulative histogram of the histogram shown before (Figure 4.10), is shown in Figure 4.12. In this example threshold is set to the value which corresponds to 0.995\%. For our cases the value of 0.5\% gave near-optimal threshold estimation. But it did not work for volumes containing AVM pathology since there about 1\% occupation value should be assumed.

Although results obtained by global thresholding can be sufficient for viewing they have some drawbacks when used in later processing. The main problem is that such segmented vessel tree is not a single object but rather multiple objects close to each other. The preferred result would be set of voxels which is well connected. Set of points is well connected if for each pair of points there exists a path from one point to another.
Figure 4.11: Global thresholding results using: suboptimal level (a) and optimal level (b).

Figure 4.12: Cumulative histogram.

contained within the set. That is why segmentation methods based on region growing or fuzzy connectedness are preferred.

4.3.2 Fuzzy Segmentation

When simple thresholding of the image does not give satisfying results, e.g. due to nonuniform shading, fuzzy connectedness based method is often used. It can provide good segmentation results even in the presence of noise. This algorithm has been successfully applied to a variety of medical images. The theory of fuzzy connectedness based segmentation is described next as presented in [34].

The idea is that we take a seed voxel which certainly belongs to the foreground object
and calculate fuzzy connectedness of all the other voxels to the given one. Fuzzy connectedness is a map which says for every voxel how tightly connected (number between 0 and 1) it is to the seed voxel. This map is then thresholded leaving only those voxels having connectedness value higher than the threshold and they form a fuzzy object. Usually threshold of 0.5 is used meaning that the certainty that the two voxels belong to the same object is greater than 50%. The higher the threshold the smaller the resulting object gets.

A fuzzy affinity is defined as a function $\psi$ which assigns to each ordered pair of voxels from volume $V$ a real value between 0 and 1, with the following properties.

\begin{align}
\forall c \in V, \psi(c, c) &= 1 \\
\forall c, d \in V, \psi(c, d) &= \psi(d, c) \quad (4.6)
\end{align}

This function described how close the relationship is between two voxels in question. This influences whether these two voxels should belong to the same object.

A sequence of voxels in which consecutive voxels are adjacent is called a chain. A pair of adjacent voxels is called a link. Each link has its strength assigned according to affinity function. The strength of a chain is the strength of its weakest link.

It is necessary to define appropriate fuzzy affinity function. One which is typically used is

\[
\psi(c, d) = \begin{cases} 
0 & \text{if } c \text{ and } d \text{ are not adjacent} \\
\frac{1}{2}[g_1(f(c) + f(d)) + g_2(|f(c) - f(d)|)] & \text{otherwise}
\end{cases}
\quad (4.7)
\]

where

\[
g_1(x) = e^{-\frac{(x-m_1)^2}{2\sigma_1^2}}, \quad g_2(x) = e^{-\frac{(x-m_2)^2}{2\sigma_2^2}}
\quad (4.8)
\]

The values of means and standard deviations: $m_1$, $\sigma_1$, $m_2$, and $\sigma_2$ need to be estimated. These values can be known from statistical observations or can be obtained from local neighborhood of couple of points that belong to the foreground object. These points can either be selected by a user or can be obtained by other segmentation procedures (e.g. global threshold with threshold set high). The fuzzy affinity of two adjacent voxels will be high if those two voxels have $f(c) + f(d)$ and $|f(c) - f(d)|$ typical for the object that wants to be segmented.

With every fuzzy affinity function we can associate fuzzy connectedness function $\mu_\psi(c, d)$ which assigns a real value between 0 and 1 to every pair of voxels. This value is the strength of the strongest chain between the two voxels. Using fuzzy connectedness function and seed voxel $o$, we create fuzzy connectedness map as $f(c) = \mu_\psi(o, c)$.

Segmentation is robust in the sense that if instead of finding the connectedness map for voxel $o$ and threshold it at level $t$ to get a fuzzy object, we find the connectedness map of any other voxel of this fuzzy object and threshold that map with the same $t$, we end up with the same fuzzy object. Additionally the obtained fuzzy object is well-connected.

Standard algorithm for calculating fuzzy connectedness map $f$ using seed voxel $o$ relies on Dynamic programming technique. Dynamic programming is an algorithmic technique where problem is broken into subproblems, and these subproblems are solved and the solutions cached (this is called memoization), in case they need to be solved again. Queue data structure is utilized.
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Algorithm 1 Dynamic programming algorithm for calculating connectedness map

1: Put $o$ into Queue.
2: $f(o) = 1$, $f(c) = 0$ for $c \neq o$. {Initialization}
3: while Queue is not empty do
4: remove $d$ from Queue.
5: for every voxel $c$ that is adjacent to $d$ do
6: $v = \min(f(d), \psi(c,d))$.
7: if $v > f(c)$ then
8: Put $c$ into Queue.
9: $f(c) = v$.
10: end if
11: end for
12: end while

The creation of fuzzy connectedness map is the most time-consuming task of the algorithm. It takes 5 minutes on 3GHz machine for our datasets to complete this step. Once the connectedness map has been obtained, the cost of fuzzy segmentation is the same as that of thresholding.

Performance can be improved by use of greedy algorithms. Greedy algorithm always takes the best local solution while optimizing and is thus quite fast but for the cost of ending up in local optimum [35].

Result of fuzzy segmentation is shown in Figure 4.13. The resulting object is well-

![Image](image.png)

Figure 4.13: Result of fuzzy segmentation.

connected. Image of the slice of Fuzzy connectedness map shown together with the same slice of the original volume is visualized in Figure 4.14.
4.4 3D Vessel Tree Labeling

Once the vessel tree is segmented and represented as a binary object labeling of different vessels within the vessel tree is possible. The algorithm for vessel tree labeling was available as a library routine and we are not familiar with the inner workings. We can only show the result of the algorithm, which is shown in Figure 4.15. Each label is presented with different color (or gray level).

The result is not perfect as there are vessels which are presented with multiple labels.
We intend to research in the future, labeling based on skeleton of the vessel tree, which should give better results if suitable skeleton is found.

4.4.1 3D Object Elongatedness

In order to avoid expensive skeletonization process of 3D objects corresponding to short vessels which are not elongated at all we would like first to estimate the elongatedness of such objects. The theory goes as follows.

Body when rotated around some axis has angular momentum.

\[ \vec{L} = I \vec{\omega} \] (4.9)

\( I \) is moment of inertia and \( \vec{\omega} \) angular velocity. Moment of inertia is to rotational motion as mass is to linear motion. The greater the concentration of material away from the object’s centroid, the larger the moment of inertia.

