Applications of Statistical Methods in Quantitative Magnetic Resonance Imaging

Patrik Brynolfsson
Abstract

Magnetic resonance imaging, MRI, offers a wide range of imaging methods that can be employed in the characterization of tumors. MRI is generally used in a qualitative way, where radiologists interpret the images for e.g. diagnosis, follow-ups, or assessment of treatment response. In the past decade, there has been an increased interest in quantitative imaging, which give repeatable measurements of anatomy, biological processes or functions. Quantitative imaging allows for an objective analysis of the images, which are grounded in underlying physical properties of the tissues. The aim of this thesis was to improve quantitative measurements in dynamic contrast enhanced MRI (DCE-MRI), and to improve the texture analysis of diffusion weighted MRI (DW-MRI).

DCE-MRI measures perfusion, which is the delivery of blood, oxygen and nutrients to the tissues. The examination involves continuously imaging the region of interest, e.g. a tumor, while injecting a contrast agent (CA) in the blood stream. By analyzing how fast and how much CA leaks out into the tissues, the cell density and the permeability of the capillaries can be estimated. Tumors often have an irregular and broken vasculature, and DCE-MRI can aid in tumor grading or treatment assessment. One step that is crucial when performing DCE-MRI analysis is the quantification of CA in the tissue. The CA concentration is difficult to measure accurately due to uncertainties in the imaging, properties of the CA, and models of the patient physiology. In Paper I, the possibility of using two aspects of the MRI data, phase and magnitude information, for improved CA
quantification, is explored. We found that the combination of phase and magnitude information improved the CA quantification in regions with high CA concentration, and was more advantageous for high field strength scanners.

DW-MRI measures the diffusion of water in and between cells, which reflects the cell density and structure of the tissue. The structure of tumor tissue can give insights into the prognosis of the disease. Tumors are heterogeneous, both genetically and in the distribution of cells, and tumors with high intratumoral heterogeneity have poorer prognosis. This heterogeneity can be measured using e.g. texture analysis. In 1973, Haralick et al. presented a texture analysis method using a gray level co-occurrence matrix, GLCM, to gauge the spatial distribution of gray levels in the image. This method of assessing texture in images has been successfully applied in many areas of research, from satellite images to medical applications. Texture analysis in treatment outcome assessment is studied in Paper II, where we showed that texture can distinguish between groups of patients with different survival times, in images acquired prior to treatment start.

However, this type of texture analysis is not inherently quantitative in the way it is computed today. This was studied in Paper III, where we investigated how texture features were affected by five parameters related to image acquisition and pre-processing. We found that the texture feature values were dependent on the choice of these imaging and preprocessing parameters. In Paper IV, a novel method for computing Haralick texture features was presented, which makes the texture features asymptotically invariant to the size of the GLCM. This method allows for better comparison of textures between images that have been analyzed in different ways.

In conclusion, the work in this thesis and the included papers contribute to the knowledge in quantitative imaging of cancers using DCE-MRI and texture analysis of DW-MRI. The improvements in CA quantification using phase and magnitude has potential to increase the accuracy of DCE-MRI examinations. Furthermore, the analysis of current texture feature weaknesses together with the introduction of invariant Haralick
features can increase the usability of texture features in medical image analysis.
Populärvetenskaplig sammanfattning


DCE-MRI mäter perfusion, den process som förser vävnad med syre och näringsämnen från blodbanan. Undersökningen innebär att man avbildar det misstänkt sjuka området, t.ex. en tumör, samtidigt som man injicerar ett kontrastmedel i blodet. Genom att analysera hur snabbt och hur mycket kontrastmedel som läcker ut i tumören kan man bestämma celltätheten och permeabiliteten av kapillärerna i tumören. Tumörer förses ofta med blod från oregelbundna och trasiga kärl, och DCE-MRI kan på så vis hjälpa till att fastställa tumörgrad eller utvärdera behandlingsrespons. Ett viktigt steg vid analysen av bilddatat är att fastställa kontrastmedel-
skoncentrationen i vävnaden. Denna koncentration är svår att mäta p.g.a. osäkerheter i avbildningen, egenskaper hos kontrastmedlet och modeller av patientens fysiologi. I det första delarbetet (Paper I) undersöks möjligheten att använda två olika aspekter av MR-datat, fas- och magnitudinformation, för att förbättra skattningen av konstrastmedelskoncentrationen. Resultatet visade att skattningen blev bättre med denna metod i områden med hög koncentration, och fungerade bättre för MR-kameror med hög fältstyrka.


Sammanfattningsvis bidrar denna avhandling och de inkluderade delarbetena till kunskapen runt kvantitativ avbildning av cancer med DCE-MRI, och texturanalys av diffusionsviktade bilder. Den förbättrade metoden för skattning av kontrastmedelskoncentration kan öka noggrannheten i DCE-
undersökningar, och analysen av svagheter i nuvarande metoder för texturanalys samt introduktionen av invarianta texturparametrar kan förbättra användningen av texturanalys för tillämpningar inom cancerutvärdering.
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Finally, I want to thank my family; Mamma, Pappa, Anna and Emil, Johan and Emma, and last but definitely not least, Rebecca, for making my life wonderful!
List of Papers

Paper I

Combining phase and magnitude information for contrast agent quantification in dynamic contrast-enhanced MRI using statistical modeling.

Paper II

ADC texture - An imaging biomarker for high-grade glioma?

Paper III

Haralick texture features from apparent diffusion coefficient (ADC) MRI images depend on imaging and pre-processing parameters.
Accepted for publication, Scientific Reports

Paper IV

Gray-level invariant Haralick texture features.
Löfstedt T, Brynolfsson P, Asklund T, Nyholm T, Garpebring A

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# Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>2D</td>
<td>Two-dimensional</td>
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<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
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<td>CA</td>
<td>Contrast agent</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>DW</td>
<td>Diffusion weighted</td>
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<tr>
<td>DWI</td>
<td>Diffusion weighted imaging</td>
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<tr>
<td>EES</td>
<td>Extra vascular extra cellular space</td>
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<td>FA</td>
<td>Flip angle</td>
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<tr>
<td>GLCM</td>
<td>Gray level co-occurrence matrix</td>
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<td>IGRT</td>
<td>Image guided radiotherapy</td>
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<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td><strong>pH</strong></td>
<td>Potential of hydrogen</td>
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<td>-----------</td>
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<tr>
<td><strong>RF</strong></td>
<td>Radio-frequency</td>
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<tr>
<td><strong>SPGR</strong></td>
<td>Spoiled gradient recalled</td>
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<tr>
<td><strong>SVM</strong></td>
<td>Support vector machine</td>
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<tr>
<td><strong>VMAT</strong></td>
<td>Volumetric modulated arc therapy</td>
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Chapter 1

Introduction

Cancer is the second leading cause of death in Sweden, and the leading cause of death in people under 80 years of age\(^1\). The incidence of cancer has increased continuously since 1970, partly due to better diagnostic methods and screening programs, but also due to a more sedentary lifestyle, increasing overweight and obesity, alcohol intake and unhealthy tanning. Although the cancer incidence rate has increased by about 1 % annually, the mortality rate has dropped continuously in the same period. This is a positive trend, however the cost of cancer will continue to increase. According to the Swedish institute for Health Economics, the annual cost of cancer to the Swedish society is approximately 36 billion SEK, and is predicted to reach 70 billion SEK by 2040.\(^2\). The reason is better diagnostic methods, earlier detection and more effective treatments.

Treatment depends on the type of cancer, and is usually some combination of radiotherapy, surgery, chemotherapy and immunotherapy\(^3\) Radiotherapy has been used to treat cancer since the late 19th century\(^4\), and the developments from the most rudimentary radiation sources to the techniques used today are vast. Beginning in the 1980s, linear accelerators began replacing the older Cobalt-60 sources\(^5\), which used the radioactive element Cobalt as a radiation source. Linear accelerators can generate...
higher energy photons, and contrary to Cobalt-60 machines, the source does not decay over time. With the development of computed tomography (CT), treatment plans and delivery could be made in 3D. Magnetic resonance imaging (MRI) and positron emission tomography (PET) has further advanced the method of dose delivery using e.g. intensity modulated radiation therapy (IMRT)\(^6\), image guided radiation therapy (IGRT)\(^7\) and volumetric modulated arc therapy (VMAT)\(^8\). With the new techniques, the dose can be delivered with high precision. Taking advantage of this, studies looking at boosting dose to regions with suspected higher risk of relapse using functional or molecular imaging techniques like diffusion weighted MRI, dynamic contrast enhanced MRI or PET are under way\(^9\)–\(^13\).

MRI is a very useful tool for detecting and tracking tumors. It is based on manipulating and detecting signals from hydrogen nuclei in the body using magnetic fields\(^14\). Hydrogen is the most abundant element in the human body, it is found in most molecules and all tissues in the human body. Using pulse sequences that manipulate the spin state of hydrogen nuclei, it is possible to form images showing many different properties of the underlying tissues. However, MR examinations are inherently qualitative and not quantitative. The range of the pixel values in MR images depends on factors that have more to do with the scanner hardware and software than the actual tissue being imaged, i.e. the images are inherently qualitative. Other imaging modalities, like CT or PET, give interpretable values, reflecting e.g. tissue electron density in CT\(^15\), or tracer uptake in PET\(^16\). In order to compare values from different examinations, or to base a diagnosis on the values of pixels, they have to reflect some property of the underlying tissue. There are several quantitative measurement strategies of interest when studying the properties of tumors. Two methods, dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted imaging (DWI), have been studied in this thesis.

The measurement of perfusion can be important when characterizing the properties of a tumor\(^17\)–\(^18\). DCE-MRI uses a contrast agent (CA) to measure the permeability of vessels, by studying how much and how quickly the CA
leaves the blood and enters the surrounding tissue. A highly permeable vasculature can be an effect of abnormal cell growth in tumors, where the vasculature is often malformed and disorganized. The examination procedure is quite straightforward; the patient is injected with the CA while in the scanner, and the region of the suspected malignancy is imaged continuously for 5–10 minutes. The signal intensity will increase due to the presence of the CA, and by studying the duration and magnitude of the change in intensity, information about the vasculature can be obtained.

