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FUNCTIONAL IMAGING OF BREAST TISSUES
WITH MAGNETIC RESONANCE MAMMOGRAPHY

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Master Thesis

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ΠΕΡΙΛΗΨΗ

Η μαγνητική τομογραφία μαστών (MRM) είναι μια πολύ υποσχόμενη τεχνική, αφού προσφέρει απεικόνιση των μαστών με υψηλή διακριτική ικανότητα αλλά και εγγενή ικανότητα διάκρισης διαφόρων τύπων μαλακών ιστών, χωρίς τη χρήση ιοντίζουσας ακτινοβολίας.

Η προσθήκη δυναμικής απεικόνισης των ιστών του μαστού με τη χρήση παραμαγνητικής σκιαγραφικής ουσίας στο εξεταστικό πρωτόκολλο ισχυροποίησε τη μέθοδο αφού υπάρχει σημαντική διαφοροποίηση στην αιμοδυναμική συμπεριφορά ανάμεσα σε καλοήθεις και κακοήθεις παθήσεις λόγω του αγγειακού δικτύου που δημιουργούν οι μεταβολικές αναγκές των καρκινικών κυττάρων.

Υπολογιστικά συστήματα αυτόματης διάγνωσης που διατίθενται εμπορικά, πραγματοποιούν φαρμακοκινητική ανάλυση της δυναμικής συμπεριφοράς των ιστών του μαστού με χρήση μαθηματικών αλγορίθμων όπως ο αλγόριθμος τριών χρονικών σημείων (3TP). Από τέτοιες αναλύσεις εξάγονται ποσοτικές παράμετροι που έχουν ευθεία συσχέτιση με διάφορα χαρακτηριστικά της υποκείμενης παθολογίας και μπορούν να συγκριθούν με τα αποτελέσματα ιστολογικών μελετών. Παρόλα αυτά είναι γενικά αποδεκτό ότι για να επιτυχεί ακριβής υπολογισμός των παραμέτρων αυτών απαιτείται η επιλογή ειδικού εξεταστικού πρωτοκόλλου με μεγάλες απαιτήσεις σε χρονική διακριτική ικανότητα. Η επιλογή απλών μαθηματικών μοντέλων για την υπολογισμό συστημάτων ιστών και μολύνσεων με έμμεση συνάφεια με την παθολογία μας δίνει τη δυνατότητα να ελαχιστοποιήσουμε τον όγκο δεδομένων που παρέχει η εξέταση σε ένα σετ εικόνων και να κάνουμε τη διαδικασία της διάγνωσης πιο γρήγορη και ασφαλή από ό,τι παρουσιάζεται σήμερα στην κλινική ρουτίνα.

Η σειρά των εικόνων της δυναμικής μελέτης των εξετάσεων μαγνητικής τομογραφίας μαστών 55 ασθενών αναλύθηκαν για αυτή τη μελέτη. Ακτινολόγοι με εξειδίκευση στην εξέταση κατέταξαν όλες τις ανιχνευθείσες παθολογικές περιοχές κατά BIRADS. Έγινε προσέγγιση των πειραματικών τιμών των pixels των δυναμικών σειρών με ένα απλό διγραμμικό μοντέλο και εξαγωγαν χάρτες ποσοτικών παραμέτρων έκπλυσης σήματος (washout), χρόνου μέγιστης ενίσχυσης (time to peak) και ενίσχυσης (washin). Στη συνέχεια αυτές τις παράμετροι χρησιμοποιήθηκαν ως απόχρωση (Hue), κορεσμό (Saturation) και ένταση (Value) της χρωματικής κλίμακας HSV. Με αυτή την αντιστοίχιση δημιουργήθηκαν χάρτες λειτουργικής απεικόνισης οι οποίες και χρησιμοποιήθηκαν για το χαρακτηρισμό της παθολογίας. Για τον τελικό χαρακτηρισμό εκτιμήθηκαν ρέοντα σε αυτό τον τομέα και χαρακτηρισμό σε αυτόν τον τομέα (μέθοδος Kuhl).

Τα αποτελέσματα των δυο μεθόδων συγκρίθηκαν με τα αποτελέσματα της ιστολογικής εξέτασης των ελεγχθέντων παθολογικών και υπολογιστήκηκε η απόδοση της κάθε μεθόδου. Αυτή βρέθηκε Az=0.88±0.05 για την προτεινόμενη μέθοδο και Az=0.86±0.05 για την κλασική, με χρήση ανάλυσης ROC. Τα αποτελέσματα αυτά υποδεικνύουν ότι δεν υπάρχει στατιστικώς σημαντική διαφορά μεταξύ των δυο μεθόδων, με την προτεινόμενη να παρουσιάζει κέρδος χρόνου και αυξημένη επαναληψιμότητα.
1. ABSTRACT

Magnetic resonance mammography (MRM) is a promising technique, since it provides high resolution breast imaging with no use of ionising radiation and with inherently good soft tissue discrimination. The addition of dynamic contrast enhancement kinetics of the breast upgraded the method to a great extend, due to highly differentiated malignant vs. benign lesion hemodynamics resulting from the angiogenetic properties of cancerous cells.

Straightforward pharmacokinetic analysis, such as the 3TP algorithm, has been implemented in commercially available CAD systems. Quantitative parameters can be extracted that directly correspond to different aspects of the underlying pathology and can be compared to biopsy results. However, there is a general understanding that straightforward pharmacokinetic analysis (3TP model) requires a very demanding imaging protocol in order to be able to measure such parameters accurately. Fitting the experimental data of the dynamic series to simple mathematical models extracting quantitative features provides a means to evaluate and to shrink the big amount of data of the study to one set of images, in order make the diagnostic process faster and more robust. That could facilitate the clinical routine.

The dynamic series of the MRM examinations of the 55 patients were analyzed in this study. Radiologists specialized in MRM have identified and characterized all suspicious lesions according to BIRADS lexicon. Dynamic data were fitted pixel-wise to a simple bilinear model to extract washout, time to peak and washin parameters. Subsequently, those parameters were mapped to Hue, Saturation and Value, respectively, of an HSV color model, which was utilized for characterizing the lesions. In addition, Hue heterogeneity was qualitatively assessed for the characterization of lesions. In addition, observers evaluated the haemodynamic properties of the lesions with the conventional hand-drawn ROI based technique (Kuhl system).

The results of the two methods were then compared to the histological ground truth to derive their classification performance. Classification performance for the proposed and the conventional one was Az=0.88±0.05 and Az=0.86±0.05, respectively, by means of ROC analysis. Results indicate no statistically different performance between the two methods, with the proposed one offering time savings and reproducibility.
2. THEORY

2.1 WHAT IS MRI

2.1.1 THE HISTORY OF MRI

Magnetic resonance imaging (MRI) is an imaging technique used primarily in medical settings to produce high quality images of the inside of the human body. MRI is based on the principles of nuclear magnetic resonance (NMR), a spectroscopic technique used by scientists to obtain microscopic chemical and physical information about molecules. The technique was called magnetic resonance imaging rather than nuclear magnetic resonance imaging (NMRI) because of the negative connotations associated with the word nuclear in the late 1970's. MRI started out as a tomographic imaging technique, that is, it produced an image of the NMR signal in a thin slice through the human body. MRI has advanced beyond a tomographic imaging technique to a volume imaging technique. In 2003, there were approximately 10,000 MRI units worldwide, and approximately 75 million MRI scans per year performed.

Felix Bloch and Edward Purcell, both of whom were awarded the Nobel Prize in 1952, discovered the magnetic resonance phenomenon independently in 1946. In the period between 1950 and 1970, NMR was developed and used for chemical and physical molecular analysis. In 1971 Raymond Damadian showed that the nuclear magnetic relaxation times of tissues and tumors differed, thus motivating scientists to consider magnetic resonance for the detection of disease. [5] In 1973 the x-ray-based computerized tomography (CT) was introduced by Hounsfield. [6]. This date is important to the MRI timeline because it showed hospitals were willing to spend large amounts of money for medical imaging hardware. Magnetic resonance imaging was first demonstrated on small test tube samples that same year by Paul Lauterbur [7]. He used a back projection technique similar to that used in CT. In 1975 Richard Ernst proposed magnetic resonance imaging using phase and frequency encoding, and the Fourier Transform [8]. This technique is the basis of current MRI techniques. A few years later, in 1977, Raymond Damadian demonstrated MRI called field-focusing nuclear magnetic resonance. In this same year, Peter Mansfield developed the echo-planar imaging (EPI) technique [9]. This technique will be developed in later years to produce images at video rates (30 ms / image).

Edelstein and co-workers demonstrated imaging of the body using Ernst's technique in 1980. A single image could be acquired in approximately five minutes by this technique. By 1986, the imaging time was reduced to about five seconds, without sacrificing too much image quality. The same year people were developing the NMR microscope, which allowed approximately 10 μm resolution on approximately one cm samples. In 1987 echo-planar imaging was used to perform real-time movie imaging of a single cardiac cycle [10]. In this same year Charles Dumoulin was perfecting magnetic resonance angiography (MRA), which allowed imaging of flowing blood without the use of contrast agents [11].