In case of rotation around principal axes, the angular momentum is parallel to the angular velocity and the moment of inertia is a scalar value. For an arbitrary rotation, axis moment of inertia is a tensor, usually represented by a matrix. For 2D object, moment of inertia can be obtained through central moments.

\[
I_{2D} = \begin{bmatrix}
M_{20} & M_{11} \\
M_{11} & M_{02}
\end{bmatrix}
\]

\( M_{20}, M_{11} \) and \( M_{02} \) are called second moments and for binary object \( b \) they are defined as:

\[
M_{20} = \sum_x \sum_y (x - c_x)^2 b(x, y)
\]

\[
M_{11} = \sum_x \sum_y (x - c_x)(y - c_y) b(x, y)
\] (4.10)

\[
M_{02} = \sum_x \sum_y (y - c_y)^2 b(x, y)
\]

Where center of mass has coordinates \( c_x \) and \( c_y \).

The same can be done for 3D object where the moment of inertia is

\[
I_{3D} = \begin{bmatrix}
M_{200} & M_{110} & M_{101} \\
M_{110} & M_{020} & M_{011} \\
M_{101} & M_{011} & M_{002}
\end{bmatrix}
\]
and second moments are.

\[ M_{200} = \sum_x \sum_y \sum_z (x - c_x)^2 b(x, y, z) \]

\[ M_{020} = \sum_x \sum_y \sum_z (y - c_y)^2 b(x, y, z) \]

\[ M_{002} = \sum_x \sum_y \sum_z (z - c_z)^2 b(x, y, z) \]

\[ M_{110} = \sum_x \sum_y \sum_z (x - c_x)(y - c_y) b(x, y, z) \]  \hspace{1cm} (4.11)

\[ M_{101} = \sum_x \sum_y \sum_z (x - c_x)(z - c_z) b(x, y, z) \]

\[ M_{011} = \sum_x \sum_y \sum_z (y - c_y)(z - c_z) b(x, y, z) \]

Where center of mass has coordinates \( c_x, c_y, \) and \( c_z \).

To find whether the label presents the elongated object we would like to find principal axes of that object for which is

\[ I\vec{\omega} = \lambda \vec{\omega} \]  \hspace{1cm} (4.12)

This is actually the problem of diagonalization of matrix \( I \) and finding its eigenvalues and eigenvectors. Eigenvectors present the principal axis and eigenvalues the moment of inertia around these axes. Inertia Matrix is always symmetric. This implies that all the eigenvalues will be real. Additionally if the eigenvalues are distinct the corresponding eigenvectors (our principal axes) will be orthogonal.

Actually we do not have to find the eigenvectors it is enough to get the eigenvalues. If object is elongated it should have one eigenvalue significantly smaller than the rest. We required that the smallest eigenvalue should be at least 10 times smaller than the largest one. The corresponding eigenvector would be pointing in the direction of the object elongatedness.

Exactly the same results can be achieved using the principal components analysis (PCA). Building covariance matrix required by PCA is a mathematical equivalent of \( I \) matrices defined in eq. 4.4.1 and eq. 4.4.1. So the corresponding eigenvalues are also equivalent.

Results on two potential vessel objects are shown in Figure 4.16. At the top of the figure, three eigenvalues are shown. It is seen how the difference between the smallest and the largest eigenvalue of the elongated object is couple of orders of magnitude.

### 4.5 3D Vessel Centerline Extraction

Once each vessel is assigned a different label, the next step is the centerline extraction. We are interested in the centerline of the vessel for two reasons. First the length and the average width of the vessel is easy to estimate once the centerline is known. Second, it is
easy to partition the vessel into smaller segments having bordering planes perpendicular to the centerline. These segments will be needed later for velocity estimation.

One approach to estimate the centerline is to find the skeleton of the vessel. Skeleton can be defined as the locus of the centers of all the maximal inscribed hyper-spheres and presents a thinned approximation of the object. Example of skeleton of a 2D rectangle is shown in Figure 4.17. In the same figure it is shown how skeleton is sensitive to noise. Skeleton should fulfill the following requirements:

- Geometrical. The skeleton must be in the middle of original object and also be invariant to translation, rotation and scale.
- Topological. The skeleton must retain the topology of the original object.

There are numerous methods for performing 2D skeletonization. However extension to 3D skeletonization is difficult. In general the skeletonization of 3D object is not a set of curves but a set of curves and surfaces. Additionally these surfaces (surface skeleton) can
be turned into curves (curve skeleton). Other terms in use for surface and curve skeleton are medial surface and medial line, respectively.

Example of finding a skeleton of 3D rectangle (rectangular box) is shown in Figure 4.18. As seen on these pictures the resulting curve skeleton is not necessarily one voxel thick so additional thinning step is required.

![Figure 4.18: Skeleton of a 3D rectangle.](image)

Not all objects can have a curve skeleton. Objects with holes, like e.g. hollow cylinder, cannot be represented by curve skeleton. However since we have elongated, tube like objects, curve skeleton is a very suitable representation.

The skeletonization procedure that we used is based on distance transform and thinning process [36], [37]. As we did not develop this skeletonization procedure, since we were able to use it as a library routine, we are not acquainted with all the details of implementation. The procedure for skeletonization is summarized in the next subsections.

### 4.5.1 Distance Transform

First step is to perform the Distance transform (DT). DT gives each point of the object its distance to the nearest boundary. It requires a metric definition first. The most simple one is city-block distance. The distance transform is performed in two scans.

For 2D case, the first scan starts from top-left most pixel and goes toward bottom right. The second scan goes exactly the opposite way. In the first scan, distance value of the object pixel is being incremented by one from the left or top neighbour depending which one has smaller distance value. In the second scan the value of the previous step is compared to the newly incremented value from the smaller between right and bottom neighbour. The smaller value from the two steps is taken. Example is shown in Figure 4.19. It is straightforward to extend this procedure to 3D.

### 4.5.2 Surface Skeleton

In 3D, distance transform value of each voxel can be interpreted as a radius of inscribed sphere. If that sphere is not included in any other sphere then this voxel is called center of the maximal sphere. Those are voxels having local maximum value of DT.
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Figure 4.19: Distance transform.

From distance transform surface skeleton can be found as set of voxels that are centers of the maximal sphere. This also means that this operation is reversible. It is possible to reconstruct the original object from this surface skeleton. The surface skeleton, maximally two voxels thick at places where the original object had even thickness, is centered within the object and is symmetric.

4.5.3 Curve Skeleton

The next step is to turn surface skeleton into curve skeleton. This is achieved using thinning. The thinning is iterative operation where border points are being inspected whether they can be deleted without jeopardizing topology preserving property. This iterative operation stops when there are no deletable points left.

In order to know whether the voxel is deletable some classification of voxels is first necessary. Of interest are: junction, edge, and curve voxels. This identification can be accomplished by observing 3x3x3 neighbourhood of each voxel. Also some end point (voxels with only one neighbour) detection is required. These end points should not be deleted in order for the skeleton to preserve the shape and extremities of the object. Since distance transform was performed at the very beginning all the voxels of the final curve skeleton have appropriate distance values.