The next step is to extract information about the tissues. This is far from straightforward, with many available analysis methods, and underlying physiological and pharmacokinetic models\textsuperscript{19–21}. Some models are non-parametric, and simply extract characteristics from the enhancement curve. They are easy to calculate, but do not in general convey detailed information about the underlying physiology. Parametric models assume some specific relation between the signal and parameters related to e.g. vascularity, cell density or blood volume. These models are more powerful, but are also much more complicated, see e.g. Sourbron \textit{et al.}\textsuperscript{21}. One step in many models is to estimate the CA concentration in the blood and tissues. This step is crucial to obtain reliable physiological parameters, but is notoriously difficult. The effect of the CA \textit{in vivo} (\textit{in vivo} relaxivity) and uncertainties in signal models, are two issues that make this task difficult. The work presented in Paper I is aimed at improving the CA quantification, using statistical methods to combine two aspects of the MRI data, magnitude and phase information.

DWI shows how easily water can move on a micro-scale in different tissues\textsuperscript{22,23}. Tumors often have a high cell density, and disorganized structure, which leads to restricted interstitial water movement\textsuperscript{24–29}. DWI is used extensively in diagnosis, treatment planning and follow-up\textsuperscript{30}. An increased cell density can be indicative of tumor growth, and DWI taken together with other MR images or findings from \textit{e.g.} biopsies, can help in diagnosis and grading of the tumor\textsuperscript{31–33}. Usually the maximum or mean diffusion value inside a suspected or confirmed tumor is used. Any spatial information regarding the diffusion restriction distribution is ignored.
This additional information might inform on properties of the tumor that could influence e.g. the probability of treatment response\textsuperscript{34} or tumor grading\textsuperscript{35,36}. The work presented in Paper II investigates how the spatial information in diffusion data can provide information regarding survival in patients with high-grade glioma.

One way to quantify the spatial distribution is to use texture analysis. Haralick \textit{et al.}\textsuperscript{37} proposed a method for extracting textural information from images in the early 1970s, and this method has been used in image analysis applications ranging from satellite data\textsuperscript{37–39} to food science\textsuperscript{40–42}. In recent years, the concept of radiomics\textsuperscript{43,44} and the interest in extracting more information from medical images has led to an increase in the number of publications using texture analysis in the medical arena, see Fig. 1.1. The Haralick texture features are computed based on the relation between values of neighboring pixels in an image. Prior to computing texture features, some preprocessing steps must usually be performed,
like reducing the number of gray levels in the image, a process called quantization\textsuperscript{45,46}. The resulting texture features are highly dependent on the quantization method, and cannot be considered quantitative, since they will change depending on the analysis method. The sensitivity of texture analysis to imaging parameters such as noise and resolution, and to analysis methods such as quantization, has been investigated in \textbf{Paper III}. In \textbf{Paper IV}, a modified set of texture features are proposed, that are much less sensitive to the analysis methods, while at the same time retaining most of the properties of the original features.

\section*{1.1 Aim}

MRI plays an important role in many aspects of the cancer treatment work flow; from diagnosis, to treatment planning and treatment follow-up. There are, however, still many areas where research is needed to further our understanding of the biological mechanisms of cancer, and how to capture them in an MRI examination. The aim of this thesis was to improve quantitative methods in MRI, applied to tumor characterization. An accurate contrast agent quantification is very important in the DCE-MRI analysis work flow. Using phase and magnitude information to improve this step has been one focus of this thesis. The application of texture analysis in medical imaging has been gaining a lot of interest. Investigating the strengths and weaknesses of these methods has been the other focus. More specifically, the work has been aimed to:

1. Improve the CA quantification accuracy in DCE-MRI by using phase and magnitude data
2. Evaluate the merits of texture analysis in clinical applications
3. Investigate shortcomings of current texture analysis methods using Haralick features
4. Develop more robust texture analysis features, to address the current shortcomings of texture analysis using Haralick features.
Chapter 2

Tumor biology

The term cancer is a collection of over 100 types of malignant neoplasms\textsuperscript{47}, which have some properties in common, like abnormal cell growth and the potential to invade other tissues. There are many causes of cancer, like smoking, poor dietary habits, exposure to radiation and certain infections. However, the underlying mechanisms are the same: a change in the genetic makeup of healthy cells.

Cells are constantly subjected to hazards in our environment, \textit{e.g.} radiation and chemicals. This occasionally causes damage to the cell DNA, a \textit{mutation}, in particular in cells with high rates of cell divisions, like epithelial cells, which are the cause of about 80\% of all cancers\textsuperscript{48}. Usually these damages are corrected by DNA repair mechanisms, or the cell undergoes programmed cell death, apoptosis, but occasionally, these mechanisms fail. In a cell with reduced DNA repair mechanisms, mutations can accumulate. If several mutations occur in genes that promote cell growth and inhibit cell division, the cell is on a path towards becoming a tumor cell.

At first, the cells increase in number and density, but have a normal cell organization. At some point down the line towards a cancer, the cells start to exhibit a disorganized growth, and finally they begin to lose the
specific characteristics and properties of the original cell type, they become poorly differentiated. However, some tumors lack the ability to invade neighboring tissue, or to metastasize. They are termed benign tumors, and are not considered cancerous. If the cells lose respect for boundaries to neighboring tissues, it is a malignant tumor, a cancer\textsuperscript{47}.

2.1 Malignant tumor characteristics

Hanahan \textit{et al.}\textsuperscript{47,49} define six properties, or hallmarks, in common in all cancers; self sufficiency in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. In the following sections, a description of these properties and how they can be measured using specific MRI techniques are presented.

2.1.1 Increased growth rate

As a consequence of the first two hallmarks of cancer, malignant cells divide at a rate higher than healthy tissue. The increased growth rate of cancer cells leads to amassing clusters of cells, tumors. Many tumors have an elevated pressure in the tumor bulk\textsuperscript{50}, due to cell growth in a confined space. Further, as the tumor grows, the internal organization of cells decreases\textsuperscript{51}. An effect of these two properties is the decreased ability of water molecules to move in the space between cells, see Figures 2.1 and 3.6. Water molecules move constantly due to their thermal energy, a phenomenon also known as Brownian motion. This random motion, and how it is affected by the cell density and tissue structure, can be quantified using diffusion weighted MRI, DW-MRI.
Figure 2.1 | Tumor characteristics. A schematic illustration of the characteristics of healthy cells, to the left, and a tumor growth to the right. The tumor has a higher density of cells, more erratic vasculature which is highly permeable and leaky. The tumor is heterogeneous, and consists of cells with different properties and mutations.

2.1.2 Vascular generation

Another property of cancer cells is their ability to form their own blood supply, a process called angiogenesis. If a tumor without blood circulation is to grow larger than about 1-2 mm in diameter\textsuperscript{52} it will need to generate a vascular support to facilitate supply of oxygen and nutrients, as well as to remove waste products\textsuperscript{53}. However, the blood vessel development in tumors is not a controlled process\textsuperscript{54}, the blood vessels are immature and leaky\textsuperscript{55} and the permeability to large molecules is high\textsuperscript{56}. These features can be assessed using dynamic contrast enhanced (DCE) MRI. In a DCE-MRI exam, a contrast agent is injected in the blood stream of the patient, and the rate of blood leakage due to the lack of vascular integrity can be assessed by the change in signal intensity in the tumor over time.
2.1.3 Heterogeneity

Within a tumor there can be cancer cells with different morphological and phenotypical properties such as metabolism, motility and proliferation\textsuperscript{57}. Tumor heterogeneity has been found in many types of cancer, including prostate, brain, breast, and head and neck cancers\textsuperscript{58}. If all cancer cells within a tumor were equally sensitive to the given therapy, a treatment that successfully kills tumor cells quicker than they divide would eventually lead to a cure\textsuperscript{59}. However, due to the heterogeneity of the tumor cells, some cells might be less affected by the treatment and can prevent a complete cure. The effect would be an initial reduction of the tumor, or response to the therapy, followed by a regrowth of the tumor cells that were not affected by the treatment\textsuperscript{59}. Thus, the tumor heterogeneity might affect the treatment strategies and outcome for many types of cancer. One way to assess tumor heterogeneity is to use texture analysis\textsuperscript{60,61}. This approach quantifies the local intensity variations in a region of interest, so that it is possible to identify regions with varying patterns and degree of heterogeneity.
Chapter 3

MRI physics and applications

MRI uses the magnetic properties of atomic nuclei to form images. This chapter will give a basic review of magnetic resonance imaging, from the underlying physics to imaging techniques. The main references for this chapter are Levitt\textsuperscript{62} and Hanson et al.\textsuperscript{63}.

3.1 Magnetic properties of matter

All matter is made up of atoms. An atom is a positively charged nucleus of protons and neutrons (nucleons), surrounded by a negatively charged cloud of electrons. MRI almost exclusively utilizes the hydrogen nucleus, \textit{i.e.} a proton, for imaging, so the following discussion will be focused on the properties of the proton.

Besides mass and electric charge, there are two intrinsic properties of the proton that are of special importance for MRI: spin and magnetic moment. Spin is the intrinsic angular momentum of a particle, so named because the particle behaves as if it is spinning around its own axis. This view has long been abandoned, spin is known to be an intrinsic property of the particle and not the result of the particle actually spinning, but
Figure 3.1 | Protons precessing under the influence of a magnetic field. The upper row shows three protons, in the absence of an external magnetic field. The arrows indicate the orientation of the spin. When an external magnetic field, $B_0$, is present, the protons begin to precess around the direction of the magnetic field. Without any external perturbations, the angle of the spin w.r.t. $B_0$ will remain unchanged.

the name still sticks. Protons are spin-1/2-particles, meaning that the spin quantum number of protons is $s = 1/2$. Analogous to classical mechanics, where a spinning charged particle will generate a magnetic moment, charged particles with an intrinsic angular momentum will have a magnetic moment. The magnetic moment is, roughly speaking, a description of how strongly a particle will interact with an external magnetic field. The stronger the magnetic moment, the stronger the torque will be for the particle to align to the external magnetic field.