In 1991, Richard Ernst was rewarded for his achievements in pulsed Fourier Transform NMR and MRI with the Nobel Prize in Chemistry. In 1992 functional MRI (fMRI) was developed. [12,13]. This technique allows the mapping of the function of the various regions of the human brain. Five years earlier many clinicians thought echo-planar imaging's primary applications was to be in real-time cardiac imaging. The development of fMRI opened up a new application for EPI in mapping the regions of the brain responsible for thought and motor control. In 1994, researchers at the State University of New York at Stony Brook and Princeton University demonstrated the imaging of hyperpolarized $^{129}$Xe gas for respiration studies [14].
In 2003, Paul C. Lauterbur of the University of Illinois and Sir Peter Mansfield of the University of Nottingham were awarded the Nobel Prize in Medicine for their discoveries concerning magnetic resonance imaging. MRI is clearly a young, but growing science.

### 2.1.2 THE BASICS OF MRI

Magnetic resonance imaging is based on the absorption and emission of energy in the radio frequency range of the electromagnetic spectrum. It is clear from the attenuation spectrum of the human body why x-rays are used, but why did it take so long to develop imaging with radio waves, especially with health concerns associated with ionizing radiation such as x-rays? Many scientists were taught that you can not image objects smaller than the wavelength of the energy being used to image. MRI gets around this limitation by producing images based on spatial variations in the phase and frequency of the radio frequency energy being absorbed and emitted by the imaged object.

![Figure 1: Representation of the electromagnetic spectrum and properties of different frequency ranges](image)

**Electromagnetic Radiation**

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>10^18</th>
<th>10^15</th>
<th>10^12</th>
<th>10^9</th>
<th>10^6</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microwave</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Spin**

Spin is a fundamental property of nature like electrical charge or mass. Spin comes in multiples of 1/2 and can be positive or negative. Protons, electrons, and neutrons possess spin. Individual unpaired electrons, protons, and neutrons each possess a spin of 1/2. When placed in a magnetic field of strength B, a particle with a net spin can absorb a photon, of frequency v. The frequency v depends on the gyromagnetic ratio, γ of the particle.

\[ v = \gamma B \]

For hydrogen, \( \gamma = 42.58 \text{ MHz} / \text{T} \).

The shell model for the nucleus tells us that nucleons, just like electrons, fill orbitals. When the number of protons or neutrons equals 2, 8, 20, 28, 50, 82, and 126, the orbitals are filled. Because nucleons have spin, just like electrons do, their spin can pair up when the orbitals are being filled and cancel out. Almost every element in the periodic table has an isotope with a
non zero nuclear spin. NMR can only be performed on isotopes whose natural abundance is
high enough to be detected. Some of the nuclei which are of interest in MRI are listed below.

<table>
<thead>
<tr>
<th>Nuclei</th>
<th>Unpaired Protons</th>
<th>Unpaired Neutrons</th>
<th>Net Spin</th>
<th>γ (MHz/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹H</td>
<td>1</td>
<td>0</td>
<td>1/2</td>
<td>42.58</td>
</tr>
<tr>
<td>²H</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6.54</td>
</tr>
<tr>
<td>³¹P</td>
<td>1</td>
<td>0</td>
<td>1/2</td>
<td>17.25</td>
</tr>
<tr>
<td>²³Na</td>
<td>1</td>
<td>2</td>
<td>3/2</td>
<td>11.27</td>
</tr>
<tr>
<td>¹⁴N</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3.08</td>
</tr>
<tr>
<td>¹³C</td>
<td>0</td>
<td>1</td>
<td>1/2</td>
<td>10.71</td>
</tr>
<tr>
<td>¹⁹F</td>
<td>1</td>
<td>0</td>
<td>1/2</td>
<td>40.08</td>
</tr>
</tbody>
</table>

When the proton is placed in an external magnetic field, the spin vector of the particle aligns
itself with the external field, just like a magnet would. There is a low energy configuration or
state where the poles are aligned N-S-N-S and a high energy state N-N-S-S.

TRANSITIONS

This particle can undergo a transition between the two energy states by the absorption of a
photon. A particle in the lower energy state absorbs a photon and ends up in the upper energy
state. The energy of this photon must exactly match the energy difference between the two
states. The energy, E, of a photon is related to its frequency, ν, by Plank’s constant (h =
6.626x10⁻³⁴ J s).

\[ E = h \nu \]

In NMR and MRI, the quantity ν is called the resonance or the Larmor frequency.

ENERGY LEVEL DIAGRAMS

The energy of the two spin states can be represented by an energy level diagram. Since ν = γ
B and E = h ν, the energy of the photon needed to cause a transition between the two spin
states is

\[ E = h \gamma B \]

When the energy of the photon matches the energy difference between the two spin states an
absorption of energy occurs. In the NMR experiment, the frequency of the photon is in the
radio frequency (RF) range. In NMR spectroscopy, ν is between 60 and 800 MHz for
hydrogen nuclei. In clinical MRI, ν is typically between 15 and 80 MHz for hydrogen
imaging.

The simplest NMR experiment is the continuous wave (CW) experiment. There are two ways
of performing this experiment. In the first, a constant frequency, which is continuously on,
probes the energy levels while the magnetic field is varied. The energy of this frequency is
represented by the blue line in the energy level diagram. The CW experiment can also be
performed with a constant magnetic field and a frequency which is varied.

Figure 2: The energy level diagram
BOLTZMANN STATISTICS

When a group of spins is placed in a magnetic field, each spin aligns in one of the two possible orientations. At room temperature, the number of spins in the lower energy level, \( N^+ \), slightly outnumbers the number in the upper level, \( N^- \). Boltzmann statistics tells us that 
\[
\frac{N^-}{N^+} = e^{\frac{E}{kT}}.
\]
E is the energy difference between the spin states; k is Boltzmann's constant, \( 1.3805 \times 10^{-23} \) J/Kelvin; and T is the temperature in Kelvin.

As the temperature decreases, so does the ratio \( N^-/N^+ \). As the temperature increases, the ratio approaches one.

The signal in MRI results from the difference between the energy absorbed by the spins which make a transition from the lower energy state to the higher energy state, and the energy emitted by the spins which simultaneously make a transition from the higher energy state to the lower energy state. The signal is thus proportional to the population difference between the states.

There are two other factors, which influence the MRI signal: the natural abundance of the isotope and biological abundance. The natural abundance of an isotope is the fraction of nuclei having a given number of protons and neutrons, or atomic weight. For example, there are three isotopes of hydrogen, \(^1\text{H}, ^2\text{H}, \text{and} ^3\text{H}\). The natural abundance of \(^1\text{H}\) is 99.985%. The following table lists the natural abundances of some nuclei studied by MRI [15].

<table>
<thead>
<tr>
<th>Element</th>
<th>Symbol</th>
<th>Natural Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>(^1\text{H})</td>
<td>99.985</td>
</tr>
<tr>
<td></td>
<td>(^2\text{H})</td>
<td>0.015</td>
</tr>
<tr>
<td>Carbon</td>
<td>(^{13}\text{C})</td>
<td>1.11</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>(^{14}\text{N})</td>
<td>99.63</td>
</tr>
<tr>
<td></td>
<td>(^{15}\text{N})</td>
<td>0.37</td>
</tr>
<tr>
<td>Sodium</td>
<td>(^{23}\text{Na})</td>
<td>100</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>(^{31}\text{P})</td>
<td>100</td>
</tr>
<tr>
<td>Potassium</td>
<td>(^{39}\text{K})</td>
<td>93.1</td>
</tr>
<tr>
<td>Calcium</td>
<td>(^{41}\text{Ca})</td>
<td>0.145</td>
</tr>
</tbody>
</table>

The biological abundance is the fraction of one type of atom in the human body. The following table lists the biological abundances of some nuclei studied by MRI [16].

<table>
<thead>
<tr>
<th>Element</th>
<th>Biological Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen (H)</td>
<td>0.63</td>
</tr>
<tr>
<td>Sodium (Na)</td>
<td>0.00041</td>
</tr>
<tr>
<td>Phosphorus (P)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Carbon (C)</td>
<td>0.094</td>
</tr>
<tr>
<td>Oxygen (O)</td>
<td>0.26</td>
</tr>
<tr>
<td>Calcium (Ca)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Nitrogen (N)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

RELAXATION PROCESSES

At equilibrium, the net magnetization vector lies along the direction of the applied magnetic field \( B_0 \) and is called the equilibrium magnetization \( M_0 \). In this configuration, the Z component of magnetization \( M_Z \) equals \( M_0 \). \( M_Z \) is referred to as the longitudinal magnetization. There is no transverse (\( M_X \) or \( M_Y \)) magnetization at this state. It is possible to change the net magnetization by exposing the nuclear spin system to energy of a frequency equal to the energy difference between the spin states. If enough energy is put into the system,
it is possible to saturate the spin system and make $M_Z=0$. The time constant which describes how $M_Z$ returns to its equilibrium value is called the spin lattice relaxation time ($T_1$). The equation governing this behaviour as a function of the time $t$ after its displacement is:

\[ M_Z = M_0 \left( 1 - e^{t/T_1} \right) \]  

($1$)

$T_1$ is the time needed to reduce the difference between the longitudinal magnetization ($M_Z$) and its equilibrium value by a factor of $e$. If the net magnetization is placed along the $-Z$ axis, it will gradually return to its equilibrium position along the $+Z$ axis at a rate governed by $T_1$. The equation governing this behaviour as a function of the time $t$ after its displacement is:

\[ M_Z = M_0 \left( 1 - 2e^{t/T_1} \right) \]  

(fig3)  

(2)

Figure 3: $T1$ relaxation diagrams

Again, the spin-lattice relaxation time ($T_1$) is the time to reduce the difference between the longitudinal magnetization ($M_Z$) and its equilibrium value by a factor of $e$. If the net magnetization is placed in the XY plane it will rotate about the $Z$ axis at a frequency equal to the frequency of the photon which would cause a transition between the two energy levels of the spin, the Larmor frequency. In addition to the rotation, the net magnetization starts to dephase because each of the spin packets making it up is experiencing a slightly different magnetic field and rotates at its own Larmor frequency. The longer the elapsed time, the greater the phase difference. The time constant which describes the return to equilibrium of the transverse magnetization, $M_{XY}$, is called the spin-spin relaxation time, $T_2$. (fig. 4)

\[ M_{XY} = M_{XY0} e^{-t/T_2} \]

(fig. 4)

Figure 4: $T2$ relaxation diagram

$T_2$ is always less than or equal to $T_1$. The net magnetization in the XY plane goes to zero and the longitudinal magnetization grows in until we have $M_0$ along $Z$. Any transverse magnetization behaves the same way. The transverse component rotates about the direction of applied magnetization and de-phases. $T_1$ governs the rate of recovery of the longitudinal magnetization. Two factors contribute to the decay of transverse magnetization.  
1) molecular interactions (said to lead to a pure $T_2$ molecular effect)  
2) variations in $B_0$ (said to lead to an inhomogeneous $T_2$ effect).