4.5.4 Skeleton Pruning

In order for the curve skeleton to be useful in real applications, pruning of some branches is necessary. As seen previously in Figure 4.17 skeleton can have spurious branches due to noise.

Pruning process starts from peripheral branches and goes iteratively layer by layer. Peripheral branch is the one which has an end point on one side and branching point on the other. Along a branch a number of “significant” (based on their identity found in the previous step) voxels is calculated and compared to the total number of voxels in the branch. If that ratio is above some threshold this branch is preserved otherwise it is being deleted. Also brute-force pruning can be performed to automatically eliminate all the branches which consist of number of voxels which is below some threshold number [38].

Smoothing of the original object, simplifying the surface skeleton, and curve skeleton pruning are some usual operations performed to tackle the noise sensitivity of the skeletonization process. Since vessel label should have a skeleton which is a single line with no branches at all, the longest path through the skeleton is found and used as centerline of the vessel. Thus the result is 26-connected line where each voxel has only one neighbour.
and known distance transform value. One typical result for a vessel object is shown in Figure 4.20.

![Figure 4.20: Skeleton of a vessel object.](image)

### 4.6 3D Vessel Partitioning

To find TD signals from two distant regions of the vessel we first need to partition the vessel. Then we can take the first and last segment and find TD signals in them. We need to make a choice of the size of each segments. As the segments become larger the TD signal will be smoother but time resolution will decrease. We decided to use segments of width equal to the size of 10 voxels.

To create vessel segments, we first created their border planes which are perpendicular to the centerline and the distance along centerline between them is 10 voxels. The number of centerline voxels is smaller than 10 if they are touching each other only in one point or in edge since such distance is longer than face to face distance.

Plane normal vector was built from three consecutive points of the centerline and an intersection of this plane and vessel provided us with the borders between segments. Border planes are shown in Figure 4.21. Once the border planes of each segment are known, using the region growing algorithm, the segment can be extracted. Border planes are making sure that the grown region is localized within these borders. Resulting segments from vessel partitioning procedure is shown in Figure 4.22. In that image the small light gray regions on each side of the vessel are not being considered as valid segments (result in the figure consists of 5 segments). Since we wanted all regions to be equally long we had to leave some parts at the end of the vessel unsegmented.
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4.7 3D Projection

X-ray imaging device is of projective nature, so the images obtained are determined by projections of 3D objects. Since using the 3DRA we are able to obtain the volume which is being imaged and since the same device is used for acquiring the volume and DSA images by knowing the spatial relationship between imaging plane, volume and the camera position, we are able to co-register 3D volume with 2D images.

The spatial relationship between the three objects: camera, volume and imaging plane is shown in Figure 4.23. The imaging device supplies us with the following information which we require:

- Camera center position, volume center position and imaging plane center position are known.
- The size of volume and image in each dimension is known in millimeters as well as
in the number of voxels/pixels.

- Rotation transformation matrix for the volume around its center

In order to perform segmentation of the vessels in 2D image we would like to project 3D vessel points, which we have segmented in the previous section, onto 2D image. 3D projection is a mathematical transformation used to project 3D points onto a 2D plane. This is achieved by a series of multiplication with square matrices of 4x4 size (since homogenous coordinates are used). In the next discussion we assume column vectors are used.

We would like to have a transformation which turns voxel coordinates to projected image pixel coordinates on the imaging plane. To achieve this we first have to go from volume coordinate system to world coordinate system in which the volume is situated. From the world coordinate system we then turn to the camera coordinate system. In the camera coordinate system we can then easily perform projection onto the imaging plane [39]. Each of these transforms can be represented by a 4x4 matrix (since homogenous coordinates are used). Then the 3D projection matrix is obtained by multiplying all of these transform matrices.

\[
\text{Pixel} = \text{Perspective transform} \times \text{Camera transform} \times \text{World transform} \times \text{Voxel}.
\]

Both pixel and voxel coordinates are represented as 4D column vector.
**4.7.1 World Transform**

Our input volume is a cube. We denote with $V_{dim}$ the length of the cube’s edge in millimeters and with $V_{size}$ the number of voxels in each dimension. $Ov$ is the origin of the volume in world coordinates.

First we need to translate the voxel coordinates so that they are around the center of the volume origin which is in the middle not on one corner of our volume.

$$T_{trans1} = \begin{bmatrix} 1 & 0 & 0 & -V_{size}/2 \\ 0 & 1 & 0 & -V_{size}/2 \\ 0 & 0 & 1 & -V_{size}/2 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Then we build a scaling transform matrix to turn voxel coordinates into world units (millimeters).

$$T_{scale} = \begin{bmatrix} V_{dim}/V_{size} & 0 & 0 & 0 \\ 0 & V_{dim}/V_{size} & 0 & 0 \\ 0 & 0 & V_{dim}/V_{size} & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

In our datasets the volume had to be also rotated (around volume origin) using the matrix $T_{rot}$ supplied by the imaging device.

Finally all the voxels should be translated depending on where the origin of the volume is in the world coordinates.

$$T_{trans2} = \begin{bmatrix} 1 & 0 & 0 & Ov_x \\ 0 & 1 & 0 & Ov_y \\ 0 & 0 & 1 & Ov_z \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

So the world transform of the voxel $v$ is:

$$T_w = T_{trans2}T_{rot}T_{scale}T_{trans1}$$

$$v' = T_wv$$

**4.7.2 Camera Transform**

In this step we need to transform all the points in the world coordinates into a camera coordinate system. $Oc$ and $Oi$ are positions of camera and imaging plane origins, respectively, in world coordinates. The line corresponding to $z$-axis of camera coordinate system is defined by two points. The position of the camera origin and the position of the imaging plane origin. The transformation is obtained by aligning the world and camera coordinate system axes.
First we translate camera origin to world origin using the following matrix.

\[
T_{\text{trans}} = \begin{bmatrix}
1 & 0 & 0 & -O_c x \\
0 & 1 & 0 & -O_c y \\
0 & 0 & 1 & -O_c z \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

Then we rotate around z-axis backwards (anti-clockwise for right-hand coordinate systems) by angle \( \alpha \).

\[
T_{\text{rotz}} = \begin{bmatrix}
\cos(-\alpha) & -\sin(-\alpha) & 0 & 0 \\
\sin(-\alpha) & \cos(-\alpha) & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

Next we rotate around y-axis backwards by angle \( \beta \).

\[
T_{\text{roty}} = \begin{bmatrix}
\cos(-\beta) & 0 & \sin(-\beta) & 0 \\
0 & 1 & 0 & 0 \\
-\sin(-\beta) & 0 & \cos(-\beta) & 0 \\
0 & 0 & 0 & 1
\end{bmatrix} = \begin{bmatrix}
\cos(\beta) & 0 & -\sin(\beta) & 0 \\
0 & 1 & 0 & 0 \\
\sin(\beta) & 0 & \cos(\beta) & 0 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