However, when a torque acts on an object with angular momentum, the result is not a rotation to align the object with the direction of the torque. Instead, the object begins to precess around the direction of the torque forming a cone, as illustrated in Fig. 3.1. The angle between the spin axis and the external magnetic field does not change. The angular velocity $\omega$ of the precession is determined by the external magnetic field $B$ and the
gyromagnetic ratio $\gamma$:
\[
\omega = -\gamma B,
\]  
(3.1)
called the Larmor frequency. The gyromagnetic ratio is specific to each nucleus, and for a hydrogen nucleus it is $267.5 \times 10^6$ rad s$^{-1}$ T$^{-1}$ or 42.58 MHz T$^{-1}$. The minus sign in Eq. (3.1) implies that the rotation is in the clockwise direction around the magnetic field.

### 3.2 The MRI experiment

Let us consider a set of water molecules, H$_2$O, at room temperature. The thermal energy of the water is distributed between the kinetic translational and rotational energy, and the energy of the electron excitations (vibrational energy can be ignored at room temperature). The water molecules are moving and tumbling and colliding with each other, and when no external magnetic field is applied, the magnetic moment of the two hydrogen nuclei in each molecule are randomly distributed, so the net magnetization of the proton nuclei in water is zero. If we apply a magnetic field $B_0$ to the water, the hydrogen nuclei will experience a torque as long as they are not parallel with the external field. This torque will make the hydrogen nuclei precess around the direction of $B_0$, with the Larmor frequency. The net magnetization of the water is still zero, as the precession alone does not change the bulk magnetization. However, as the water molecules are constantly moving and colliding with each other, they will also experience the much weaker magnetic fields generated from the electron clouds surrounding the hydrogen and oxygen atoms. These fields are tiny compared to the magnetic field used in an MRI, but they still influence the precession of the hydrogen nuclei a small amount. The hydrogen nuclei will precess in cones around the net magnetic field, i.e. the total magnetic field experienced by each hydrogen nucleus. This field varies somewhat due to the tumbling and colliding, but one field component is always stationary, the external magnetic field. As the water molecules tumble around, it is ever so slightly more energetically favorable to be pointing in the general direction of the applied magnetic field.
This will skew the distribution of the spin orientations slightly, enough to magnetize the water by a small amount.

The net magnetization is tiny compared to the applied magnetic field, it is much too small to be measured. The trick used in NRM and MRI is to change the orientation of the net magnetization, and measure the magnetization in the transverse plane. This is achieved by applying a second magnetic field, $B_1$, which rotates at the Larmor frequency. The protons also precess at the Larmor frequency, so in the frame of reference of the hydrogen nuclei this is a stationary field. As the net magnetic field experienced by the hydrogen nuclei changes, the net magnetization of the water effectively starts precessing around $B_1$ as well. The effect is a spiraling of the net magnetization from being parallel with $B_0$, to having a gradually larger component in the $x$-$y$ plane, as illustrated in Fig. 3.2. By timing the duration of $B_1$ just right, it is possible to set the net magnetization to any desired angle with respect to the main magnetic field. This angle is referred to as the flip angle (FA). The signal is measured in the $x$-$y$ plane, where the rotating magnetization induces a current in coil elements tuned to the Larmor frequency. A FA of 90° will induce a large signal, whereas small FA will give a weaker signal response.

### 3.2.1 Spin relaxation

After application of the $B_1$ field, a component of the net magnetization of the water is in the transverse plane, rotating at the Larmor frequency around $B_0$. Without any interactions between hydrogen nuclei and other atoms and molecules, the magnetization would precess in the transverse plane almost indefinitely. However, the constant interaction between the hydrogen nuclei and the surrounding magnetic field fluctuations from other molecules and from local variations in $B_0$ affects the net magnetization in two ways, described in the following sections.
Figure 3.2 | The effect on the net magnetization from applying a rotating $B_1$ field in the $xy$-plane. The net magnetization vector starts precessing around the rotating $B_1$ component. The result is a spiral (blue line), from an angle of $0^\circ$ with respect to $B_0$, past the $xy$-plane at $90^\circ$, to an inversion of the net magnetization at $180^\circ$ and all the way back to a magnetization parallel to $B_0$. The resulting flip angle is determined by the timing of $B_1$. The measured signal is the component in the $x$-$y$ plane (orange line).

Transverse relaxation

The transverse relaxation is a process in which the magnetization in the transverse plane decays due to dephasing of the spins. As stated earlier, each hydrogen nucleus experiences a slightly different magnetic field due to perturbations from neighboring molecules and from neighboring atoms within the molecule. This will affect the Larmor frequency of each hydrogen nucleus, and with time the hydrogen nuclei will lose phase coherence. On average, they will still be precessing with the same frequency, but they will not be in sync, and the net magnetization, and thus also the measured signal, will decay over time, see Fig. 3.3. This process is called transverse relaxation,

The transverse relaxation is dependent on the medium in question. Hy-
Transverse relaxation

The gray region in the circles represents the distribution of phase in an ensemble of spins, with a magnetic component in the xy-plane. The phase coherence is gradually lost, which leads to a diminishing magnetization in the xy-plane.

Hydrogen nuclei bound to a larger molecule, or to a solid, will dephase faster, since each hydrogen nucleus will experience a local magnetic perturbation for a longer period of time. Table 3.1 shows transverse relaxation times for a number of tissues and substances. The transverse relaxation in enamel or cortical bone is extremely short, making these tissues very difficult to image using MRI.

Longitudinal relaxation

The longitudinal relaxation is the same process as described in Section 3.2 for spins aligning with the main magnetic field, this is a gradual buildup of the longitudinal net magnetization see Fig. 3.4. It is slightly more energetically favorable to be precessing with the cone pointing anti-parallel to $B_0$, and hence there will be a gradual buildup of a slight magnetization of the water again. This process is in general slower than the transverse relaxation. The longitudinal relaxation also depends on the medium in which the hydrogen nuclei is bound, but not in the same, simple manner as for the transverse relaxation. Simply put, the longitudinal relaxation is the shortest if the molecules tumble and collide in the same time scale as the Larmor frequency.
Table 3.1 | Longitudinal and transverse relaxation times. Relaxation times at 1.5 T for different tissues.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Longitudinal relaxation, $T_1$ [ms]</th>
<th>Transverse relaxation, $T_2$ [ms]</th>
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<tbody>
<tr>
<td>Blood</td>
<td>1441 ± 120 $^{64}$</td>
<td>290 ± 30 $^{64}$</td>
</tr>
<tr>
<td>White matter</td>
<td>615 ± 12 $^{65}$</td>
<td>69 ± 2 $^{65}$</td>
</tr>
<tr>
<td>Gray matter</td>
<td>1124 ± 50 $^{64}$</td>
<td>95 ± 8 $^{64}$</td>
</tr>
<tr>
<td>Liver</td>
<td>576 ± 30 $^{66}$</td>
<td>46 ± 6 $^{66}$</td>
</tr>
<tr>
<td>Prostate</td>
<td>1317 ± 85 $^{66}$</td>
<td>88 ± 1 $^{66}$</td>
</tr>
<tr>
<td>Muscle, Skeletal</td>
<td>1008 ± 20 $^{64}$</td>
<td>44 ± 6 $^{64}$</td>
</tr>
<tr>
<td>Dental enamel</td>
<td></td>
<td>0.07 $^{67}$</td>
</tr>
<tr>
<td>Cortical bone</td>
<td>130 $^{67}$</td>
<td>0.46 ± 0.04 $^{67}$</td>
</tr>
</tbody>
</table>

Figure 3.4 | Longitudinal relaxation. The magnetization gradually recovers, from a net magnetization in the $xy$-plane after a 90° RF pulse.
3.3 Image formation

The previous section gave a brief overview of how a set of spins can be manipulated in the presence of two magnetic fields; the static $B_0$ field and the time-varying $B_1$ field. Now we will look at how we can use these fields to collect information about the system we are measuring and form images. The following sections will describe the simplest form of image acquisition, a 2D cartesian sampling of the signal generated from the precessing protons, using a single receiver coil. However, there are many ways to generate an image, e.g. 3D sampling, non-cartesian sampling, parallel imaging or compressed sensing\textsuperscript{68,69}.

3.3.1 Radio-frequency pulse

The $B_1$ field, used to tip the net magnetization on the transverse plane, is a radio-frequency (RF) magnetic pulse. The frequency of the $B_1$ field is tuned to the Larmor frequency of the system. The shape, magnitude and duration of the pulse varies, depending on the desired effect on the spins. In general, the integral of the RF pulse amplitude over time determines the flip angle. By increasing the duration or the amplitude of the RF pulse, any flip angle can be achieved\textsuperscript{68}.