The combination of these two factors is what actually results in the decay of transverse magnetization. The combined time constant is called $T_2*$ and is given the symbol $T_2^*$. The
relationship between the $T_2$ from molecular processes and that from inhomogeneities in the magnetic field is as follows.

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_{2\text{inhomo}}}$$  \hspace{1cm} (3)

**ROTATING FRAME OF REFERENCE**

We have just looked at the behavior of spins in the laboratory frame of reference. It is convenient to define a rotating frame of reference which rotates about the $Z$ axis at the Larmor frequency. We distinguish this rotating coordinate system from the laboratory system by primes on the X and Y axes, $XY'$. A magnetization vector rotating at the Larmor frequency in the laboratory frame appears stationary in a frame of reference rotating about the $Z$ axis. In the rotating frame, relaxation of $M_Z$ magnetization to its equilibrium value looks the same as it did in the laboratory frame.

A transverse magnetization vector rotating about the $Z$ axis at the same velocity as the rotating frame will appear stationary in the rotating frame. A magnetization vector travelling faster than the rotating frame rotates clockwise about the $Z$ axis. A magnetization vector travelling slower than the rotating frame rotates counter-clockwise about the $Z$ axis.

**PULSED MAGNETIC FIELDS**

A coil of wire placed around the X axis will provide a magnetic field along the X axis when a direct current is passed through the coil. An alternating current will produce a magnetic field which alternates in direction. In a frame of reference rotating about the $Z$ axis at a frequency equal to that of the alternating current, the magnetic field along the $X'$ axis will be constant.

This is the same as moving the coil about the rotating frame coordinate system at the Larmor Frequency. In magnetic resonance, the magnetic field created by the coil passing an alternating current at the Larmor frequency is called the $B_1$ magnetic field. When the alternating current through the coil is turned on and off, it creates a pulsed $B_1$ magnetic field along the $X'$ axis.

The spins respond to this pulse in such a way as to cause the net magnetization vector to rotate about the direction of the applied $B_1$ field. The rotation angle depends on the length of time the field is on, $\tau$, and its magnitude $B_1$.

$$\theta = 2\pi \gamma \tau B_1$$

A $90^\circ$ pulse is one which rotates the magnetization vector clockwise by 90 degrees about the $X'$ axis. A $90^\circ$ pulse rotates the equilibrium magnetization down to the $Y'$ axis. In the laboratory frame the equilibrium magnetization spirals down around the $Z$ axis to the $XY$ plane.

A $180^\circ$ pulse will rotate the magnetization vector by 180 degrees. A $180^\circ$ pulse rotates the equilibrium magnetization down to along the $-Z$ axis. The net magnetization at any orientation will behave according to the rotation equation. For example, a net magnetization vector along the $Y'$ axis will end up along the $-Y'$ axis when acted upon by a $180^\circ$ pulse of $B_1$ along the $X'$ axis.

A rotation matrix can also be used to predict the result of a rotation. Here $\theta$ is the rotation angle about the $X'$ axis, $[X', Y', Z]$ is the initial location of the vector, and $[X'', Y'', Z'']$ the location of the vector after the rotation.

$$\begin{bmatrix} X'' \\ Y'' \\ Z'' \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\theta & \sin\theta \\ 0 & -\sin\theta & \cos\theta \end{bmatrix} \begin{bmatrix} X' \\ Y' \\ Z \end{bmatrix}$$  \hspace{1cm} (4)
**SPIN RELAXATION**

Time varying fields at the Larmor frequency cause transitions between the spin states and hence a change in $M_z$. There is a distribution of rotation frequencies in a sample of molecules. Only frequencies at the Larmor frequency affect $T_1$. Since the Larmor frequency is proportional to $B_0$, $T_1$ will therefore vary as a function of magnetic field strength. In general, $T_1$ is inversely proportional to the density of molecular motions at the Larmor frequency. The rotation frequency distribution depends on the temperature and viscosity of the solution. Therefore $T_1$ will vary as a function of temperature. The temperature of the human body does not vary by enough to cause a significant influence on $T_1$. The viscosity does however vary significantly from tissue to tissue and influences $T_1$. Fluctuating fields which perturb the energy levels of the spin states cause the transverse magnetization to dephase. The number of molecular motions less than and equal to the Larmor frequency is inversely proportional to $T_2$. In general, relaxation times get longer as $B_0$ increases because there are fewer relaxation-causing frequency components present in the random motions of the molecules.

**BLOCH EQUATIONS**

The Bloch equations are a set of coupled differential equations which can be used to describe the behaviour of a magnetization vector under any conditions. When properly integrated, the Bloch equations will yield the $X'$, $Y'$, and $Z$ components of magnetization as a function of time.

\[
\frac{dM_{x'}}{dt} = (\omega_0 - \omega)M_{y'} - \frac{M_{x'}}{T_2}
\]

\[
\frac{dM_{y'}}{dt} = -(\omega_0 - \omega)M_{x'} + 2\pi\gamma B_1 M_z - \frac{M_{y'}}{T_2}
\]

\[
\frac{dM_z}{dt} = -2\pi\gamma B_1 M_{y'} - \frac{(M_z - M_{z0})}{T_1}
\]

(5)

**2.1.3 IMAGING PRINCIPLES**

**MAGNETIC FIELD GRADIENT**

If each of the regions of spin was to experience a unique magnetic field we would be able to image their positions. A gradient in the magnetic field is what will allow us to accomplish this. A magnetic field gradient is a variation in the magnetic field with respect to position. A one-dimensional magnetic field gradient is a variation with respect to one direction, while a two-dimensional gradient is a variation with respect to two. The most useful type of gradient in magnetic resonance imaging is a one- dimensional linear magnetic field gradient. A one-dimensional magnetic field gradient along the x axis in a magnetic field, $B_0$, indicates that the magnetic field is increasing in the x direction. The symbols for a magnetic field gradient in the x, y, and z directions are $G_x$, $G_y$, and $G_z$. 


FREQUENCY ENCODING

The point in the center of the magnet where \((x,y,z) = 0,0,0\) is called the isocenter of the magnet. The magnetic field at the isocenter is \(B_o\) and the resonant frequency is \(\nu_o\). If a linear magnetic field gradient is applied to a hypothetical volume with different spin containing regions, these regions experience different magnetic fields. The result is an NMR spectrum with more than one signal. The amplitude of the signal is proportional to the number of spins in a plane perpendicular to the gradient. This procedure is called frequency encoding and causes the resonance frequency to be proportional to the position of the spin.

\[
\nu = \gamma \left( B_o + x G_x \right) = \nu_o + \gamma x G_x \quad (6)
\]
\[
x = \left( \nu - \nu_o \right) / \left( \gamma G_x \right) \quad (7)
\]

This principle forms the basis behind all magnetic resonance imaging.

SLICE SELECTION

Slice selection in MRI is the selection of spins in a plane through the object. The principle behind slice selection is explained by the resonance equation. Slice selection is achieved by applying a one-dimensional, linear magnetic field gradient during the period that the RF pulse is applied. A 90° pulse applied in conjunction with a magnetic field gradient will rotate spins which are located in a slice or plane through the object.
PHASE ENCODING GRADIENT

The phase encoding gradient is a gradient in the magnetic field $B_0$. The phase encoding gradient is used to impart a specific phase angle to a transverse magnetization vector. The specific phase angle depends on the location of the transverse magnetization vector.

If a gradient in the magnetic field is applied along the $X$ direction the spin vectors will precess about the direction of the applied magnetic field at a frequency given by the resonance equation.

$$\nu = \gamma (B_0 + x G_x) = \nu_0 + \gamma x G_x$$  \hspace{1cm} (8)

While the phase encoding gradient is on, each transverse magnetization vector has its own unique Larmor frequency. If the gradient in the $X$ direction is turned off, the external magnetic field experienced by each spin vector is, for all practical purposes, identical. Therefore the Larmor frequency of each transverse magnetization vector is identical. The phase angle, $\phi$, of each vector, on the other hand, is not identical. The phase angle is the angle between a reference axis, say the $Y$ axis, and the magnetization vector at the time the phase encoding gradient has been turned off. Thus vectors with different phase angles can be assigned at different positions.