Now the z axes are aligned. Then we rotate by 90 degrees around z axis and flip the x axis in order to align x and y axes of camera and world. This two operations combined can be written as

\[
T_{\text{rotflip}} = \begin{bmatrix}
0 & -1 & 0 & 0 \\
-1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{bmatrix}
\]

All these steps are visualized in Figure 4.24. The whole camera transformation of point \( v \) can be summarized as

\[
T_c \cdot v' = T_{\text{rotflip}}T_{\text{roty}}T_{\text{rotz}}T_{\text{trans}}v
\]

### 4.7.3 Perspective Projection

The final step is a projection onto imaging plane. Perspective transform is used as opposed to orthographic (parallel). Obtaining projected x component of a 3D point is shown in Figure 4.25. Analogous is done for y component. Hence the perspective transform matrix is

\[
T_p = \begin{bmatrix}
1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 1/d & 0
\end{bmatrix}
\]
Finally image coordinates of a pixel which is a projection of point \((x, y, z)\) from camera coordinate system is:

\[
x' = \frac{x}{z} d
\]

\[
y' = \frac{y}{z} d
\]\n
(4.13)

Now we have all the transforms necessary to perform 3D projection of a volume. We traverse each voxel of a segmented vessel in a volume and project it to obtain the
corresponding image pixel. There are two ways to present projected result. One is by producing purely binary image showing whether one or more vessel voxels project on the particular pixel or not. The other approach is that each pixel has a value which corresponds to the number of vessel voxels which project onto that pixel thus giving a measure of vessel thickness. Both type of results are shown in Figure 4.26.

The resulting images are fraught with holes. The problem is that due to perspective projection and discrete volume the neighboring voxels can project to non-adjacent pixels leaving a hole in between. The only way to solve this problem is to perform the inverse operation instead of projecting voxels onto pixels. Traverse all the pixels of the image and try to find out whether a line of projection is passing through any voxels that belong to the vessel object.

4.7.4 Ray Casting

The idea that we find a line of projection for each pixel of the image is called ray casting. By casting rays from pixels we try to detect whether that ray intersects with any voxels
that belong to object (vessel). To obtain the equation of the line (ray) we can use the projection matrix from the previous section but this time we start from pixel and try to find the voxel. However this inverse transform, as seen from equation 4.13, is not unique and instead of voxel coordinate we get infinite set of coordinates that are on the line.

We need to detect all the voxels that intersect that line. This problem is similar to 2D line drawing problem in computer graphics. There we need to detect which pixels to draw in order for them to form a discrete version of ideal line. Such algorithm is known as Bresenham algorithm. There are two version of it. One has a simpler implementation and the result is a set of pixels which form a nice representation of ideal line. The other version called supercover, results in a set of all the pixels that ideal line intersects. These two different approaches are shown in Figure 4.27. Obviously we are more interested in the supercover algorithm since it can be used to detect any obstacles on the ray’s path.

The supercover algorithm can be summarized as follows. For the sake of simplicity we assume that the line is being drawn in the direction of higher x and y coordinates. From starting pixel we would like to detect whether the line leaves that pixel through the top horizontal border or right vertical. We calculate the distance from the line to the top right corner of the pixel. If that error is positive that means that the line left via top horizontal border and we advance y coordinate by 1, otherwise it left through the right vertical border and then we advance x coordinate by 1. That way we obtain the new pixel coordinate and we repeat the process.

However we need to use 3D extension of that algorithm since our lines are in 3D. This algorithm gives all the voxels that are intersecting that line and we need to check whether any of the voxels belong to the segmented vessel. 3D extension is obtained with the help of using 2D algorithm for solving 2D subproblems as shown in Figure 4.28.

Results of 3D projection ray casting is shown in Figure 4.29. No artifacts exist as with projection matrix approach but ray casting is much more computational demanding.
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4.8 Velocity and Flow Estimation

As shown in section 4.1 methods based on DD signals have so far performed the best results. However most of these results were achieved using the phantom vessels where no vessel overlapping occurred and where the vessel centerline was perpendicular to the imaging direction. Otherwise the DD signals would have misleading profiles.

Since we only had access to the real patient datasets we decided that the most robust method would be the one based on measuring the transit time of contrast agent through the vessel and thus calculating average velocity and flow. We are aware that this method is not robust to pulsatile flow conditions, which are always present, but the flow variation should not be that strong in the head (where we perform our studies) as in the other body regions closer to the heart. In general, the arterial flow is reported to be constant during diastole while venous flow is constant during the entire heart cycle [29].
If we manage in the future to compensate for the vessel overlapping, by suitable interpolation, and do appropriate correction for angulation of the vessels then we will focus more on the development of DD based methods.

### 4.8.1 Vessel Transit Time Estimation

We start from already partitioned vessel. The idea is to find the two most distant segments of the vessel, which do not have problem with overlapping vessels, and measure the TD signal in them. From TD signals we need to estimate time of arrival (TA) of contrast agent to each of the two chosen vessel segments.

When we obtain time of arrival for each segment then the difference of that parameter is the estimated vessel transit time (VTT) parameter. Since from the centerline we know the distance between the two segments as well as average radius of the vessel we have enough information to find both the blood velocity and the blood flow of the vessel.

From TD signals one actually detects the frame number of the sequence when the contrast arrives. To transform the difference in frame numbers ($\Delta N$) into meaningful physical unit, such as seconds, we need to divide that number by frames per second ($FPS$) parameter of the imaging study.

$$\Delta T = \frac{\Delta N}{FPS} \text{[s]}$$

In a similar fashion, distance between the segments ($\Delta L$) and average radius ($\bar{r}$) are expressed in number of voxels and need to be transformed into millimeters. Dimensions of the voxel cube are known from the dimensions of the volume ($V_{dim}$) (in $\text{[mm]}$) and the number of voxels along the volume ($V_{size}$).

$$\Delta S = \frac{V_{dim}}{V_{size}} \Delta L \quad \text{[mm]}$$

$$R = \frac{V_{dim}}{V_{size}} \bar{r} \quad \text{[mm]}$$

Finally the velocity can be found and is most commonly expressed in $\text{[cm/s]}$ instead of $\text{[mm/s]}$.

$$V = \frac{1}{10} \frac{\Delta S}{\Delta T} \quad \text{[cm/s]}$$

Blood flow is found from the velocity and vessel cross-section area.

$$F = V \left( \frac{R}{10} \right)^2 \pi \quad \text{[cm}^3 = \text{ml/s]}$$

$$F = 60F \quad \text{[ml/min]}$$

Now we will focus on estimating TA parameter from TD signals. There are two most popular methods:

- Time it takes for the peak contrast density value to arrive.
- Time it takes for the half-peak contrast density value to arrive.