If the $B_1$ field is not spatially homogeneous, the flip angle will vary with position. This can cause a variation in intensity in the image, reduced signal to noise ratio, or incomplete fat suppression\textsuperscript{68}. The longitudinal relaxation time $T_1$ can be measured by acquiring images of the same region, with different flip angles\textsuperscript{70}. This is a common method for creating $T_1$ maps used in dynamic contrast enhanced MRI, described in Section 3.4.2. If the images suffer from inhomogeneous flip angles, the longitudinal relaxation times of the $T_1$ maps will not be accurate. To overcome this, the $B_1$ homogeneity can be measured\textsuperscript{71}, or a special type of RF pulse can be used, an adiabatic excitation pulse\textsuperscript{68}. A drawback of the adiabatic pulses is the increase in specific absorption rate, SAR, the rate of energy absorption from an RF field in the human body\textsuperscript{68}.
Figure 3.5 | Gradients applied in the acquisition of an axial 2D slice. A slice selection gradient is applied in the z direction at the same time as the RF pulse. The gradient makes the $B_0$ field vary in magnitude in the z direction, as indicated by the size of the arrows. Only spins in the section indicated in the left figure will be in resonance with the RF pulse, and will be flipped into the xy plane. A phase encoding gradient is applied in the y direction prior to readout. The $B_0$ field is pointing towards the reader, the arrows are seen from the top. The frequency encoding gradient is applied in the x direction, at the the same time as the signal is measured.

3.3.2 Gradients

If we want to form an image from the signal of the precessing spins, we need the signal to vary with position. This is achieved by using magnetic gradients. The magnetic gradients increase or decrease the magnitude of the main magnetic field $B_0$ in the x, y or z directions, see Fig. 3.5. This means that the Larmor frequency will have a spatial dependence, and the rate of precession will be different depending on position. There are in general three types of gradients with different functions when imaging a 2D slice; slice selection gradient, phase encoding gradient and readout or frequency encoding gradient.

The slice selection gradient is applied at the same time as the radio-frequency pulse. This gradient prevents all spins in the system to be influenced by the RF pulse. Only spins in the spatial position where the RF pulse matches the Larmor frequency will be affected, see Fig. 3.5.

Readout gradient If we apply a magnetic gradient that varies the mag-
plitude of $B_0$ in one direction of the $xy$ plane, for example $x$ direction, while we detect the signal in the transverse plane, we will measure a sum of many different frequencies, depending on where in the scanner the signal originated, see Fig. 3.5. This is called frequency encoding, and the gradient is usually referred to as the readout gradient.

**Phase encoding gradient** Applying a readout gradient in the $x$-direction will only give spatial information in one dimension. To gain information in the $y$-direction we cannot simply apply the $y$-gradient simultaneously; it would be impossible separate the signal from spins with mirrored positions in the $x$ and $y$ directions. The solution is to add a second gradient in the $y$ direction prior to turning on the readout gradient. The effect of this gradient is to add a spatially dependent phase in the $y$ direction. This process must be repeated many times, and each time a different phase is added. The net result is a signal that has a unique combination of phase difference and frequency for every point in space in the transverse plane. Now the signal is spatially encoded, and it is possible to convert the signal to an image.

### 3.3.3 K-space

When the readout gradient is applied and the signal is acquired, the data is stored in a row of a matrix. Each row represents one readout, with a specific phase encoding. This is the raw data from the MR scanner. Since each position in the scanner has a uniquely associated frequency and phase, due to the gradients, the resulting signal is in the spatial frequency domain, and the raw data is said to be in *k-space* ($k$ is the standard notation for wavenumbers). In order to calculate an image from this data, we need to convert the spatial frequencies to intensities in an image. This is done using the Fourier transform,

$$
\mathcal{F}^{-1}\{\text{k-space}\} \rightarrow \text{image} \quad (3.2)
$$

$$
\mathcal{F}\{\text{image}\} \rightarrow \text{k-space} \quad (3.3)
$$

where $\mathcal{F}$ is the Fourier transform and $\mathcal{F}^{-1}$ is the inverse Fourier transform.
3.4 Pulse sequences

A pulse sequence is a set of RF pulses and gradients that will produce a specific type of image. The timing of the RF pulses and the gradients with respect to the transverse and longitudinal relaxations can produce images that e.g. suppress signal from fat, suppress signal from water, separate signals from water and fat, generate contrast between tissues with different transverse relaxation (T$_2$-weighted) or generate contrast between tissues with different longitudinal relaxation (T$_1$-weighted), to give a few examples. There are two imaging techniques that have been used extensively in this thesis, DWI and DCE-MRI, which will be described in more detail below.

3.4.1 Diffusion weighted imaging

As discussed in Chapter 2, malignant tumors have a higher density of cells and the tissues are more disorganized than healthy tissue. As a consequence, water molecules between cells in a tumor are generally less mobile than molecules in the surrounding healthy tissue, see Fig. 3.6. MRI can be used to measure the random movement of water molecules, diffusion, to assess the cellular density. To measure water diffusivity, two extra gradients are added to a T2-weighted spin echo pulse sequence, before and after the refocusing 180° RF pulse$^{22}$. The effect of the first diffusion gradient, is to add a phase to the protons of the water molecules depending on their position. Then, a 180° RF pulse is applied, which effectively inverts the phase from the first diffusion gradient, after which an identical diffusion gradient is applied. If there has been no movement of the water molecules between the first and second diffusion gradients, there will be no net phase added to the molecules. The second gradient will cancel the effect of the first gradient. However, the greater the net displacement of each water molecule between the first and second gradients, the more phase will be added, which effectively reduces the signal. A diagram showing the principles of a diffusion sequence, with the effect of two compartments of water with different diffusivity can be
Figure 3.6 | Diffusion of water can be impeded by cell density. In tumors (to the right in the figure), higher cell density and more disorganized tissues impede water movement, compared to healthy tissue (to the left). By measuring the net displacement of water over time, the mean diffusivity of water can be estimated. A low mean diffusivity can be an indication of a malignant tumor.

The amount of diffusion weighting in the image can be described by

$$S = S_0 e^{-\gamma^2 \delta^2 (\Delta - \frac{\delta}{3}) g^2 D} = S_0 e^{-bD},$$

(3.4)

where

$$b = -\gamma^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right) g^2,$$

(3.5)

$\gamma$ is the gyromagnetic ratio, $\delta$ and $\Delta$ are timings of the pulse sequence, shown in Fig. 3.7, $g$ is the gradient amplitude, and $D$ is the diffusion coefficient which describes how easily the water moves. By increasing the $b$-value, the diffusion weighting in the resulting image will increase. This means that signals from regions with high water mobility will diminish, while regions with low water mobility will be less affected. This model assumes that the duration, $\delta$, of the diffusion gradient is short enough so that the molecular motion can be neglected.
Figure 3.7 | The diffusion gradients and the effect on water hydrogen spins.
A simplified pulse sequence diagram, showing only the RF pulses and the diffusion gradients, together with the spins in high mobility and low mobility regions. For stationary spins, the phase added by the two diffusion gradients will cancel, giving a high signal. Moving spins will acquire a phase, depending on the net movement between the application of the gradients, which leads to a decreased signal. $\delta$ and $\Delta$ are the durations of the different parts of the diffusion sequence and $g$ is the gradient amplitude, they determine the amount of diffusion weighting in the resulting image.

So far, the direction of the diffusion gradients has been neglected. However, water mobility can be directional dependent due to structures or fibers in the tissues, a phenomenon called anisotropy. Because of the anisotropy, the measured diffusion coefficient can be very dependent on the direction of the gradients. Therefore, it is more appropriate to talk about the apparent diffusion coefficient (ADC). Normally, the ADC is measured in three orthogonal directions, and the average value describes the mean ADC of the tissue. The resulting ADC map is in units of $\text{mm}^2/\text{s}$, which is a quantitative measurement.

Diffusion weighted imaging (DWI) is used extensively to identify and characterize tumors in many anatomical regions, including brain, prostate, cervix, breast, and liver, and to monitor treatment response. Figure 3.8 shows an example of a diffusion weighted image of a high-grade glioma in the right temporal lobe. Fig. 3.8a is a contrast enhanced T1-weighted image, Fig. 3.8b is a diffusion weighted image with $b = 800 \text{ s/mm}^2$, 

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Figure 3.8 | DWI in a brain tumor (a) shows a T1-weighted contrast enhanced image of a high grade glioma in the right temporal lobe. (b) shows a diffusion weighted image with \( b = 800 \text{ s/mm}^2 \). (c) shows the corresponding ADC map. Regions with low diffusivity have a low value in the ADC map. The solid arrow indicates the tumor. The hollow arrows show a region with low diffusivity.

and Fig. 3.8c shows the corresponding ADC map. In Fig. 3.8b, regions with low diffusivity are bright, and the corresponding ADC map is dark. The quantitative measurements retrieved from the ADC map allow for objective comparisons and evaluations, which makes DWI a very useful and attractive tool for investigating the properties of tumors.

3.4.2 Dynamic contrast enhanced MRI

For tumors without blood supply to grow larger than 1–2 mm in diameter, they need to grow their own blood supply for transport of oxygen, nutrients and waste products. As described in Chapter 2, the vessels are often leaky, a property which can be studied using perfusion measurements. Perfusion is the passage of blood through the capillary bed, where the nutrients and waste exchange between the blood and tissue occur. There are several techniques for studying perfusion using MRI, in this thesis I have focused on Dynamic contrast enhanced MRI, DCE-MRI.

The basic principle of DCE-MRI is to inject the patient with a contrast agent (CA), and study the subsequent T1 shortening from the leakage of the contrast agent into the tissues. A high local CA concentration will have a large impact on the T1 and the intensity of the signal, which indicates a region with high permeability. An overview of a DCE-MRI examination can be seen in Fig. 3.9.
Figure 3.9 | DCE-MRI of a glioma in the right temporal lobe. A DCE-MRI examination of a patient with a high grade glioma involves acquiring an image every 3-10 s for 5-10 minutes. The change in signal over time (shown in the curves on the right) is due to the amount of contrast agent that leaks from the blood plasma into the extravascular, extracellular space (EES). According to the Kety model, the transfer rate between the plasma and the EES is denoted $K_{\text{trans}}$, and is an indication of how permeable the vessels are. In healthy brain tissue, there is almost no contrast agent, due to an intact blood-brain barrier.