FOURIER TRANSFORM TOMOGRAPHIC IMAGING

One of the best ways to understand an imaging sequence is to examine a timing diagram for the sequence. The timing diagram for an imaging sequence has entries for the radio frequency, magnetic field gradients, and signal as a function of time. The simplest FT imaging sequence contains a $90^\circ$ slice selective pulse, a slice selection gradient pulse, a phase encoding gradient pulse, a frequency encoding gradient pulse, and a signal (fig. 7).

The pulses for the three gradients represent the magnitude and duration of the magnetic field gradients. The first event to occur in this imaging sequence is to turn on the slice selection gradient. The slice selection RF pulse is applied at the same time. The slice selective RF pulse is an apodized sinc function shaped burst of RF energy. Once the RF pulse is complete the slice selection gradient is turned off and a phase encoding gradient is turned on. Once the phase encoding gradient has been turned off a frequency encoding gradient is turned on and a signal is recorded. The signal is in the form of a free induction decay. This sequence of pulses is usually repeated 128 or 256 times to collect all the data needed to produce an image. The time between the repetitions of the sequence is called the repetition time, TR. Each time the
sequence is repeated the magnitude of the phase encoding gradient is changed. The magnitude is changed in equal steps between the maximum amplitude of the gradient and the minimum value.

The slice selection gradient is always applied perpendicular to the slice plane. The phase encoding gradient is applied along one of the sides of the image plane. The frequency encoding gradient is applied along the remaining edge of the image plane. The following table indicates the possible combination of the slice, phase, and frequency encoding gradient.

<table>
<thead>
<tr>
<th>Slice Plane</th>
<th>Slice</th>
<th>Phase</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>XY</td>
<td>Z</td>
<td>X or Y</td>
<td>Y or X</td>
</tr>
<tr>
<td>XZ</td>
<td>Y</td>
<td>X or Z</td>
<td>Z or X</td>
</tr>
<tr>
<td>YZ</td>
<td>X</td>
<td>Y or Z</td>
<td>Z or Y</td>
</tr>
</tbody>
</table>

To examine the sequence from a macroscopic perspective of the spin vectors we consider a cube of spins placed in a magnetic field. The cube is composed of several volume elements each with its own net magnetization vector. If we wish to image a slice in the XY plane, as the $B_0$ magnetic field is along the Z axis, the Slice selection gradient is applied along the Z axis. The RF pulse rotates only those spins packets within the cube which satisfy the resonance condition. These spin packets are located within an XY plane. The location of the plane along the Z axis with respect to the isocenter is given by

$$Z = \frac{\Delta \nu}{\gamma G_s}$$

where $\Delta \nu$ is the frequency offset from $\nu_0$ (i.e. $\nu - \nu_0$), $G_s$ the magnitude of the slice selection gradient, and $\gamma$ the gyromagnetic ratio. Spins located above and below this plane are not affected by the RF pulse. Once rotated into the XY plane these vectors would precess at the Larmor frequency given by the magnetic field each was experiencing. If the magnetic field was uniform, each of the precessional rates would be equal. In the imaging sequence a phase encoding gradient is applied after the slice selection gradient. Assuming this is applied along the X axis, the spins at different locations along the X axis begin to precess at different Larmor frequencies. When the phase encoding gradient is turned off the net magnetization vectors precess at the same rate, but possess different phases, determined by the duration and magnitude of the phase encoding gradient pulse.

Once the phase encoding gradient pulse is turned off a frequency encoding gradient pulse is turned on. Assuming it is applied along the -Y direction, the frequency encoding gradient causes spin packets to precess at rates dependent on their Y location.

What we have accomplished is that each of the net magnetization vectors is characterized by a unique phase angle and precessional frequency. If we had a means of determining the phase and frequency of the signal from a net magnetization vector we could position it within one of all the picture elements.

A simple Fourier transform is capable of this task for a single net magnetization vector located somewhere within the selected 2D slice space. There needs to be one phase encoding gradient step for each location in the phase encoding gradient direction. Therefore if we wish to resolve 256 locations in the phase encoding direction we will need 256 different magnitudes of the phase encoding gradient and will record 256 different free induction decays.

**IMAGE RESOLUTION**

When two features in an image are distinguishable, they are said to be resolved. The ability to resolve two features in an image is a function of many variables; $T_2$, signal-to-noise ratio, sampling rate, slice thickness, and image matrix size. Resolution is a measure of image quality. Resolution is inversely proportional to the distance of two resolvable features.
It is easy to see the relationship between resolution, Field Of View (FOV), and number of data points, N, across an image (fig. 8). Two features located in less a distance than FOV/N, cannot be resolved. Increasing the number of data points will decrease the pixel size, but not necessarily improve the resolution. Even with a noiseless image and optimal contrast, we may not be able to resolve two features the size of a pixel because of the $T_2^*$ decay (fig. 9).

A magnetic resonance image can be thought of as a convolution of the NMR spectrum of the spins with their spatial concentration map. If we assume a one-dimensional image, $h(x)$, consisting of a single type of spin, $g(x)$ is the distribution of the spins, $f(\nu)$ is the NMR spectrum of the spins, and $f(\nu G_x^{-1} \gamma^{-1})$ is the NMR spectrum in distance units in the presence of the magnetic field gradient $G_x$, then

$$h(x) = g(x) \otimes f(\nu G_x^{-1} \gamma^{-1}).$$

The full line width in Hz at half height, $\Gamma$ is

$$\Gamma = (\pi T_2^*)^{-1}.$$

Therefore, the pixel size should be chosen to be approximately equal to $(\pi G_x \gamma T_2^*)^{-1}$.

![Image of two images with different resolution](image1.png)

**Figure 8:** Two images of the same object with different resolution. In the left image the pixel size does not allow the two spots to be resolved.

![Image of two images with different T2* decay](image2.png)

**Figure 9:** Two images of an infinitely small point source of NMR signal. The left has a long $T_2^*$ and the right a short $T_2^*$. Both images were recorded with a pixel size much less than $(\pi G_x \gamma T_2^*)^{-1}$.

### 2.1.4 Basic Imaging Techniques

**Spin-Echo Imaging**

The timing diagram for a spin-echo imaging sequence has entries for the RF pulses, the gradients in the magnetic field, and the signal (fig. 10). A slice selective 90° RF pulse is applied in conjunction with a slice selection gradient. A period of time equal to TE/2 elapses and a 180° slice selective 180° pulse is applied in conjunction with the slice selection gradient. A phase encoding gradient is applied between the 90° and 180° pulses. The phase encoding gradient could be applied after the 180° pulse, however if we want to minimize the TE period the pulse is applied between the 90° and 180° RF pulses.
The frequency encoding gradient is applied after the 180° pulse during the time that echo is collected. The recorded signal is the echo. The FID, which is found after every 90° pulse, is not used. One additional gradient is applied between the 90° and 180° pulses. This gradient is along the same direction as the frequency encoding gradient. It dephases the spins so that they will rephase by the center of the echo. This gradient in effect prepares the signal to be at the edge of k-space by the start of the acquisition of the echo.

The entire sequence is repeated every TR seconds until all the phase encoding steps have been recorded.

Figure 10: Spin Echo pulse sequence timing diagram.

**INVERSION RECOVERY IMAGING**

An inversion recovery sequence which uses a spin-echo sequence to detect the magnetization will be presented. The RF pulses are 180-90-180.

The timing diagram for an inversion recovery imaging sequence has entries for the RF pulses, the gradients in the magnetic field, and the signal (fig. 11). A slice selective 180° RF pulse is applied in conjunction with a slice selection gradient. A period of time equal to TI elapses and a spin-echo sequence is applied.

The remainder of the sequence is equivalent to a spin-echo sequence. This spin-echo part recorded the magnetization present at a time TI after the first 180° pulse. (A 90-FID sequence could be used instead of the spin-echo.) All the RF pulses in the spin-echo sequence are slice selective. The RF pulses are applied in conjunction with the slice selection gradients. Between the 90° and 180° pulses a phase encoding gradient is applied. The phase encoding gradient is varied in 128 or 256 steps between Gφm and -Gφm.

The phase encoding gradient could not be applied after the first 180° pulse because there is no transverse magnetization to phase encode at this point. The frequency encoding gradient is applied after the second 180° pulse during the time that echo is collected.

The recorded signal is the echo. The entire sequence is repeated every TR seconds.

An advantage of using an inversion recovery sequence is that it allows nulling of the signal from one component due to its T1. The signal intensity is zero when TI = T1/ln2.

Figure 11: The Inversion Recovery pulse sequence timing diagram.
GRADIENT RECALLED ECHO IMAGING

The imaging sequences mentioned thus far have one major disadvantage. For maximum signal, they all require the transverse magnetization to recover to its equilibrium position along the Z axis before the sequence is repeated. When the $T_1$ is long, this can significantly lengthen the imaging sequence. If the magnetization does not fully recover to equilibrium the signal is less than if full recovery occurs. If the magnetization is rotated by an angle $\theta$ less than 90° its $M_z$ component will recover to equilibrium much more rapidly, but there will be less signal since the signal will be proportional to the $\sin\theta$. So we trade off signal for imaging time. In some instances, several images can be collected and averaged together and make up for the lost signal.

The gradient recalled echo imaging sequence is the application of these principles. In this imaging sequence a slice selective RF pulse is applied to the imaged object. This RF pulse typically produces a rotation angle of between 10° and 90°. A slice selection gradient is applied with the RF pulse.