It is difficult to say which one is better. Half-peak to Half-peak method gives more robust results but peak-to-peak method is more physically meaningful.
Peak to Peak

Contrast agent during its travel through vascular system is getting mixed with blood and gradually dispersing as it is getting diluted. The least affected area is the center of the contrast agent where the concentration is the strongest. So it is reasonable to use that point as time of arrival of the agent. This point is seen as the moment TD signal achieves its peak. So this method is based on detecting peak moments of TD signals.

Half-peak to Half-peak

Unfortunately peak to peak method has a problem with TD signals which have similar values around the peak so the signal appears as flat and the exact peak location is difficult to estimate accurately.

To overcome this problem, usually the moment the TD signal reaches half-peak value is taken as time of arrival. The nice property of this approach is that it is robust to TD signals with flat peak since all values close to the peak will have very similar TA parameter. So the exact location and value of peak is not that important. This is visualized in Figure 4.30.

![Figure 4.30: Half-peak method for VTT estimation.](image)

Additionally it is possible to achieve subframe accuracy with suitable interpolation (we used linear) since half-peak value is usually reached between the two frames.

4.9 Experimental Results

In this section experimental results of estimating blood velocity and flow will be presented. The estimation steps are performed automatically on every vessel of the vessel tree and here we will show the results for the two different artery vessels. One artery is the carotid artery which is the biggest vessel in the vessel tree. The other artery belongs to the group of tiny arteries. All the steps of calculation will be explained and supported with images.

4.9.1 Example no. 1 - the Carotid Artery

This is the largest vessel in our dataset and the blood flow should be the highest since it delivers the blood to the entire brain hemisphere.

The carotid vessel together with its centerline is shown in Figure 4.31. Vessel is par-
Figure 4.31: Vessel of interest (a) and its centerline (b).

Figure 4.32: Vessel segments.

The vessel is projected onto 2D. Vessel segments also need to be projected so that they can be checked for vessel overlapping criteria. Here the overlapping does not come from other vessels but from its own neighbouring segments because vessel is bending. Vessel segment needs to have at least 50% of its projected pixels unoccluded to be used in later processing. First, the two most distant segments are projected and if one of them has overlapping problems then the adjacent segment is tried and so on. Result of projection is shown in Figure 4.33. It is seen how couple of segments from the top side had to be skipped.

On the zoomed image (Figure 4.33 (b)) two segments that will be used are depicted. The lighter gray part of the projected segment is the part actually being used for TD signal construction. The rest had to be discarded because of the overlap with neighbouring segments.

Now DSA sequence can be observed. Three frames that show contrast propagation through carotid artery are shown in Figure 4.34.
TD signals that are measured in the two regions and the denoising result are shown in Figure 4.35. TD signals are measured as average value per frame of all the pixels of the segment. The two signals are then normalized and shown together in Figure 4.36. We can estimate the peak to peak distance as well as half-peak to half-peak distance. This is shown in Figure 4.37. The estimated values are quite similar. The reason for this is that contrast profile is rich with fluctuations and peak sticks out nicely, it is not smooth so peak estimation is fairly accurate. The estimated values for this example are shown in Table 4.1.

### 4.9.2 Example no. 2

This example of tiny artery will be presented with the same steps as the carotid example previously. Vessel with its segments that we are interested in is shown in Figure 4.38. Its projection to 2D together with projection of the whole vessel tree is shown in Figure 4.39.
Now ideally we would take the two most distant vessel segments. However we first have to test whether a segment is overlapped by other vessels. If overlap is detected then the new segment, closer to the center, is being investigated until two segments with no overlapping vessels are found. Projection of two such vessel segments is shown in Figure 4.40. It can be seen that couple of segments (lower part) had to be skipped due to vessel overlap.
CHAPTER 4. BLOOD FLOW AND VELOCITY IN ARTERIES

<table>
<thead>
<tr>
<th>parameter</th>
<th>peak-peak</th>
<th>half peak-half peak</th>
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</thead>
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<tr>
<td>$\Delta S$ [mm]</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>$\Delta N$ [frames]</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>$\Delta T$ [s]</td>
<td>0.16</td>
<td>0.13</td>
</tr>
<tr>
<td>$2R$ [mm]</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>$V$ [cm/s]</td>
<td>25</td>
<td>30.7</td>
</tr>
<tr>
<td>$F$ [ml/min]</td>
<td>392</td>
<td>481.5</td>
</tr>
</tbody>
</table>

Table 4.1: Results for carotid artery.

![Figure 4.38: Vessel of interest (a) and its segments (b).](image1)

![Figure 4.39: Projected vessel tree (a) with zoomed version (b).](image2)

Now a DSA sequence is required. One frame of the sequence with denoted vessel tree projection as well as one with denoted vessel of interest projection is shown in Figure 4.41

From this sequence we measure TD signal as average value of pixels that form two
CHAPTER 4. BLOOD FLOW AND VELOCITY IN ARTERIES

Figure 4.40: Projection of two valid segments.

Figure 4.41: DSA sequence frame with projected vessels.

vessel segments per frame. TD signal and denoised version of each segment is shown in Figure 4.42.

Figure 4.42: TD signals of two vessel segments.

Those two signals shown together are in Figure 4.43.
The estimated contrast arrival moments using two available methods are shown in Figure 4.44. These two values differ significantly (almost by factor 2) and the problem is that the top of these TD signals is flat so peak estimate is very inaccurate.

![Figure 4.44: VTT estimation](image)

The estimated values for this example are shown in Table 4.2.

<table>
<thead>
<tr>
<th>parameter</th>
<th>peak-peak</th>
<th>half peak-half peak</th>
</tr>
</thead>
<tbody>
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<td>43.3</td>
</tr>
<tr>
<td>$\Delta N$ [frames]</td>
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<tr>
<td>$\Delta T$ [s]</td>
<td>1.1</td>
<td>0.44</td>
</tr>
<tr>
<td>$2R$ [mm]</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>$V$ [cm/s]</td>
<td>3.9</td>
<td>9.84</td>
</tr>
<tr>
<td>$F$ [ml/min]</td>
<td>1.5</td>
<td>3.817</td>
</tr>
</tbody>
</table>

Table 4.2: Results for the tiny artery.
4.9.3 Estimation difficulties

Short vessels can hinder the estimation accuracy since then TD signals are pretty close to each other. Additionally, since time difference appears in denominator of the equation to calculate the velocity then small changes in that estimate will severely alter the velocity magnitude.

Other vessels that are overlapping the vessel of interest have effect of reducing the useful length of the vessels.

Pulsating heart influences the outlook of TD signals. Since we only measure passing of the front of the contrast agent this is dependant on current state of heart activity. Whether it in systole or diastole phase.