There are several models describing the exchange of contrast agent between the blood stream and the tissue. One of the most commonly used models is the extended Kety model\textsuperscript{72,73}, where two compartments are considered: the extravascular extracellular space (EES), and blood plasma. The exchange rate of contrast agent can be described by:

\begin{equation}
    v_e \frac{dC_e(t)}{dt} = K_{\text{trans}} [C_p(t) - C_e(t)],
\end{equation}

where $C_e$ is the CA concentration in the EES, $C_p$ is the CA concentration in plasma, $v_e$ is the fractional volume of the EES, and $K_{\text{trans}}$ is the volume transfer constant between the plasma and the EES. If we want to estimate the CA concentration in the tissue as a whole, $C_t$, we can assume that the concentration in tissue is the fractional concentration of the EES and the plasma combined, \textit{i.e.} $C_t = v_p C_p + v_e C_e$, where $v_p$ is the fractional volume of plasma. Putting this assumption in Eq. (3.6) and integrating
gives
\[ C_t(t) = v_p C_p(t) + K_{trans} \int_0^t C_p(\tau) \cdot \exp \left[ -\frac{K_{trans}(t - \tau)}{\nu_e} \right] d\tau. \] (3.7)

CA quantification

To estimate \( \nu_e, \nu_p \) and \( K_{trans} \) from MR images using Eq. (3.7), we must find a way to estimate the CA concentration in the tissue and the blood. The pulse sequence commonly used for DCE-MRI is the spoiled gradient echo (SPGR) sequence, which has the signal equation
\[ S(t) = S_0 \frac{1 - e^{-TR/T_1(t)}}{1 - e^{-TR/T_1(t)} \cos \theta} e^{-TE/T_2^*(t)}, \] (3.8)
where \( TR \) is the repetition time, \( \theta \) is the flip angle and \( TE \) is the echo time. The change in signal over time depends on the CA concentration through the reduced relaxation times, \( T_1 \) and \( T_2^* \). The relations between magnetic relaxation and the CA concentration are:
\[ \frac{1}{T_1(t)} = \frac{1}{T_{10}} + r_1 C(t), \] (3.9)
\[ \frac{1}{T_2^*(t)} = \frac{1}{T_{20}^*} + r_2^* C(t), \] (3.10)
where \( T_{10} \) is the longitudinal relaxation in the absence of the CA, \( T_{20}^* \) is the transverse relaxation in a gradient echo sequence, in the absence of the CA, \( r_1 \) and \( r_2^* \) are the relaxivities of the CA, and \( C \) is the CA concentration. Usually, we can assume that \( TE \ll T_2^*(t) \), and the last term in Eq. (3.8) is dropped.

To measure the CA concentration using Eqs. (3.8) and (3.9), \( T_{10} \) and \( S(0) \) must be known. \( S(0) \) is measured prior to the injection of the CA, and is referred to as a baseline measurement. \( T_{10} \) can also be measured prior to the injection of the CA, or a standard reference value for the tissue of interest can be used\(^{74}\).
It is deceptively simple to assume that we can find the CA concentration through Eqs. (3.8) and (3.9), if we know $T_{10}$ and $S(0)$. There are, however, sources of error that makes CA quantification a challenge.

The relaxivity, $r_1$, of the CA varies with pH, temperature, magnetic field strength and the surrounding macromolecular content. At high CA concentrations, found in plasma at the bolus peak, the assumption $T E \ll T^*_2(t)$ might not be valid anymore, and the transverse relaxivity, $r^*_2$ comes into play as well. Blood has been shown to have a non-linear relationship between $1/T^*_2$ and CA, and differ a lot from water.

Another source of error is the RF spoiling. Equation (3.8) assumes a perfect spoiling between successive excitations, i.e. that the transverse magnetization is destroyed. The RF spoiling normally used in SPGR sequences can be insufficient, and Eq. (3.8) might not be valid. This will have an impact on the CA quantification. Further, inhomogeneous flip angles across the image can introduce errors in the $T_1$ estimation, if using the variable flip angle method, and errors when Eq. (3.8) is inverted.

Many of the problems of quantifying CA concentration using MR images can be circumvented by using the phase information. The MR signal, acquired from an inverse Fourier transform of k-space, is complex, and for most MR applications the magnitude of the complex data is used, the phase information is discarded. However, there is a simple linear relationship between the phase and the contrast agent concentration. The difficulty in using the phase to quantify CA concentration lies in the fact that it is nonlocal; the phase is a convolution between the underlying CA concentration and the magnetic field from a dipole. Finding the CA concentration by deconvolving the phase is an ill-posed problem. There are solutions for certain geometries, such as straight cylinders, or to calculate the susceptibility through multiple orientation sampling, but it is difficult to find a general solution to incorporate phase and magnitude information when quantifying the CA.
Chapter 4

Texture analysis

As discussed in Chapter 2, as tumors develop, there can be multiple genotypes present within the same tumor, exhibiting differences in metabolism, motility and proliferation. Tumor heterogeneity can affect the therapeutic response, and it can be difficult to identify this heterogeneity from small biopsy samples. Texture analysis of MR images is a promising method for analyzing the heterogeneous properties of tumors in a non-invasive way.

4.1 What is texture?

Texture usually refers to properties of a surface. A surface can be e.g. smooth, rough, coarse or fine to the touch. This is determined by how much and how quickly the surface changes elevation under our fingertips. Variations with high spatial frequencies, like the fine threads that composes a silk cloth will be perceived as smooth, whereas variations with a low spatial frequency, like the fibers in a wooden plank will be perceived as rough. The difference between the high and low points will also affect the sensation of the material. By sanding the plank, the difference between the high and low points are reduced, and it will feel
smoother to the touch, although the distance between fibers have not changed.

Variations that are larger than our finger tips will not be perceived as texture, but as a curvature of the surface. We do not describe a piano keyboard as rough, although it changes elevation drastically with a low spatial frequency.

Analogous to our sensation of surface texture, the texture of images can also be defined. In this case, the texture describes how quickly and drastically gray levels in the image changes between neighboring pixels or voxels. We can compare adjacent pixels, or any pairs of pixels in the image, but if we start to compare pixels over large distances in the image we might not be analyzing texture, but larger features in the image.

There are several approaches to quantifying image texture, such as Gabor filters\textsuperscript{83}, local binary patterns\textsuperscript{84} and wavelets\textsuperscript{85}. In this thesis I have focused on a method introduced by Haralick in 1973\textsuperscript{37}, where texture features are defined by first creating a gray level co-occurrence matrix, GLCM, which counts how often every combination of gray levels pairs occur as neighbors within an image. From the GLCM we can calculate texture features of the image, describing e.g. contrast (large differences in neighboring pixels) or homogeneity (small differences in neighboring pixels).

### 4.2 GLCM

The gray level co-occurrence matrix, GLCM, is a matrix that counts the co-occurrence of neighboring gray levels in the image, or the region of the image from which the GLCM is created. The GLCM is a square matrix that has the dimension of the number of gray levels in the region of interest (ROI). The GLCM acts like a counter for every combination of gray level pairs in the image. The GLCM is constructed by iterating through each voxel in the image and comparing its value (the reference value) to the neighbor gray level in a specific direction (the neighboring value). The
Figure 4.1 | A description of how Haralick’s texture features are computed.

In a 4×4 image ROI, three gray levels are represented by numerical values from 1 to 3. The GLCM is constructed by considering the relation of each voxel with its neighborhood. In this example, we only look at the neighbor to the right. The GLCM acts like a counter for every combination of gray level pairs in the image. For each voxel, its value and the neighboring voxel value are counted in a specific GLCM element. The value of the reference voxel determines the column of the GLCM and the neighbor value determines the row. In this ROI, there are two instances when a reference voxel of 3 “co-occurs” with a neighbor voxel of 2 (indicated in solid, blue), and there is one instance of a reference voxel of 3 with a neighbor voxel of 1 (indicated in dashed, red). The normalized GLCM represents the frequency or probability of each combination to occur in the image. The Haralick texture features are functions of the normalized GLCM, where different aspects of the gray level distribution in the ROI are represented. For example, diagonal elements in the GLCM represent voxels pairs with equal gray levels. The texture feature “contrast” gives elements with similar gray level values a low weight but elements with dissimilar gray levels a high weight.

neighboring voxels can be defined arbitrarily, but is usually set to the closest voxel in one or more directions. For clarity, in this discussion it will be initially set to the voxel to the right of the reference voxel, which can be expressed as the (1,0) neighbor, 1 pixel in the x direction and 0 pixels in the y direction, see Fig. 4.1.

The GLCM does not track the gray level values on a voxel basis, but on a gray level basis. This means that the size of the GLCM is determined by the number of gray levels in the image, not the number of voxels. Each element in the GLCM is a counter for a specific combination of gray
values of the reference and neighbor voxels in the image. The value of
the reference voxel determines the row, and the value of the neighboring
voxel determines the column.

To avoid directional dependence, the GLCM is usually constructed in the
“forward” and “backward” direction, i.e. the (1,0) and (-1,0) neighbors in
this example. This will make the GLCM symmetric, since the reference and
neighbor voxel values will switch places in the two directions. Note that
a GLCM created using the (-1,0) neighbor is the transpose of the GLCM
created using the (1,0) neighbor. A symmetric GLCM can be obtained by
creating the GLCM in one direction and adding its transpose to itself. It
can now be called a horizontal GLCM rather than a right or left neighbor
GLCM.

It is common to compute GLCMs in the horizontal, vertical and two
diagonal directions, in the case of adjacent neighbors, and summing the
GLCMs. This GLCM will not have any directional dependence at all. This
can of course be done for neighbors that are not adjacent as well, like the
16 pixels that are two pixels from the reference voxel.