A phase encoding gradient is applied next. The phase encoding gradient is varied between $G_{\phi m}$ and $-G_{\phi m}$ in typically 128 or 256 equal steps as was done in all the other sequences. A dephasing frequency encoding gradient is applied at the same time as the phase encoding gradient so as to cause the spins to be in phase at the center of the acquisition period. This gradient is negative in sign from that of the frequency encoding gradient turned on during the acquisition of the signal. An echo is produced when the frequency encoding gradient is turned on because this gradient refocuses the dephasing which occurred from the dephasing gradient. A period called the echo time (TE) is defined as the time between the start of the RF pulse and the maximum in the signal. The sequence is repeated every TR seconds. The TR period could be as short as tens of milliseconds (fig. 12).

![Gradient Echo pulse sequence timing diagram](image)

Figure 12: Gradient Echo pulse sequence timing diagram.

IMAGE CONTRAST

In order for pathology or any tissue for that matter to be visible in a magnetic resonance image there must be contrast or a difference in signal intensity between it and the adjacent tissue. The signal intensity, $S$, is determined by the signal equation for the specific pulse sequence used. Some of the intrinsic variables are the:

- Spin-Lattice Relaxation Time, $T_1$
- Spin-Spin Relaxation Time, $T_2$
- Spin Density, $\rho$
- $T_2^*$

The spin density is the concentration of signal bearing spins. The instrumental variables are the:
Repetition Time, TR  
Echo Time, TE  
Inversion Time, TI  
Rotation (flip) Angle, θ  
$T_2^*$  

$T_2^*$ falls on both lists because it contains a component dependent on the homogeneity of the magnetic field and the molecular motions. The signal equations for the pulse sequences presented are:

**Spin-Echo**

\[
S = k \rho (1 - \exp(-TR/T_1)) \exp(-TE/T_2) 
\]

(9)

**Inversion Recovery (180-90)**

\[
S = k \rho (1 - 2\exp(-TI/T_1) + \exp(-TR/T_1)) 
\]

(10)

**Inversion Recovery (180-90-180)**

\[
S = k \rho (1 - 2\exp(-TI/T_1) + \exp(-TR/T_1)) \exp(-TE/T_2) 
\]

(11)

**Gradient Recalled Echo**

\[
S = k \rho (1 - \exp(-TR/T_1)) \sin \theta \exp(-TE/T_2^*) / (1 - \cos \theta \exp(-TR/T_1)) 
\]

(12)

In each of these equations, \(S\) represents the amplitude of the signal in the frequency domain spectrum. The quantity \(k\) is a proportionality constant which depends on the sensitivity of the signal detection circuitry on the imager. The values of \(T_1, T_2,\) and \(\rho\) are specific to a tissue or pathology. The following table lists the range of \(T_1, T_2,\) and \(\rho\) values at 1.5T for tissues found in a magnetic resonance image of the human head [17].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>(T_1) (s)</th>
<th>(T_2) (ms)</th>
<th>(\rho)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>0.8 - 20</td>
<td>110 - 2000</td>
<td>70-230</td>
</tr>
<tr>
<td>White</td>
<td>0.76 - 1.08</td>
<td>61-100</td>
<td>70-90</td>
</tr>
<tr>
<td>Gray</td>
<td>1.09 - 2.15</td>
<td>61 - 109</td>
<td>85 - 125</td>
</tr>
<tr>
<td>Meninges</td>
<td>0.5 - 2.2</td>
<td>50 - 165</td>
<td>5 - 44</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.95 - 1.82</td>
<td>20 - 67</td>
<td>45 - 90</td>
</tr>
<tr>
<td>Adipose</td>
<td>0.2 - 0.75</td>
<td>53 - 94</td>
<td>50 - 100</td>
</tr>
</tbody>
</table>

The contrast, \(C\), between two tissues A and B will be equal to the difference between the signal for tissue A, \(S_A\), and that for tissue B, \(S_B\).

\[
C = S_A - S_B 
\]

\(S_A\) and \(S_B\) are determined by the signal equations given above. For any two tissues there will be a set of instrumental parameters which yield a maximum contrast (fig. 13,14).

Figure 13: Graphical presentation of the contrast between two tissues in a spin-echo sequence as a function of TR.
To assure that signals from all phase encoding steps possess the same signal properties a few equilibrating cycles through the sequence are added to the beginning of every image acquisition. The amount of transverse magnetization from a 90° pulse reaches an equilibrium value after a few TR cycles. This practice lengthens the imaging time by a few TR periods. The magnetic resonance community has adopted nomenclature to signify the predominant contrast mechanism in an image. An image whose contrast is predominantly caused by differences in $T_1$ of the tissues is called a $T_1$-weighted image. Similarly for $T_2$ and $\rho$, the images are called $T_2$-weighted and spin or proton density weighted images. The following table contains the set of conditions necessary to produce weighted images.

<table>
<thead>
<tr>
<th>Weighting</th>
<th>TR Value</th>
<th>TE Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$</td>
<td>$\leq T_1$</td>
<td>$&lt; T_2$</td>
</tr>
<tr>
<td>$T_2$</td>
<td>$&gt; T_1$</td>
<td>$\geq T_2$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>$&gt; T_1$</td>
<td>$&lt; T_2$</td>
</tr>
</tbody>
</table>

SIGNAL AVERAGING

The signal-to-noise ratio (SNR) of a tissue in an image is the ratio of the average signal for the tissue to the standard deviation of the noise in the background of the image. The signal-to-noise ratio may be improved by performing signal averaging. Signal averaging is the collection and averaging together of several images. The signals are present in each of the averaged images so their contribution to the resultant image add. Noise is random so it does not add, but begins to cancel as the number of spectra averaged increases. The signal-to-noise improvement from signal averaging is proportional to the square root of the number of images averaged ($N_{ex}$). $N_{ex}$ is more commonly referred to as the number of excitations.

$$\text{SNR} \propto \sqrt{N_{ex}}.$$ 

2.1.5 IMAGING HARDWARE

HARDWARE OVERVIEW

Figure 15 displays a schematic representation of the major systems on a magnetic resonance imager and a few of the major interconnections. This overview briefly states the function of each component. Some will be described in detail later in this chapter.
At the top of the schematic representation we find the components of the imager located in the scan room of a magnetic resonance imager. The magnet produces the $B_0$ field for the imaging procedure. Within the magnet are the gradient coils for producing a gradient in $B_0$ in the X, Y, and Z directions. Within the gradient coils is the RF coil. The RF coil produces the $B_1$ magnetic field necessary to rotate the spins by $90^\circ$ or $180^\circ$. The RF coil also detects the signal from the spins within the body. The patient is positioned within the magnet by a computer controlled patient table. The table has a positioning accuracy of 1 mm. The scan room is surrounded by an RF shield. The shield prevents the high power RF pulses from radiating out through the hospital. It also prevents the various RF signals from television and radio stations from being detected by the imager. Some scan rooms are also surrounded by a magnetic shield which contains the magnetic field from extending too far into the hospital. In newer magnets, the magnet shield is an integral part of the magnet. The heart of the imager is the computer. It controls all components on the imager. The RF components under control of the computer are the radio frequency source and pulse programmer. The source produces a sine wave of the desired frequency. The Pulse programmer shapes the RF pulses into apodized sinc pulses. The RF amplifier increases the pulses power from milli Watts to kilo Watts. The computer also controls the gradient pulse programmer which sets the shape and amplitude of each of the three gradient fields. The gradient amplifier increases the power of the gradient pulses to a level sufficient to drive the gradient coils.

The array processor, located on some imagers, is a device which is capable of performing a two-dimensional Fourier transform in fractions of a second. The computer off loads the Fourier transform to this faster device.

The operator of the imager gives input to the computer through a control console. An imaging sequence is selected and customized from the console. The operator can see the images on a video display located on the console or can make hard copies of the images on a film printer.

THE MAGNET

The imaging magnet is the most expensive component of the magnetic resonance imaging system. Most magnets are of the superconducting type (fig. 16).
A superconducting magnet is an electromagnet made of superconducting wire. Superconducting wire has a resistance approximately equal to zero when it is cooled to a temperature close to absolute zero (-273.15°C or 0 K) by emersing it in liquid helium. Once current is caused to flow in the coil it will continue to flow as long as the coil is kept at liquid helium temperatures. (Some losses do occur over time due to infinitely small resistance of the coil. These losses are on the order of a ppm of the main magnetic field per year.)

The length of superconducting wire in the magnet is typically several miles. The coil of wire is kept at a temperature of 4.2K by immersing it in liquid helium. The coil and liquid helium is kept in a large dewar. The typical volume of liquid Helium in an MRI magnet is 1700 liters. In early magnet designs, this dewar was typically surrounded by a liquid nitrogen (77.4K) dewar which acts as a thermal buffer between the room temperature (293K) and the liquid helium. In later magnet designs, the liquid nitrogen region was replaced by a dewar cooled by a cryocooler or refrigerator. This design eliminates the need to add liquid nitrogen to the magnet (fig. 17).

**GRADIENT COILS**

The gradient coils produce the gradients in the $B_0$ magnetic field [18]. They are room temperature coils which because of their configuration create the desired gradient. Since the horizontal bore superconducting magnet is most common, the gradient coil system will be described for this magnet (fig. 18).
Assuming the standard magnetic resonance coordinate system, a gradient in \( B_0 \) in the \( Z \) direction is achieved with an antihelmholtz type of coil. Current in the two coils flow in opposite directions creating a magnetic field gradient between the two coils. The \( B \) field at one coil adds to the \( B_0 \) field while the \( B \) field at the center of the other coil subtracts from the \( B_0 \) field.