4.9.4 Validation

Most of the other algorithms discusses in section 4.1 were validated on imaging studies done either by computer simulation or in-vitro. Unfortunately, we did not have access to such equipment. Typical in-vitro studies consist of contrast injected into straight long (∼15 cm) cylindrical phantoms driven by a pump and flow measured by electromagnetic flow meters. If real datasets were used it was mostly on femoral artery which is quite long and has few problems with overlapping.

We do not have exact velocity values for our tested datasets available, we can only compare the values that we have estimated with values that are generally reported to exist in these arteries, in clinical publications.

In Carotid, average velocity is ∼ 38 cm/s with maximum systolic being ∼ 108 cm/s. In basal cerebral arteries, values between 30-80 cm/s are considered normal. In AVM pathology average velocity can be around 109 cm/s.

In one study, measurements were obtained using Transcranial doppler ultrasound system. Some values they report [40] are given in Table 4.3. MCA, ACA, PCA stand for middle, anterior and posterior cerebral artery respectively. It is seen that flow velocities in basal cerebral arteries range widely and are age dependent.

<table>
<thead>
<tr>
<th>artery</th>
<th>age group 1</th>
<th>age group 2</th>
<th>age group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA</td>
<td>81 ± 20</td>
<td>73 ± 19</td>
<td>59 ± 11</td>
</tr>
<tr>
<td>ACA</td>
<td>56 ± 14</td>
<td>53 ± 16</td>
<td>51 ± 12</td>
</tr>
<tr>
<td>PCA</td>
<td>52 ± 12</td>
<td>51 ± 12</td>
<td>40 ± 9</td>
</tr>
</tbody>
</table>

Table 4.3: Results (mean and std.dev.) reported with Transcranial doppler.
Chapter 5

Perfusion Estimation

After contrast is injected into the vascular system three distinct phases of contrast propagation can be observed in the DSA sequence. First there is the artery phase when most of the contrast is still in artery vessels. Then comes the capillary phase when contrast is entering the capillaries and tissue is getting perfused. At the end there is the venous phase when the contrast left the tissues and is now resident mostly in the veins. Three DSA frames from the acquired sequence, representing each phase, is shown in Figure 5.1.

![Artery phase](image1.png) ![Capillary phase](image2.png) ![Venous phase](image3.png)

Figure 5.1: Three phases of contrast propagation

In the previous chapter we were mostly concerned with the artery phase but in this one we will be interested in activities during the capillary phase. Unlike the bulk blood flow estimation, which was shown in the previous chapter, blood flow at the capillary level, called perfusion, has to be estimated with different means. The capillaries are so small that they cannot be seen in the image (neither in 3D nor 2D) and hence TD signal in them cannot be measured. However we are actually more interested in a region of tissue filled with capillaries not the capillary itself. Clinicians are often interested in how the contrast material representing quantity of blood is divided between different tissue regions of the brain.

The approach is to measure the TD signals of such tissue regions. The ideal TD signal looks similar to the one shown in Figure 5.2a. Real TD signals have far from ideal profile.
That is why denoising is needed as was explained in detail in chapter 3. To get some functional information of the tissue, we are interested in some measurable parameters of this TD signal. Some typical parameters of interest are shown in Figure 5.2b. The parameters are named as follows:

1. Time of arrival. Time from start of the measurement till the start of the contrast uptake.
3. Time to peak i.e. time of uptake
5. Wash out rate. Slope at the end of the signal.
6. Brevity of enhancement. How long does the enhancement last
7. Area under the signal.

Later we will try to link these signal parameters to perfusion related values.

Other modalities, due to longer contrast injection and acquisition time, experience recirculation effect which disturbs parameter estimation. Recirculation appears when the same contrast is imaged passing several times through the vascular system. Because the high frame rate enables short acquisition times, the X-ray imaging does not experience the recirculation effect and the observed signals are free from it. However due to its projective imaging it is possible that the same region is traversed by different parts of contrast agent multiple times via different overlapping vessels.
5.1 Parameter Estimation

To help the parameter estimation process we would like to find couple of feature points of the signal. Four feature points are of interest which coarsely describe the signal. The first one is the point when the uptake starts. Then comes the point when the uptake is finished and the signal has values close to the peak level for some period of time. Then the point when this peak level is finished and finally point when the contrast is washed out. These feature points of TD signal are shown in Figure 5.3a. By knowing the feature locations, we can build the simplified model of the signal. From this simplified model it is easy to estimate the parameters, especially the average slopes of the uptake and wash-out.

![Figure 5.3: TD signal feature points](image)

Calculation of parameters from the four feature points (1-4 from left to right) goes as follows:

- Time of arrival is equal to the first feature point position.
- Maximum enhancement is equal to difference of average value between the second and the third feature point and value of the first feature point.
- Time to peak is the difference in positions between the second and the first feature point.
- Wash in rate is equal to slope that connects the first and the second feature point.
- Wash out rate is equal to slope that connects the third and the fourth feature point.
- Brevity of enhancement is equal to distance between the middle positions of the two slopes defined above.
- Area under the curve is calculated as sum of values from the first to the last feature point where each value is equal to sample value minus value of the first feature point.

One problem present regions that are not reached by contrast material at all. Since they contain pure noise, any feature extraction is pointless and would produce subsequently misleading signal parameter values. One measure that can be used to detect such areas is
obtained by observing the peak signal value. Peak value gives us the maximum enhancement of the region in question. All regions having peak value below some threshold are considered not perfused at all and hence all the parameters are automatically assigned to 0. However if this threshold is set too high, some holes may appear in the tissue region which could lead the clinician to false conclusion that this region is infarcted.

5.1.1 Feature Extraction

Now we will focus on the detection of the feature points of TD signals in tissue which is traversed by contrast agent. All the processing of the TD signal is performed off-line when all the images of the DSA sequence are already acquired and stored in memory.

We define tolerance for signal’s fluctuations to be 10% of the signal’s amplitude. Using this, we can denote two signal levels which crossing of the signal will give us the feature points. One level is defined as zero level plus tolerance. The other is defined as peak value minus tolerance. The uptake is considered to be started only when the first level is crossed. The uptake is considered finished when the second level is reached. Again the washout is considered to be starting when the second level is crossed and considered finished when the first level is reached.

Examples of real TD signals and their feature points are shown in Figure 5.4. TD signal in Figure 5.4 (a) is lacking the washout phase so the last feature point could not be detected.

![Figure 5.4: Two TD signals with feature points](image)

5.2 Physical Interpretation

Physical quantities that we are most interested in are:

- **Perfusion or regional cerebral blood flow (rCBF).** Defined as volume of arterial blood delivered to the tissue per minute per tissue volume [ml/min/100g]. It is related to the amount of energy distributed to the cells of the particular tissue.
• **Regional cerebral blood volume** (rCBV). Defined as the fraction of the tissue volume occupied by blood. If the tissue volume is known it can be measured in [ml/100g]. It is a sort of capacity of the tissue to accept blood. It makes sense only if contrast agent remains intravascular otherwise the fraction would be close to 1.