4.2.1 Quantization

As stated in the previous section, and illustrated in Fig. 4.1, the size of
the GLCM is determined by the number of gray levels in the image. The
number of gray levels in an image can be in the thousands, or tens of
thousands, making the GLCM very large, and sparse. To limit the size
of the GLCM, it is common to quantize the image prior to creating the
GLCM. The quantization is a transform, mapping the voxel values in the
image or ROI, with initial gray level range \([a,b]\) to \([1,N]\) where \(N\) is the
number of gray levels,

\[
 \varphi : [a, b]^{M \times K} \rightarrow [1, N]^{M \times K}.
\]

The importance of this process is illustrated in Fig. 4.2, where a quanti-
zation is applied on an image, with the same number of gray levels but
with different minimum and maximum values \([a,b]\) selected. The texture
in the tumor, dashed outline, is very different.
Figure 4.2 | The effect of using different minimum and maximum values when quantizing the image. The images show how different minimum and maximum values influence the result when quantizing the original image, prior to constructing the GLCM. (a) shows the original image with 4096 gray levels. In (b) the image has been quantized to 8 gray levels, and the minimum and maximum gray levels have been set to that of the ROI, dashed outline. In (c), the image has been quantized to 8 gray levels and minimum and maximum gray levels have been set based on the entire image. There are large regions of uniform gray levels in (c), the texture is very different compared to (b), and the only difference is how the maximum and minimum gray levels were chosen.

4.2.2 Normalization

The final step is to normalize the GLCM, according to

\[ p(i, j) = \frac{P(i, j)}{\sum_{i,j}^N P(i, j)}. \]

The normalized GLCM does not represent the number of neighboring voxels, but the probability of the voxels in an image to have a specific gray level co-occurrence.

4.3 Haralick texture features

From the GLCM we can compute texture features. To understand the idea behind the texture features, some properties of the GLCM will be clarified:
1. It has the same number of rows and columns as the number of gray levels in the quantized image.

2. Diagonal elements describe neighbor pairs with the same voxel values.

3. Elements far from the diagonal describe neighbor pairs with very different voxel values.

By e.g. summing the diagonal elements, we obtain the fraction of voxel neighbors in the image with identical values. This property can be interesting, but we miss out on information regarding the other voxel neighbors in the image. Most Haralick features are weighted sums of the GLCM matrix, with the weights emphasizing different properties of the image. Contrast, for example, is defined as:

$$\text{Contrast} = \sum_{i=1}^{N} \sum_{j=1}^{N} (i - j)^2 p(i, j),$$

(4.1)

where the sum is weighted by the squared distance to the diagonal, \((i - j)^2\). Elements on the diagonal will be given a weight of zero, and elements far off the diagonal will be given a high weight. By comparing this property between two images we can determine which image has the largest differences between neighboring voxels.

In a similar way many properties of the image can be computed. The texture features used in papers II – III are described in Table 4.1 and Table 4.2.
<table>
<thead>
<tr>
<th>Notation</th>
<th>Meaning</th>
<th>Note</th>
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<td>( p(i, j) )</td>
<td>Element ( i, j ) in the GLCM</td>
<td></td>
</tr>
<tr>
<td>( N )</td>
<td>Number of gray levels</td>
<td></td>
</tr>
<tr>
<td>( p_x(i) )</td>
<td>( \sum_{i=1}^{N} p(i, j) )</td>
<td>Equal for symmetric GLCM</td>
</tr>
<tr>
<td>( p_y(j) )</td>
<td>( \sum_{i=1}^{N} p(i, j) )</td>
<td></td>
</tr>
<tr>
<td>( \mu_x )</td>
<td>( \sum_{i=1}^{N} \frac{i}{N} \cdot p_x(i) )</td>
<td>Equal for ( \mu_x ), symmetric GLCM</td>
</tr>
<tr>
<td>( \mu_y )</td>
<td>( \sum_{j=1}^{N} \frac{j}{N} \cdot p_y(j) )</td>
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<td>( \sigma_x^2 )</td>
<td>( \sum_{i=1}^{N} (i - \mu_x)^2 \cdot p_x(i) )</td>
<td>( \sigma_x^2 ), Equal for symmetric GLCM</td>
</tr>
<tr>
<td>( \sigma_y^2 )</td>
<td>( \sum_{j=1}^{N} (j - \mu_y)^2 \cdot p_y(j) )</td>
<td></td>
</tr>
<tr>
<td>( p_{x+y}(k) )</td>
<td>( \sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j) )</td>
<td>( k = 2, 3, \ldots, 2N )</td>
</tr>
<tr>
<td>( p_{x-y}(k) )</td>
<td>( \sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j) )</td>
<td>( k = 0, 1, \ldots, N - 1 )</td>
</tr>
<tr>
<td>( HX )</td>
<td>( - \sum_{i=1}^{N} p_x(i) \cdot \log p_x(i) )</td>
<td>Equal for symmetric GLCM</td>
</tr>
<tr>
<td>( HY )</td>
<td>( - \sum_{i=1}^{N} p_y(i) \cdot \log p_y(i) )</td>
<td></td>
</tr>
<tr>
<td>( HXY )</td>
<td>( - \sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j) \cdot \log p(i, j) )</td>
<td></td>
</tr>
<tr>
<td>( HXY1 )</td>
<td>( - \sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j) \cdot \log [p_x(i) \cdot p_y(j)] )</td>
<td></td>
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<tr>
<td>( HXY2 )</td>
<td>( - \sum_{i=1}^{N} \sum_{j=1}^{N} p_x(i) \cdot p_y(j) \cdot \log [p_x(i) \cdot p_y(j)] )</td>
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Table 4.2 | Haralick texture features computed from GLCMs. There was an error in the definition of *Sum variance* in Haralick *et al.*\textsuperscript{37}, which has been corrected.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Equation</th>
<th>Ref.</th>
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<tr>
<td>Autocorrelation</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} (i \cdot j) p(i, j)$</td>
<td>38</td>
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<tr>
<td>Cluster Prominence</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} (i + j - 2\mu)^3 p(i, j)$</td>
<td>37</td>
</tr>
<tr>
<td>Cluster shade</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} (i + j - 2\mu)^3 p(i, j)$</td>
<td>37</td>
</tr>
<tr>
<td>Contrast</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} (i \cdot j)^2 p(i, j)$</td>
<td>37</td>
</tr>
<tr>
<td>Correlation</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} \frac{(i \cdot j) p(i, j) - \mu_x \mu_y}{\sigma_x \sigma_y}$</td>
<td>37</td>
</tr>
<tr>
<td>Difference entropy</td>
<td>$-\sum_{k=0}^{N-1} p_{x-y}(k) \log p_{x-y}(k)$</td>
<td>37</td>
</tr>
<tr>
<td>Difference variance</td>
<td>$\sum_{k=0}^{N-1} (k - \mu_{x-y})^2 p_{x-y}(k)$</td>
<td>37</td>
</tr>
<tr>
<td>Dissimilarity</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N}</td>
<td>i - j</td>
</tr>
<tr>
<td>Energy</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j)^2$</td>
<td>37</td>
</tr>
<tr>
<td>Entropy</td>
<td>$-\sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j) \log p(i, j)$</td>
<td>37</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} \frac{p(i, j)}{1 + (i - j)^2}$</td>
<td>38</td>
</tr>
<tr>
<td>Information measure of correlation 1</td>
<td>$\frac{HXY - HXY1}{\max(HX, HY)}$</td>
<td>37</td>
</tr>
<tr>
<td>Information measure of correlation 2</td>
<td>$\sqrt{1 - \exp[-2(HXY2 - HXY1)]}$</td>
<td>37</td>
</tr>
<tr>
<td>Inverse difference</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} p(i, j) \log p(i, j)$</td>
<td>37</td>
</tr>
<tr>
<td>Maximum probability</td>
<td>$\max p_{x+y}$</td>
<td>38</td>
</tr>
<tr>
<td>Sum average, $\mu_{x+y}$</td>
<td>$\sum_{k=2}^{2N} kp_{x+y}(k)$</td>
<td>37</td>
</tr>
<tr>
<td>Sum entropy</td>
<td>$-\sum_{k=2}^{2N} p_{x+y}(k) \log p_{x+y}(k)$</td>
<td>37</td>
</tr>
<tr>
<td>Sum of squares</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} (i - \mu)^2 p(i, j)$</td>
<td>37</td>
</tr>
<tr>
<td>Sum variance</td>
<td>$\sum_{k=2}^{2N} (k - \mu_{x+y})^2 p_{x+y}(k)$</td>
<td>37</td>
</tr>
</tbody>
</table>
4.4 Gray level invariant GLCM

There are a few shortcomings of the Haralick texture features. Texture features calculated from GLCM matrices of different sizes from the same image will give different texture feature values. For most texture features it is easy to see why this happens. Consider the contrast texture feature again. It is weighted by the distance from the diagonal, so the larger the GLCM, the farther away from the diagonal we can find elements in the GLCM. The contrast texture feature value will depend on the size of the GLCM, even though it is computed from the same image. Similar size dependences will be seen for most Haralick features, since they are defined in an analogous fashion.

To compare texture feature values from different images, the images must be quantized to the same number of gray levels and the same upper and lower value, as described in Paper III. To illustrate the effect of different quantizations, Fig. 4.3 compares the same image, quantized to different number of gray levels and different maximum values, and compare the texture features computed from the different GLCMs. As can be seen, some texture features are more sensitive to these variations than others.