The \( X \) and \( Y \) gradients in the \( B_0 \) field are created by a pair of figure-8 coils. The \( X \) axis figure-8 coils create a gradient in \( B_0 \) in the \( X \) direction due to the direction of the current through the coils. The \( Y \) axis figure-8 coils provides a similar gradient in \( B_0 \) along the \( Y \) axis.

![Gradient coil configuration for horizontal bore superconducting MR Imagers](image)

**Figure 18:** Gradient coil configuration for horizontal bore superconducting MR Imagers

**RF COILS**

RF coils create the \( B_1 \) field which rotates the net magnetization in a pulse sequence [19]. They also detect the transverse magnetization as it precesses in the XY plane. RF coils can be divided into three general categories;
1) transmit and receive coils,
2) receive only coils and
3) transmit only coils.

Transmit and receive coils serve as the transmitter of the \( B_1 \) fields and receiver of RF energy from the imaged object. A transmit only coil is used to create the \( B_1 \) field and a receive only coil is used in conjunction with it to detect or receive the signal from the spins in the imaged object. There are several varieties of each. The RF coil on an imager can be regarded as the lens on a camera. A photographer will use one lens for a close up shot and a different one for a wide angle long distance shot. Just as a good photographer has several lenses, a good imaging site will have several imaging coils to handle the variety of imaging situations which might arise.

An imaging coil must resonate, or efficiently store energy, at the Larmor frequency. All imaging coils are composed of an inductor, or inductive elements, and a set of capacitive elements. The resonant frequency, \( n \), of an RF coil is determined by the inductance (\( L \)) and capacitance (\( C \)) of the inductor capacitor circuit.

\[
\nu = \frac{1}{2\pi\sqrt{LC}}
\]

Some types of imaging coils need to be tuned for each patient by physically varying a variable capacitor. The other requirement of an imaging coil is that the \( B_1 \) field must be perpendicular to the \( B_0 \) magnetic field.

There are many types of imaging coils. Volume coils surround the imaged object while surface coils are placed adjacent to the imaged object. An internal coil is one designed to record information from regions outside of the coil, such as a catheter coil designed to be inserted into a blood vessel. When a receive only coil is used, a larger coil on the imager is used as the transmitter of RF energy to producing the 90\(^\circ\) and 180\(^\circ\) pulses.
2.1.6 MRI SAFETY

Although MRI does not use ionizing radiation to produce images there are still some important safety considerations which one should be familiar with. These concern the use of strong magnetic fields, radio frequency energy, time varying magnetic fields, cryogenic liquids, and magnetic field gradients.

In 1982 the US FDA set guidelines for MRI exams that covered the maximum $B_0$ field, change in magnetic field with respect to time (dB/dt), the absorption of radio frequency energy, and acoustic noise levels. In 1997, the US FDA revised these guidelines due to the accumulated data on MRI. The limits were revised again in 2003 and are summarized in the following table [20].

**FDA MRI Guidelines (2003)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_0$</td>
<td>Adults, Children, and Infants age &lt; 1 month: 8 T, neonates (infants age &lt; 1 month): 4 T</td>
</tr>
<tr>
<td>dB/dt</td>
<td>No discomfort, pain, or nerve stimulation</td>
</tr>
<tr>
<td>whole body, avg</td>
<td>4 W/Kg</td>
</tr>
<tr>
<td>head, avg</td>
<td>3 W/Kg</td>
</tr>
<tr>
<td>head or torso,</td>
<td>8 W/Kg</td>
</tr>
<tr>
<td>extremities,</td>
<td>12 W/Kg</td>
</tr>
<tr>
<td>Peak unweighted</td>
<td>140 dB</td>
</tr>
<tr>
<td>A-weighted rms</td>
<td>99 dBA</td>
</tr>
</tbody>
</table>

MRI personnel often forget about the dangers associated with ferromagnetic objects near the MRI magnet. Magnetic fields from large bore magnets can literally pick up and pull large ferromagnetic items into the bore of the magnet. Caution must be taken to keep ALL ferromagnetic items away from the magnet for two main reasons. The first reason is they can injure or kill an individual in the magnet. The second reason is they can seriously damage the magnet and imaging coils. The force exerted on a large metal object, such as a mop wringer can damage the concentric cryogenic compartments within a magnet.

Similar forces are at work on ferromagnetic metal implants or foreign matter in those being imaged. These forces can pull on these objects cutting and compressing healthy tissue. For these reasons individuals with foreign metal objects are not imaged. There are additional concerns regarding the effect of magnetic fields on electronic circuitry, specifically pacemakers. An individual with a pacemaker walking through a strong magnetic field can induce currents in the pacemaker circuitry which will cause it to fail and possibly cause death. Magnetic fields will also erase credit cards and magnetic storage media.

The United States Food and Drug Administration (USFDA) safety guidelines state that field strengths not exceeding 2.0 Tesla may be routinely used. People with pacemakers must not be exposed to magnetic fields greater than 5 gauss. A 50 Gauss magnetic field will erase magnetic storage media.

The radio frequency energy from an imaging sequence can cause heating of the tissues of the body. The USFDA recommends that the exposure to RF energy be limited. The specific absorption rate (SAR) is the limiting measure.

SAR = Joules of RF / Second / kg of body weight = Watts/kg

The recommended SAR limitations depend on the anatomy being imaged. The SAR for the whole body must be less than 0.4 W/kg. It must be less than 3.2 W/kg averaged over the head. Any pulse sequence must not rise the temperature by more than 1º Celsius and no greater than 38º C in the head, 39º C in the trunk, and 40º C in the extremities.

The USFDA recommendations for the rate of change of magnetic field state that the dB/dt for the system must be less than that required to produce peripheral nerve stimulation.

Imaging gradients do produce high acoustic noise levels. The American OSHA limits the peak acoustic noise to 200 pascals or 140 dB references to 20 micropascals.
Every MRI magnet room with a superconducting magnet should have an oxygen monitor. These devices measure the percentage of O\textsubscript{2} in the air and sound an alarm when the level falls below a set threshold. These devices are needed because leaks in the venting system that handle the boil off of cryogens could create a situation where excess N\textsubscript{2} or He in the room air would deplete the percentage of O\textsubscript{2} to a dangerous level.

2.2 BREAST

2.2.1 BREAST ANATOMY AND PHYSIOLOGY

The breast consists of 15 to 25 lobes, each of which is drained by a collecting duct terminating in the nipple. The collecting duct has several branches, which end in a terminal ductal-lobular unit (TDLU), the basic functional unit of the breast (Fig. 1). The TLDU is composed of a small segment of terminal duct and a cluster of ductules (acini), which are the actual secretory units. The functional structures are surrounded by a varying amount of fat and collagenous tissue. Microscopically, the duct system is lined by an inner epithelial cell layer along the luminal side and the outer layer of myoepithelial cells. These two layers are further surrounded by a basal lamina. A small part of the ducts at the nipple is lined by squamous epithelium. The main arterial supply is from the internal mammary and lateral thoracic arteries. The venous drainage is mainly accomplished by branches of internal thoracic veins, but variations occur. The most important lymphatic drainage is to the axilla, while less of the lymph flow is drained via internal and posterior intercostal lymphatics. The breast is affected by physiologic changes in breast morphology and function throughout life from menarche to menopause, and during each menstrual cycle. These changes are based on hormonal activity, mainly by prolactin, estrogen and progesterone. At menarche, the main events include development and growth of ductal and lobular units. At pregnancy, a remarkable rise of hormone levels induces growth and secretory activity of the breast. Post-menopausally, the breast undergoes involution characterized by atrophy of the parenchymal structures.

2.2.2 MILK PRODUCTION AND CALCIFICATIONS

The female breast is highly specialized for its primary function, the production of milk to nourish infants. The preponderance of milk-producing tissue in the breast of a female of child bearing age is typically converted to fat during the involution process that precedes the menopause. Minor involution processes also occur following the end of milk production and as part of the menstrual cycle. Milk production arises in the breast lobes. Generally, there are 15 – 20 lobes that converge on the nipple each of which spread out radially from it creating a tree-like pattern of ductal structures. Working backwards from the nipple, the lobe begins with a collecting duct that transfers the milk from the lactiferous duct to the suckling infant. The collecting duct immediately widens into a pouch-like structure called the ampulla that narrows and forms the segmental duct that is the trunk of the ductal tree. This duct branches several times, forming subsegmental ducts with correspondingly smaller diameters, before they enter a complex and important structure called the lobule. Inside the lobule, each of the subsegmental ducts further divides into 10 to 100 intralobular terminal ducts each of which end in a terminal ductile, where finally the milk is produced in sac-like units called acini, and from where it begins its voyage to the nipple. The structure surrounding the lobules is called a terminal ductal-lobular unit (TDLU) and it plays a key role in the pathology of breast cancer since it is there that many diseases arise.
2.3 OTHER BREAST IMAGING METHODS

Several methods have been used and studied in breast diagnosis, which will be shortly described below.

Clinical breast examination
Clinical breast examination (CBE) or breast self examination (BSE) with palpation of the breasts and regional lymph nodes is the basis for all evaluations (fig. 20). Cases of palpable malignant lesions with a normal mammogram have been reported [84]. Although important, clinical breast examination is unable to find small early stage malignancies. Breast lesions smaller than 1cm are usually very difficult or impossible to be detected at palpation, depending on the breast size, its density and the location of the lesion.