• **Mean transit time** (MTT). Average time it takes a molecule of contrast agent to pass through the tissue.

These three parameters are related by the *central volume principle*:

\[
\text{rCBF} = \frac{\text{rCBV}}{\text{MTT}}
\]  

(5.1)

So knowing any two of these parameters enables us to find out the third. Sometimes it is easier to estimate rCBV and MTT and obtain rCBF as a ratio of these two.

These values turned out to be very indicative for e.g. stroke assessment. If rCBV and rCBF are reduced and MTT is prolonged then the tissue is probably at risk. Unfortunately, these parameters are sensitive to vascular diseases so stenosis in carotid artery can influence the resulting parameter values.

Recently perfusion MRI and perfusion CT have been dominantly used for stroke assessment. First we would like to present the theory that is governing the algorithms of both perfusion MRI and CT [41]. Then we would like to apply it on X-ray images to see whether it can give reasonable results using that equipment also. Both perfusion MRI and perfusion CT are using TD signals from contrast agent propagation which is in that sense similar to X-ray DSA sequence. The difference is of course that MRI and CT produce volumes and each voxel belongs to only one tissue, which is unlike pixels on X-ray images which are projections of 3D body.

Every capillary region has inflow and outflow. Inflow comes through the artery vessel and outflow goes through the veins. This is illustrated in Figure 5.5.

![Diagram of capillary region with inflow and outflow](Image)

Figure 5.5: Capillary region with inflow and outflow

By observing TD signal of the capillary region we measure how much contrast material is in that region at the moment. Normally velocity of blood in capillary region is very slow. This means that the same molecules contribute to the measured density value more than once, depending on how long it takes for the molecule to traverse this region (MTT). This makes a big difference, in the way TD signals are being interpreted, compared to the
previous chapter where the bulk blood flow has considerably greater velocity and each new time sample corresponds to a different part of the contrast agent.

Assuming that an ideal, peak-only, profile of contrast is coming through the artery into the capillary region, all the material would enter the region at once and then gradually leave depending on the particular MTT value of each molecule. This is illustrated in Figure 5.6. We are not measuring at the outflow of the region but rather we are measuring how much of the material is in the region at the moment. This function $R(t)$, showing TD signal after ideal injection, is thus called residue function.

\[ I_{roi}(t) = R(t)I_a(t) \]

Figure 5.6: TD signal as impulse response

If we assume that the relationship between observed contrast in the region $I_{roi}$ and arterial TD signal $I_a$ is linear this relationship can be written as a convolution of real arterial function, called arterial input function (AIF), and impulse response (residue function).

The problem is that we do not know how the artery input function to each region looks like. So the only thing we can do is assume that this function is only a scaled version, with no dispersion of the TD signal, of one of the major arteries like carotid or sagittal sinus. The amount of scaling should be proportional to the decrease of the flow since after each bifurcation, flow is proportionally divided depending on the cross-section area of the vessel ($F \sim r^4$). This is visualized in Figure 5.7.

Figure 5.7: Flow distribution at bifurcations
Greater quantity of contrast will go to vessel with greater flow value and since intensity is proportional to quantity it should become decreased (scaled) accordingly. So, if we can detect by how much it has decreased, we have an estimate of the flow. The equation describing TD signal can now be written as

\[ I_{roi}(t) = r \cdot CBF \int_0^t I_a(\tau)R(t-\tau)d\tau \] (5.2)

We can measure \( I_{roi} \) and \( I_a \) and using deconvolution we can find \( CBF \cdot R(t) \). Since by definition of impulse response \( R(0) = 1 \) we can easily find CBF. Also CBF should be the highest point of \( CBF \cdot R(t) \) function.

\( R(t) \) as impulse response presents a sort of normalization step for TD signal \( I_{roi} \). Since different injection techniques and quantities will give different TD signals, observing just the impulse response makes that signal invariant to input profile. This is important for inter-patient comparison studies.

Once \( R(t) \) is known we can find MTT from it. \( R(t) \) describes the amount of contrast still remaining in the region since it entered instantaneously. But we would rather know how much contrast left the region once in entered. This function \( (L(t)) \) (shown in Figure 5.8a) can be found as:

\[ L(t) = 1 - R(t) \] (5.3)

\( L(t) \) is like a cumulative function \( L(t) = \int l(t)dt \). By differentiating we get a sort of histogram (similar to probability density function) that shows how many contrast molecules left at each moment. Expected value of \( l(t) \) is equal to the MTT parameter (Figure 5.8b).

\[ MTT = \int_0^\infty tl(t)dt \] (5.4)

MTT can also be found as:

\[ R(t) = 1 - \int_0^t l(u)du \]
\[ dR = -l(t)dt \]
\[ MTT = -\int_0^\infty tdR = -\left[ tR|^\infty_0 - \int_0^\infty R(t)dt \right] = \int_0^\infty R(t)dt \] (5.5)
When CBF and MTT are known CBV can be found. Also CBV can be found in another way as:

\[
CBV = \frac{\int_0^\infty I_{roi}(t)dt}{\int_0^\infty I_a(t)dt}
\]  

(5.6)

This result can be obtained from the previous equations.

### 5.2.1 Maximum Slope Model

The steps used above, relied on solving the deconvolution problem. Instead of having to calculate deconvolution, which is very noise sensitive, we can make a model of the capillary region. If this model is valid then we would simplify our estimation procedure considerably [6].

One model known as *maximum slope model* is that \( R(t) \) is constant and all the molecules have the same MTT. This corresponds to a plug type flow (like through a pipe) through capillary region as visualized in Figure 5.9.

![Figure 5.9: Contrast propagation through capillary region](image)

The result of this convolution is very convenient and we can estimate most of the parameters just from TD signal in capillary region \( I_{roi} \). How to do that is illustrated in Figure 5.10. The physical interpretation of \( I_{roi} \) signal in case of this model is as follows. There are three distinct parts of the signal. The uptake is when the contrast starts entering the tissue. The peak is achieved when some of the contrast is already starting to leave (thus we know MTT), while new material is still entering thus producing a constant intensity level. That is why peak is related to CBV since this is the indicator of the blood capacity of the tissue. When the peak level is over the contrast stops entering and is in the process of leaving the tissue.

The additional information that is required, besides the TD signal of region, is maximum value of major artery TD signal. But even without that information, relative values can be displayed.

Nice characteristic of the maximum slope model, besides that the deconvolution is unnecessary, which makes it suitable for X-ray imaging, is that only first part of TD signal is required. That means that the washout phase is not important which is very convenient since we rarely have dataset showing washout phase (probably to lower the dose amount...
CHAPTER 5. PERFUSION ESTIMATION

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Figure 5.10: Maximum slope model and parameters

the patient receives). On the other hand it requires fast injection since dispersion of agent
decreases the slope thus leading to blood flow underestimation but since in X-ray imaging
injection is performed intraarterially instead of intravenously this requirement should be
fulfilled.