To eliminate the texture feature value dependence of the GLCM size, some modifications to Haralick’s original features are suggested in Paper IV. The GLCM can be viewed as a discretization of a probability density function. In this interpretation, the features can be expressed as integrals over functions of this distribution:

\[
\int_0^1 \int_0^1 \phi(i, j, g(p^*)) \psi(p^*(i, j)) \, dj \, di, \tag{4.2}
\]

where \(p^*\) is the underlying probability density function, \(\psi\) is a function of the elements of the GLCM, \(\phi\) is a function of the indices and \(g\), where \(g\) is a vector-valued function of the GLCM. The integral in (4.2) can be approximated by a Riemann sum, getting us back to the original definition.
Figure 4.3 | Quantization effects on the image and selected texture features. The four images show the effect of using 8 and 128 gray levels to quantize the image, (the upper and lower row) and the effect of setting the maximum gray level to 10 000 and 30 000 (the left and right column), in an image where the dynamic range of the slice is 0 – 10 000, and the dynamic range of the entire volume is 0 – 30 000. The graphs on the right show how the texture features are affected by maximum values ranging from 10 000 to 30 000 for 8 and 128 gray levels. The graphs in the bottom show how texture features are affected by the number of quantization gray levels ranging from 8 – 128, for 10 000 and 30 000 gray levels.
of the texture features, with some minor changes:

\[
\int_0^1 \int_0^1 \phi(i, j, g(p^*)) \psi(p^*(i, j)) \, dj \, di \approx \sum_{i=1}^{N} \sum_{j=1}^{N} \phi\left(\frac{i}{N}, \frac{j}{N}, g(\bar{p}(i, j))\right) \psi(\bar{p}(i, j)) \Delta \Delta,
\]

where

\[\Delta = \frac{1}{N},\]

and

\[\bar{p}(i, j) = \frac{P(i, j)}{\sum_{i=1}^{N} \sum_{j=1}^{N} P(i, j) \Delta \Delta}.\]

By considering the texture features as a Riemann sum, we have to multiply the sum by a differential \(\Delta\), and normalize the GLCM such that its Riemann sum is 1. This is illustrated in Fig. 4.4. Definitions of the modified features can be found in Tables 4.3 and 4.4. Figure 4.5 shows a comparison of contrast, energy, entropy, homogeneity and autocorrelation between the original and the proposed invariant Haralick features. The original Haralick features in Figure 4.5 diverge with increasing GLCM size, whereas the invariant features quickly reach a limit.

The invariant features can be compared between different analyses, even though the size of the GLCM has changed. This is shown in Paper IV, where linear support vector machines (SVM) are used to classify images of a region of the cerebellum or a region of the prefrontal cortex using Haralick texture features. The regions used in this experiment are shown in Fig. 4.6. Twenty-four images from 9 subjects were used to train the SVMs, and 32 images from 10 different subjects were used in the test data set. Sixteen SVMs were trained on the original features, calculated from GLCM sizes of 8 – 128 in steps of 8. Another 16 classifiers were trained on the invariant features, for the same GLCM sizes. Each SVM was then used to classify the test data set, using features calculated for all GLCM sizes. The result can be seen in Fig. 4.7. The SVMs trained on the original features had a high accuracy when the training and the
test data set had similar GLCM sizes. 22% of the tests were significantly better than chance, 16% of all tests had an accuracy exceeding 90%, and 32% had an accuracy of 50%. The invariant features performed better than chance for 84% of all tests. 53% of all training and test data combinations had an accuracy exceeding 90%, and the lowest accuracy score was 62.5%.

It is obvious from Fig. 4.7 that the invariant features are insensitive to the number of gray levels used when calculating the texture features, if the lowest number of gray levels are avoided. This property means that the analysis is not restricted to a specific number of gray levels anymore, and it can be chosen on a per image basis, to minimize the noise in the GLCM. It could even be possible to use different number of gray levels when calculating different features from the same image. This could be useful if one feature converged slowly for a specific dataset, but the region of interest was small, in which case the number of gray levels should also be kept small. If the feature in question converges for a larger number of gray levels, a large GLCM could be used for this feature only, and still keep the GLCM smaller to avoid noise in the other features.
Figure 4.4 | A comparison between a standard GLCM and an invariant GLCM for different number of bins. Synthetic GLCMs generated as bivariate Gaussian distributions, for two different quantization levels, 16 and 24 gray levels. The elements of a standard GLCM sums to 1, so that the GLCM element values will decrease with increasing GLCM size. The invariant GLCMs are normalized to keep the total volume of the GLCM to 1, where each element is ascribed an area of $1/N^2$ units.
Figure 4.5 | A comparison between the original and the invariant features. The original features shown in Fig. 4.3 using the quantization limits of $[0, 10000]$ are shown to the left. The corresponding invariant Haralick features are shown to the right. The invariant features quickly reach a limit, and are independent of the number of gray levels.

Figure 4.6 | The regions of the brain used to test the invariant features in a classification model. Texture features were computed for a range of quantization gray levels from a region in the cerebellum (left) and a region in the prefrontal cortex (right).
Figure 4.7 | Heatmaps showing the accuracy of the SVMs. The horizontal axis shows the training data set gray levels, and the vertical axis the test data set gray levels, for the original features (left) and the invariant features (right). The dots indicate where the SVMs performed better than chance at $\alpha = 0.05$, Bonferroni corrected for $2 \times 16 \times 16$ tests.
Table 4.3 | Variables and notation used to compute the invariant Haralick features.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tilde{p}(i, j)$</td>
<td>Element $i, j$ in the GLCM</td>
</tr>
<tr>
<td>$N$</td>
<td>Number of gray levels</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>$\frac{1}{N}$</td>
</tr>
<tr>
<td>$\Delta_{x+y}$</td>
<td>$\frac{1}{2N-1}$</td>
</tr>
<tr>
<td>$\Delta_{ij}$</td>
<td>$\frac{1}{N^2}$</td>
</tr>
<tr>
<td>$\tilde{p}_x(i)$</td>
<td>$\sum_{j=1}^{N} \tilde{p}(i, j) \Delta$</td>
</tr>
<tr>
<td>$\tilde{p}_y(j)$</td>
<td>$\sum_{i=1}^{N} \tilde{p}(i, j) \Delta$</td>
</tr>
<tr>
<td>$\tilde{\mu}_x$</td>
<td>$\sum_{i=1}^{N} \frac{i}{N} \cdot \tilde{p}_x(i) \Delta$</td>
</tr>
<tr>
<td>$\tilde{\mu}_y$</td>
<td>$\sum_{j=1}^{N} \frac{j}{N} \cdot \tilde{p}_y(j) \Delta$</td>
</tr>
<tr>
<td>$\tilde{\sigma}_x^2$</td>
<td>$\sum_{i=1}^{N} \left( \frac{i}{N} - \tilde{\mu}_x \right)^2 \cdot \tilde{p}_x(i) \Delta$</td>
</tr>
<tr>
<td>$\tilde{\sigma}_y^2$</td>
<td>$\sum_{j=1}^{N} \left( \frac{j}{N} - \tilde{\mu}_y \right)^2 \cdot \tilde{p}_y(j) \Delta$</td>
</tr>
<tr>
<td>$\tilde{p}_{x+y}(k)$</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}(i, j) \Delta$</td>
</tr>
<tr>
<td>$\tilde{p}_{x-y}(k)$</td>
<td>$\sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}(i, j) \Delta$</td>
</tr>
<tr>
<td>$\overline{HX}$</td>
<td>$- \sum_{i=1}^{N} \tilde{p}_x(i) \cdot \log \tilde{p}_x(i) \Delta$</td>
</tr>
<tr>
<td>$\overline{HY}$</td>
<td>$- \sum_{i=1}^{N} \tilde{p}_y(j) \cdot \log \tilde{p}_y(j) \Delta$</td>
</tr>
<tr>
<td>$\overline{HXY}$</td>
<td>$- \sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}(i, j) \cdot \log \tilde{p}(i, j) \Delta_{ij}$</td>
</tr>
<tr>
<td>$\overline{HXY1}$</td>
<td>$- \sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}_x(i) \cdot \tilde{p}_y(j) \cdot \log \left[ \tilde{p}_x(i) \cdot \tilde{p}<em>y(j) \right] \Delta</em>{ij}$</td>
</tr>
<tr>
<td>$\overline{HXY2}$</td>
<td>$- \sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}_x(i) \cdot \tilde{p}_y(j) \cdot \log \left[ \tilde{p}_x(i) \cdot \tilde{p}<em>y(j) \right] \Delta</em>{ij}$</td>
</tr>
</tbody>
</table>
Table 4.4 | The invariant texture features computed from GLCMs. The table shows the modifications needed to make the features invariant to the number of gray levels. There was an error in the definition of *Sum variance* in Haralick et al.\(^{37}\), which has been corrected.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mod. Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autocorrelation</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} - \frac{j}{N} \right) \tilde{p}(i,j) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Cluster Prominence</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} + \frac{j}{N} - 2\mu \right)^3 \tilde{p}(i,j) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Cluster shade</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} + \frac{j}{N} - 2\mu \right)^4 \tilde{p}(i,j) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Contrast</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} - j \right)^2 \tilde{p}(i,j) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Correlation</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} - \tilde{\mu} \right) \left( \frac{j}{N} - \tilde{\mu} \right) \tilde{p}(i,j) \sigma_{x} \sigma_{y} \Delta_{ij} ]</td>
</tr>
<tr>
<td>Difference entropy</td>
<td>[ - \sum_{k=0}^{N} \tilde{p}<em>{x-y}(k) \log \tilde{p}</em>{x-y}(k) \Delta ]</td>
</tr>
<tr>
<td>Difference variance</td>
<td>[ \sum_{k=0}^{N} \left( k - \tilde{\mu}<em>{x-y} \right)^2 \tilde{p}</em>{x-y}(k) \Delta ]</td>
</tr>
<tr>
<td>Dissimilarity</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} - \frac{j}{N} \right)</td>
</tr>
<tr>
<td>Energy</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}(i,j)^2 \Delta_{ij} ]</td>
</tr>
<tr>
<td>Entropy</td>
<td>[ - \sum_{i=1}^{N} \sum_{j=1}^{N} \tilde{p}(i,j) \log \tilde{p}(i,j) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{\tilde{p}(i,j)}{1 + \left( \frac{i}{N} - \frac{j}{N} \right)^2} \Delta_{ij} ]</td>
</tr>
<tr>
<td>Information measure</td>
<td></td>
</tr>
<tr>
<td>of correlation 1</td>
<td>[ H_{XY} - H_{XY1} ] \frac{H_{XY1}}{\text{max}(H_{XY}, H_{XY1})} ]</td>
</tr>
<tr>
<td>of correlation 2</td>
<td>[ \sqrt{1 - \exp \left[ -2 \left( H_{XY2} - H_{XY} \right) \right]} ]</td>
</tr>
<tr>
<td>Inverse difference</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{\tilde{p}(i,j)}{1 + \left( \frac{i}{N} - \frac{j}{N} \right) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Maximum probability</td>
<td>[ \max \tilde{p}(i,j) ]</td>
</tr>
<tr>
<td>Sum average, ( \mu_{x+y} )</td>
<td>[ \sum_{k=2}^{2N} k \tilde{p}<em>{x+y}(k) \Delta</em>{i+j} ]</td>
</tr>
<tr>
<td>Sum entropy</td>
<td>[ \sum_{k=2}^{2N} \tilde{p}<em>{x+y}(k) \log \tilde{p}</em>{x+y}(k) \Delta_{i+j} ]</td>
</tr>
<tr>
<td>Sum of squares</td>
<td>[ \sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i}{N} - \mu \right)^2 \tilde{p}(i,j) \Delta_{ij} ]</td>
</tr>
<tr>
<td>Sum variance</td>
<td>[ \sum_{k=2}^{2N} (k - \mu_{x+y})^2 \tilde{p}<em>{x+y}(k) \Delta</em>{i+j} ]</td>
</tr>
</tbody>
</table>
Chapter 5