Figure 19: A sketch of the hugely complex anatomy of the breast showing the structures that are most relevant for breast cancer.

Figure 20: Schematic representation of a clinical breast examination procedure
Mammography
Mammography is currently the only imaging modality suitable for screening as well as for an evaluation of patients with clinical symptoms. It is also a commonly available method with established criteria for the evaluation and performance of examinations. Mammography performs very well in detecting tumors in fatty breast tissue and has the unique advantage of imaging microcalcifications. However, in dense breast parenchyma it can be difficult to detect a malignant lesion although microcalcifications are readily seen [85,86]. After years of practice and experience the American College of Radiology has produced a guide for the interpretation of mammograms which is in use, the BI-RADS (Breast Imaging Reporting And Data System) which offers further standardization of the method. Current developments in digital imaging might improve the overall performance of mammography increasing its sensitivity and specificity as well as decreasing the absorbed radiation dose.

Ultrasonography
Ultrasonography (US) is frequently used as a complementary method for distinguishing cysts from solid lesions and as an aid at punctures (fine needle or core biopsies) but it has not proved to be useful as a screening method [87]. With the development of small-part transducers US combined with mammography improves the detection rate of breast cancer especially in younger women with dense breasts where mammography appears of limited performance. The use of color Doppler US analyzing the blood flow of a lesion is a new method under evaluation [88]. Also currently under evaluation but promising appears to be the use of contrast media which might improve diagnosis and give new opportunities for localized treatment.

Because of its the high inter-observer variability US studies have been reported to explore reliable characteristics of breast masses at US and to define signs typical of malignant or benign lesions. So far US cannot be recommended for screening, not even for women with dense breast parenchyma, but is of adjunctive value in the differentiation of detected lesions (mammographic or palpable).
**Triple Diagnosis**

Triple diagnosis is a commonly used routine for the evaluations of breast lesions. It is a combination of clinical breast examination, mammography and fine needle aspirations [89]. In some cases where cytological evaluation is difficult (fibrotic lesions poor of cells) a core-biopsy is necessary to get a larger sample for a histopathological evaluation.

**Computed tomography.**

Chang tried computed tomography (CT) in breast examinations in 1977 and found that the use of contrast media is necessary. Computed tomography cannot be used as a screening tool for breast malignancies. It can however add useful information regarding recurrent malignancies, parasternal metastases or chest wall/skeletal engagement of breast malignancies. Clinically unsuspected lesions can thus be diagnosed rendering CT valuable when choosing therapy and planning the area for radiation treatment [90-92]. A major drawback of CT is the high radiation dose that is delivered to the patient. This makes it recommendable for few suitably selected patients.

![Computed Tomography Unit](image)

**Nuclear Medicine Imaging techniques**

Since the 80’s breast tumors have been evaluated using isotopes and many different scintigraphic techniques have been tried. During the last decade $^{99m}$Tc-Sestamibi which was used for myocardial evaluations, has gathered interest after showing accidental uptake in a breast tumor [93]. Even though scintimammography shows uptake in tumors, the signal to noise ratio is not sufficient to reliably detect tumors smaller than 1cm. Scintimammography can therefore not be used for screening but only as a complementary examination in selected cases with high specificity.

Over the recent years a lymph node evaluation method has been developed and used to detect whether the first lymph node drains lymphatic from the tumor making it possible to exclude the axillary lymph nodes from surgery [94].

Positron Emission Tomography (PET) (fig.23) is another method showing metabolic characteristics by the use of FDG (fluorodeoxyglucose) that can also be used to evaluate breast tumors and metastasizing disease. Although it shows high sensitivity its cost and technical complexity makes it scarcely available and is only recommended in a few selected cases [95,96].

![A PET scanner](image)
Thermography
Thermography is a method that, being radiation free, was initially considered to be valuable in breast diagnostics. There were findings supporting the use of thermography as a prognostic indicator [97,98]. Recent evaluations have shown that thermography has unacceptably high numbers of both false-positive and false-negative results, cannot be used as an independent prognostic indicator [99-101] and is thus not applicable in the diagnosis and detection of breast lesions.

Figure 24: A breast thermography system

Transillumination
Transillumination was originally described during the 1920-30’s. It uses red and infrared light and assesses the reflection, scattering and absorption of this light as it passes through breast tissue. During the last 50 years the method has been improved using new techniques and computer postprocessing [102-105], but at present is of no clinical use as its sensitivity is much lower than mammography and is not able to identify small lesions and lesions that are situated deep into the breast parenchyma.

Figure 25: The results of a Transillumination breast study

Electrical Impedance Scanning
A contemporary technique that is evaluated at a few sites is the electrical impedance scanning (EIS). The parameters that are evaluated are conductance and capacitance. The method is considered to recognize the changed metabolism of cancer cells, changes of cellular water content, the amount of extracellular fluid as well as membrane properties, changed orientation of malignant cells and the destruction of tight junctions and cell membranes. However the initial results are not promising making the method inapplicable in its present form for breast evaluations [106-109].
2.4 BREAST MRI

During a breast MRI examination the patient lies prone with her arms over her head on the tabletop of the MR unit having her breast placed in a dedicated double breast coil (fig. 26). In an up-to-date configuration this is usually a phased array coil which allows for higher spatial and temporal resolution of the dynamic imaging sequence (fig. 27).

Figure 26: A modern MRI system with the patient set up for a breast examination

The patient’s breasts hung pendulous inside the coil. In order to minimize the movement light pressure is usually exerted on the breasts by appropriate cushions or pressing plates integrated to the coil. A biopsy kit may also be integrated to the double breast coil designed to provide the ability to perform MR guided biopsies (fig. 27).

Figure 27: Left: a multichannel phased array breast coil configuration. Right: A phased array breast coil with a biopsy kit.

2.4.1 CONTRAST AGENTS

In 1978, Lauterbur [48] suggested the possible usefulness of paramagnetic ions as relaxation enhancers for magnetic resonance imaging. The first publications on the benefits of paramagnetic contrast agents in MRI appeared in the early 1980s [49,50]. Manganese chloride in particular, with its five unpaired electrons, was put forward as the prototype of a paramagnetic contrast enhancer. Compounds from the nitroxyl group, on the other hand, were shown to exhibit fairly good tolerance. These cyclic organic molecules owe their paramagnetic effect to one unpaired electron. This tends to give them a rather low effectiveness if compared to the relaxivity of metal ions. Apart from surprisingly good tolerance, one interesting perspective of this approach is to use this molecule as a label for biologically important compounds (e.g., glucose) in the analysis of transport and metabolic processes [51]. So far, however, none of these compounds has acquired significance in clinical practice. The first successful contrast agents were the paramagnetic ion-chelates, in
particular those containing polycarbonic acids. Experimental studies in animals were performed with a variety of metal ions and ligands such as Gd-DTPA, Fe-EHPG, Ferroxamine B and Cr-EDTA [52-55]. One representative of this class of substance, the dimeglumine salt of the gadolinium complex of diethylenetriamine pentaacetic acid, or Gd-DTPA for short, was chosen as a suitable candidate for clinical use. It is an extremely hydrophilic and stable gadolinium complex. Pharmacological studies have shown that Gd-DTPA is an almost biologically inert substance which does not interact with the organism (practically no protein binding can be measured), distributes in the interstitial space after intravenous administration and is excreted by glomerular filtration. The efficacy of a contrast agent can be further improved by the synthesis of compounds with increased relaxivity. The relaxivity of low-molecular-weight complexes is determined by their relatively short correlation time. The synthesis of higher-molecular-weight compounds leads to a prolongation of the correlation time and, hence, to an increase in the relaxivity [53]. Using a suitable high-molecular-weight backbone such as albumin, dextran or polylysine, up to 50-100 gadolinium atoms can be coupled per molecule. Because of their high molecular-weight, the compounds are distributed almost exclusively in the intravascular space and are therefore suitable for perfusion studies [56-59]. Contrast agent research has been successful in developing tissue-specific materials. One of the ultimate goals of contrast agent research is to identify a tumor-seeking material. The high sensitivity and excellent spatial resolution of MRI in combination with highly effective contrast agents may make the dream come true. According to experimental studies in animals, compounds have been created that exhibit some tumor-specific accumulation [60-62]. However, no published results exist of well controlled comparative experiments which might verify the statement. Thanks to advanced biotechnology, the synthesis of tumor-specific monoclonal antibodies has become possible. Gd-labelled antibodies have produced tumorspecific enhancement in laboratory animals [63-65]. Since most of the contrast agents administered do not accumulate in the tumor, the dose necessary to produce sufficient enhancement is still too high. Up to 10 g of a monoclonal antibody labelled with dozens of paramagnetic ions each will be required to achieve sufficient enhancement in man. Iron oxide particles (magnetites, ferrites), as small as large proteins, with superparamagnetic properties exhibit an extraordinarily strong T2-effect. Microgram quantities are sufficient to decrease the signal intensity even in a T1-weighted spin-echo sequence [66]. The combined use of MRI and new MR contrast agents will expand the potential of diagnostic imaging to new horizons. Tissue- and pathology-specific contrast enhancement will be possible using metal chelates or iron oxide particles. Blood-pool agents will augment the perfusion situation of organs or tumors. Latest developments in tumor- and receptor-specific enhancements by the use of ultrasmall iron particles may open a new dimension in radiology [67].