To summarize how are the parameters of the previous section related to the physical
parameters of interest (CBF, CBV, MTT).

• rCBV should be related to the signal height and the area under the curve parameters.

• CBF should be related to the slope of the washin period.

• MTT influences the time of uptake (time to peak) parameter.

5.3 Experimental Results

If we produce an image showing the value of the selected parameter for each region (rep-
resented as a pixel), we get an image with the functional representation instead of the
morphological one. Now the pixel values in such image do not correspond to morphological
property but to functional one. Such image can be pasted semi-transparently over the
standard X-ray image to view both the morphology and the functional behaviour at the
same time.

Normally in images showing morphology, pseudocolouring is avoided because it cre-
ates false borders that can distract the observer. False borders appear at transitions from
one hue to the next. However, color display can be very helpful in parametric or func-
tional imaging where image values represent a definite quantity such as blood flow, transit
time, or some other physiological measurement derived from the images [11].

We have performed parameter estimation on several datasets. All the datasets were
the same in respect that none of them contained a specific pathology so we are presenting
the results for just the two of them. The resulting parametric images for the first dataset
are shown in Figure 5.11. Since this datasets had missing washout phase, parameters
showing washout rate and brevity of enhancement are not shown.

If 3D volume of arteries is also available, it can be projected to mask out some arteries
since we are only currently interested in capillary regions and arteries only obstruct the
view. Masking resulting image with arteries is shown in Figure 5.12.
The resulting parametric images for the second dataset are shown in Figure 5.13. We did not have corresponding 3D volume for this dataset so no masking is available.

Since all the models here presented are relying on a number of assumptions it is difficult to put on the parametric images real quantitative results with meaningful values displayed (except those related to time). Additionally since washout phase is rarely visible in its entirety specially tuned models are required.

Currently, much safer approach would be to perform a qualitative interpretation of
Figure 5.12: Masking parametric image with artery map.

Figure 5.13: Resulting parametric images for the second dataset

The results by comparing the parameter values between the regions. Even better approach would be to compare the parameters in two hemispheres as then abnormalities are more evident. The true value of the parameters and images shown should still be explored by the clinicians.
Chapter 6

Conclusion

In this thesis we tried to use projective X-ray modality for acquiring physiological information in addition to the usual morphological imaging. X-ray equipment is widely used and enhancing it with such functional data would help clinicians significantly. Functional information has to be obtained from the standard images showing morphology with the help of injected contrast material. So the upgrade of the X-ray imaging equipment is only in software, the hardware remains mostly the same.

The two most important physiological parameters are blood flow and velocity. These parameters are of interest in both the arteries and the capillary regions. The methods required to estimate the parameters from them are different though. Arteries are visible in 2D and 3D images and can be segmented out. Capillaries on the other hand are too small and only approximate parameters for the region of the image can be found.

The basic measurement from which all the later parameters are extracted is Time-Density signal. It is obtained from a sequence of DSA images. It presents the time activity of the region (pixel) of the image through time. However such signals are very noisy and hence denoising is required. We tried two techniques. The first one is based on Wiener filtering. Although it gave satisfying results we wanted to try out wavelet-based denoising which currently presents the state of the art in denoising techniques. It turned out that wavelet denoising is slightly better than Wiener filtering especially as noise variance gets larger.

Blood flow and velocity estimation in arteries had to be supported with 3D volume of the vessel tree obtained before the DSA study. This volume is required in order to detect overlapping vessels and find the actual vessel lengths and area cross-sections. These values would be impossible to find just from 2D images due to the projective imaging being used. We based our method on measuring two Time-Density signals on distant ends of the vessel and finding time of contrast arrival to each of them. Since it is difficult to get images with high frames-per-second imaging setting, the arrival times to two regions of the vessel can get close so accurate estimation is crucial. We tried using peak and half-peak features of the signal for the time of arrival. Half-peak based estimation turned out to be more robust.

It is very difficult to get validation of our results. In other publications authors normally performed the studies on vessel phantoms. We did not have such equipment so we
could only compare our results with standard values that are reported to exist in these arteries. Our resulting values are a bit lower than expected. This difference can come from pulsatile flow effects since we measure only the passing of the front of the bolus which might happen either during systolic or diastolic phase.

Perfusion (blood flow at the capillary level) is nowadays usually estimated using perfusion MRI or perfusion CT devices. However we wanted to apply the same principles that are used on these devices to X-ray imaging. X-ray imaging has some advantages to other modalities like higher spatial and temporal resolution of images in a sequence showing contrast agent propagation. The biggest drawback is its projective imaging principle which makes a big difference compared to MRI and CT which produce volumes. We found the maximum slope model to have some characteristics which makes it suitable to apply in X-ray imaging. Again presented results are difficult to assess quantitatively. Qualitative interpretation by comparing results in different regions would be more suitable. Validation would be possible by using perfusion MRI and perfusion CT on the same patient but we did not have such studies performed.

6.1 Future Work

There are possibilities for improvement. Especially for the estimation of blood velocity in arteries. Methods based on distance-density signals are superior to our current method but they have significant problem with overlapping vessels as well as non-perpendicular imaging angle. This has to be corrected for and we plan to research in this direction. Then the result would be velocity specific to axial position in the vessel as well as time moment. Such results would be more meaningful in the situation of pulsatile flow.

Regarding the perfusion estimation some effort regarding automatic comparison of results between regions would be worth. Clinicians currently often manually compare two hemispheres of the brain to spot abnormalities. Our current results show both artery phase and capillary phase and this can be confusing to clinicians as these two phases in general do not occur simultaneously so artery vessel segmentation in 2D image, with or without the help of 3D volume, would be desirable.
Bibliography


Abstract

Blood flow and velocity are important physiological parameters, of great value to clinicians. We use X-ray imaging technique to estimate these parameters from image sequence showing propagation of injected contrast agent and with the help of 3D volume of arterial vessel tree. 3D volume is mechanically registered with 2D images so it can be projected on them. Blood flow is of interest in two distinct regions: the artery vessels and the capillary region. Blood flow in artery is based on blood velocity and vessel cross-section area estimation. Blood velocity is obtained by measuring transit time of the contrast agent through the vessel of known length. Vessel length and cross-section area can be measured from the 3D artery volume. Transit time is obtained by measuring time of arrival of contrast agent from 2D image sequence to different parts of the projected vessel. Blood flow at the capillary level is called perfusion and we based our methods on the theory behind perfusion MRI and perfusion CT modalities. Time activity signal of each region is obtained and its characteristics are linked to physiological parameters of interest using maximum slope model. The obtained results seem promising although qualitative rather than quantitative interpretation is more suitable.

Keywords: x-ray angiography, digital subtraction angiography, blood flow, blood velocity, perfusion.
Curriculum vitae

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Computer Vision
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