Summary of papers

5.1 Paper I

Combining Phase and Magnitude Information for Contrast Agent Quantification in Dynamic Contrast-Enhanced MRI Using Statistical Modeling


Aim: To investigate, using simulations, a method for improved contrast agent (CA) quantification in DCE-MRI using phase and magnitude information.

Method: A maximum likelihood (ML) estimator was developed to improve the contrast agent (CA) concentration estimates from magnitude data using both magnitude and phase information of a DCE-MRI image series. Signal models and pharmacokinetic (PK) models were used together with known relaxation times for different tissues in the head to generate synthetic DCE-MRI examinations. A number of simulations were performed to investigate the ability of the ML estimator to reduce bias and variance in the CA estimates with different amount of noise in the
data, corresponding to the range found using different coils.

**Result:** The root mean squared error in the bolus peak was reduced from 2.24 to 0.11 mM in the vessels, and from 0.16 to 0.08 mM in the tumor rim, for a noise level equivalent of a 12-channel head coil at 3T. No improvements were seen for tissues with small CA uptake, such as white matter.

**Conclusion:** Phase information reduces errors in the estimated CA concentrations. A larger phase response from higher field strengths or higher CA concentrations yielded better results. Issues such as background phase drift need to be addressed before this method can be applied *in vivo*.
5.2 Paper II

ADC texture – An imaging biomarker for high-grade glioma?


Aim: To investigate texture analysis of ADC images in conjunction with multivariate image analysis as a means for identification of pretreatment imaging biomarkers.

Method: Twenty Haralick texture features were computed in axial, coronal and sagittal projections from tumor regions in apparent diffusion coefficient (ADC) maps from 23 high-grade glioma patients. Principal component analysis was used to reduce the dimensionality from $3 \times 20$ texture features to 5 principal components.

Result: The first, third and fifth principal components could be used to separate the patients into two groups. Group I had a median survival of 1099 days, and the tumors exhibited a response to therapy three months after the end of treatment. Group II had a median survival of 345 days, and was a mixture of responders and non-responders.

Conclusion: Texture analysis of ADC maps acquired pretreatment appears to hold information on patient survival. These findings encourage further studies with a larger patient cohort.
5.3 Paper III

Haralick texture features from apparent diffusion coefficient (ADC) MRI images depend on imaging and pre-processing parameters

Brynolfsson P, Nilsson D, Torheim T, Asklund T, Thellenberg Karlsson C, Nyholm T, Garpebring A

Accepted for publication, Scientific Reports

Aim: To assess how sensitive Haralick texture features are to the choice of imaging and pre-processing parameters such as noise, resolution, ADC map construction, quantization methods and quantization bit depth.

Method: ADC maps from a glioma (GLI) data set with 72 tumors and a prostate cancer (PC) data set with 18 tumors were used in the study. Nineteen texture features were computed while varying resolution and noise in the ADC maps, the quantization method and the number of gray levels in the quantized ADC images. The choice of b-values was also varied when constructing the ADC maps in the glioma data set. Two-sample Kolmogorov-Smirnov tests were used to investigate if the texture feature distributions were significantly different when changing the investigated parameters.

Result: The number of gray levels in the quantized image significantly changed 18 of 19 features in the GLI data set and 16 of 19 features in the PC data set. Varying the noise changed all features in the GLI data set and 15 features in the PC data set. Different quantization methods changed 15 features in the GLI data set and 13 features in the PC data set. Varying the resolution changed 10 features in the GLI data set and 7 features in the PC data set. The choice of b-values did not affect any texture feature in the GLI data set.

Conclusion: Many or all texture features are sensitive to the amount of noise and resolution in the ADC map, and to the choice of quantization method and the number of gray levels in the quantized image. It is important to report imaging and pre-processing settings when reporting
results from texture analysis using Haralick features. Statistical models based on Haralick features should only be applied to data with similar noise and resolution characteristics.
5.4 Paper IV

Gray-level invariant Haralick texture features

Löfstedt T, Brynolfsson P, Asklund T, Nyholm T, Garpebring A

Aim: To develop texture features that are invariant to the number of gray levels in the image, and to evaluate the properties of the invariant features.

Method: By treating the gray level co-occurrence matrix, GLCM, as a discretized probability density function, instead of a probability mass function, the texture features can be computed as Riemann sums, which will be asymptotically independent of the quantization level. We trained linear support vector machines (SVM) to classify two regions from T1 weighted MRI images of the brain, using the original Haralick features and the invariant features, calculated from 8–128 quantization gray levels. Each SVM was then tasked to classify image regions from all quantization levels.

Result: The results showed that the invariant features approached a limit as N increased, and most original features values diverged with N. SVMs trained on the invariant features performed better than chance in 84 % of all tests, versus 22 % for SVMs trained on the original features.

Conclusion: We present a modification to Haralick texture features that makes them asymptotically invariant to the number of gray levels in the image. Statistical models using the invariant features can be constructed from images with very different quantization levels.
Chapter 6

Discussion and conclusions

Ideally, quantitative MRI has many attractive benefits such as repeatable measurements, interpretable results, and a substantially reduced risk of observer bias affecting the results. There are, however, challenges that need to be tackled to reap the rewards of quantitative measurements. In this thesis, the focus has been to improve two main areas of quantitative imaging; DCE-MRI and texture analysis of DW-MRI.

In Paper I, we used a maximum likelihood estimator to correct bias and reduce variance in CA quantification from magnitude data by combining phase and magnitude information in the estimation. This was a simulation study, and the method has not been tested in vivo. Most likely, motion correction and background phase drift must be applied to the in vivo data, since both induce a phase shift that is not connected to the CA. The method relies on the phase to correct errors in the magnitude estimate, so where there is little CA there will be a small phase shift, and thus not much extra information to use for correcting the magnitude estimate. Thus, the method was most successful for high CA concentrations and high field strengths, which gives high phase SNR. One application suitable for this framework might be data from 7 T scanners, where SAR limitations impose the use of local surface coils for spin excitations. The local transmit coils generate very non-uniform FA, which will result in a spatially
varying CA concentration estimates. Even for 1.5 T systems, where the phase response is too low to improve the CA quantification in the tumor, it will provide a more accurate estimate of arterial input function, something that will also improve the DCE analysis.

Paper II investigated the use of texture analysis to identify characteristics of ADC maps that could predict survival in patients with high grade gliomas. We could identify two groups of patients within our dataset with very different median survival time after diagnosis. Interestingly, the method did not fully separate progressive from regressive disease, but seemed to be a stronger predictor for survival. Patients in the group with a long median survival all had a regressive disease, but the group with shorter survival was a mixture between regressive and progressive disease. The texture data seem to provide additional prognostic information that is not reflected by surgical procedure or by age. This is an exciting prospect for further research.

Paper III showed that the selection of b-values did not affect any texture features from ADC images, but resolution, noise and the quantization steps influenced the results. This is supported by e.g. Mayerhoefer et al.\textsuperscript{87}, who studied how imaging parameters relating to resolution and SNR affected the texture features. It is clear that classification or prediction models based on texture features can only be applied to image data with very similar imaging characteristics such as noise and resolution, and the same preprocessing steps must be used on all data sets. It is not uncommon to omit the details of the texture analysis in the methods sections, which makes replications of the results very difficult. It is not simply the case that all texture features scale uniformly with resolution, noise, GLCM size or quantization method; the ratio between features will also change. From these results we can conclude that the Haralick texture features, as used and implemented today, is not a quantitative analysis method.

The invariant Haralick features presented in Paper IV addressed one of the problems identified in Paper III, the texture feature dependence of the number of quantization gray levels. The size of the region on which to perform the texture analysis can guide the choice of the quantization
gray levels. A small region cannot be analyzed with a large GLCM, it will become sparse and the texture features will reflect the spurious spikes in the sparse GLCM. On the other hand, a small GLCM used on a large region will reduce the finer texture as shown in Fig. 4.2. Texture features that are invariant to the GLCM size would allow for an individual choice of GLCM size for each region to be analyzed. Possibly, there could be an optimal GLCM size for a specific image that is different for different texture features. The invariant features would allow the use of different GLCM sizes for different texture features within the same region. Finally, the proposed features will take the Haralick texture analysis a lot closer to being considered a quantitative analysis method. A combination of Haralick feature values could now possibly be used to describe a unique texture, unlike the original Haralick features, where the GLCM size would be the strongest indicator of the texture values.
Chapter 7

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