2.4.2 THE HISTORY OF BREAST MRI

After the introduction of gadolinium dimeglumine as MR contrast agent, several different approaches have been developed for MRI of the breast. Heywang et al [21] were the first to use gadolinium dimeglumine for MRI of the breast. They reported strong contrast enhancement of breast cancers, whereas the normal parenchyma exhibited only weak (if any) enhancement. Heywang suggested a technique that today would be called a semidynamic acquisition: they acquired one pre-contrast and two post-contrast image stacks. The main reason for obtaining the second post-contrast stack was to ensure detection of lesions with delayed enhancement that may be missed on the first post-contrast image. Imaging was performed with limited temporal and relatively high spatial resolution. Since temporal resolution was not the main focus, a 3D gradient echo technique with fat suppression could be applied.
The approach launched by Kaiser et al [22] was designed to track the rapid signal intensity changes that occur in the early post-contrast period. The technique they proposed could be called the archetype of dynamic breast MRI: they suggested acquiring one pre-contrast and a series of post-contrast image stacks including both breasts at the highest possible temporal resolution (60 sec). Rapid imaging at that time allowed only a limited spatial resolution and acquisition of only a small number of sections [21-25], such that only half of the parenchymal volume was covered. Because rapid imaging was necessary, image subtraction was used to suppress the signal from fatty tissues, rather than applying time-consuming active fat suppression techniques.

The concept of Harms et al [23] was based on the well-established fact that malignant lesions exhibit characteristic morphologic features that distinguish them from benign lesions. To improve analysis of subtle morphologic details, they advocated a technique that may serve as the archetype of static breast imaging: imaging of one single breast with high spatial resolution before and after contrast material injection. Since temporal resolution was not an issue in this approach, 3D gradient echo imaging was used, and fat suppression ensued by means of spectral pre-pulses (which were rather time consuming).

The two fundamental schools that evolved (and that were also separated geographically) were the “dynamic school” and the “static school.” The dynamic school (most popular in European countries) attempted to distinguish benign and malignant lesions by enhancement characteristics at high temporal resolution imaging. The static school (most popular in the U.S.) attempted the same by evaluating morphologic features of enhancing lesions at high spatial resolution. Due to the severe technical constraints, particularly during the early days of breast MRI, it was necessary to choose between either temporal or spatial resolution, depending on the diagnostic criterion that was given priority. Accordingly, the fundamentally different approaches published in the literature are merely a reflection of the fact that breast MRI is technically extremely challenging. The diverging demands of an optimal temporal and spatial resolution for the detection and classification of enhancing lesions can hardly be met even with today’s equipment. Because researchers had to cope with the technical shortcomings of their equipment, they started doing breast MRI at the two ends of the spectrum of imaging techniques that are suitable for breast MRI.

It is important not to misunderstand these different approaches as being contradictory or as being competitors for the “ultimate truth.” They are not meant to be used as alternatives, but have to be understood within the clinical and technical context of the time when they were written and published. Today, owing to the technical progress that has been made, it is possible to integrate these demands rather than compromising on one or the other. Therefore, modern concepts of breast MRI strive to consider both lesion morphology and contrast enhancement kinetics [24,25]. As a consequence, today there is considerable agreement in terms of what constitutes an appropriate pulse sequence for breast MRI. It is widely accepted that temporal resolution is a necessity — not only if one wishes to evaluate contrast enhancement kinetics, but also to improve the analysis of morphological details [25-27]. This is due to the fact that lesion-to-parenchyma contrast is best only in the early post-contrast period, whereas it deteriorates progressively in the intermediate and late post-contrast phase.

### 2.4.3 THE PATHOPHYSIOLOGICAL BASIS OF BREAST MRI

The sensitivity of magnetic resonance to blood vessels provides multiple possibilities for looking at vascular remodelling during tumor angiogenesis. MR can be used for mapping blood volume, vessel permeability, flow velocity, capillary diameter and blood oxygenation. The differences between tumor angiogenesis and the normal vascular bed are detectable by many of these approaches. MR can thus be applied for clinical detection, diagnosis and prognosis of cancer, as well as for basic analysis of the biological regulation of tumor angiogenesis, and for monitoring the effect of novel antiangiogenic therapies.
Tumours are not capable of generating vessels [28]. Initially, there are only minor, pre-existing vessels encased by the tumour growth, until de novo formation of new vessels by the host is stimulated by production of angiogenic factors. Angiogenesis probably begins in venules where endothelial sprouts develop, which in later steps form a new lumen and gain access to the arterial branch of the capillary bed. Already during this stage, arteriovenous shunts as well as veno-venous connections may develop from interconnected, lower-order branches [29].

Structural abnormalities characteristic for tumour vessels that have been reported are [30]:
1. Calibre variations with dilated and narrowed segments in a single branch.
2. Elongation and coiling.
4. The normal, precapillary architecture with dichotomous branching and decreasing size and diameter of the higher-order branches is disturbed.
5. Finally, the vascular wall is incomplete. Almost invariably, there is no muscular layer (except for pre-existing vessels encased by the tumour). But there may also be gaps in the endothelium, an incomplete basal membrane, and thereby a direct tumour-to-blood contact.

The degree of abnormality of the vascular anatomy probably depends on whether structural maturation can keep pace with angiogenesis. An almost normal architecture can be found in highly differentiated tumours, whereas anaplastic tumours may only show a chaotic network of irregular vessel-like spaces without recognisable, mature elements. Such structural abnormalities cause numerous functional impairments [29]:
1. The transcapillary permeability is increased (up to eight times normal). Mural defects may even be large enough to allow extravasation of red blood cells. Generally, increased permeability causes haemoconcentration and increased viscous flow resistance. A different mechanism appears to be related to vesico-vacuolar organelles. They make substances pass across the endothelial cell itself and may, in addition to mural defects, be involved, for example, in the transcapillary exchange of MRI contrast agents. Vascular endothelial growth factor (VEGF) has been shown to increase vascular permeability [31].
2. In highly vascularised tumours the total vascular cross-sectional area is increased. This will lower the peripheral flow resistance. However, lumen irregularities may regionally increase flow resistance. Along with haemoconcentration and increased interstitial pressure, this may even lead to local stasis.
3. Interstitial pressure is near atmospheric values in normal tissue, whereas in tumours it may reach 50 mmHg or even more. The main factors attributed to interstitial hypertension are increased vascular permeability and lack of lymphatic drainage. Furthermore, the interstitial space is usually three to five times larger than normal. High interstitial pressure leads to compression of vessels inside the tumour.
4. Where arteriovenous shunts develop, a fraction of blood will bypass the capillary bed. Consequently, despite a low global flow resistance and a high global blood flow, a variable proportion of the tumour may be deprived of its blood supply. Shunt fractions are estimated to range between 8 and 43%. Tissue with only venovenous flow will be hypoxic due to slow flow velocity and low oxygen saturation of the supplied blood. The effect of such functional mechanisms is not constant throughout the tumour but highly inconstant, spatially and temporally. There may be stasis in one part and maintained flow in another part of the lesion. It is estimated that only between 20 and 80% of the tumour vessels are actually patent.

Considering also local factors, such as invasion by tumour cells, or variations in intercapillary distance, it is not surprising that vessel density and blood flow can differ between tumours by a factor of 100, and even inside a tumour by a factor of 55 [29]. Even information on global blood flow and flow resistance may be of limited relevance regarding local oxygen and nutrient supply. Numerous angiogenic factors have been identified. They appear not only to influence growth of the primary tumour but (systemically distributed) also of distant metastases, by means of a complex regulatory system of angiogenic and anti-angiogenic factors. Angiogenic factors may be either released by the tumour cells themselves, or by host cells recruited by the tumour. They may also possibly be mobilized from the extracellular matrix [28, 32]. Factors known to stimulate the release of angiogenic factors are, for example,
hypoxia (from macrophages) [33], or a p53 tumour suppressor gene defect (via a deficiency of the antiangiogenic factor thrombospondin-1) [34]. Increased levels of the angiogenic basic fibroblast growth factor (bFGF) have been found in the serum of children with brain tumours or men with prostate carcinoma [35,36].

**ASPECTS OF TUMOUR VASCULARITY**

There are different aspects of tumour vascularity which are best imaged with one or the other modality:

1. The overall volume flow in a tumour is the most difficult to measure. Such measurements would have to be performed over the lesion itself, unless it is supplied over a single vascular pedicle (which is only rarely the case). Thus far, no method has been proven to measure overall blood flow in vivo and non-invasively inside a grossly amorphous volume.
2. The presence of blood flow and its velocity are registered with Doppler sonography, if the related vessels are large enough. Doppler also permits estimation of the intratumoural flow resistance, which may reflect interstitial pressure.
3. Microvascular permeability is a major factor affecting the distribution of contrast media in the extracellular space. Together with the arrival via supplying vessels, extravasation is probably a major factor contributing to contrast enhancement with CT or MRI. Owing to radiation dose restrictions, dynamic enhancement measurements are limited to MRI. Pharmacokinetic models have been developed to extract the components of intravascular delivery and transcapillary permeation from a complex signal-time curve.
4. Finally, there are architectural criteria, best depicted with angiography, but increasingly well depicted with MR angiography. With colour Doppler, architectural features can be assessed only by the highly experienced examiner, but they are difficult to reproduce and hard to communicate. There are attempts to improve documentation of tumour vessel architecture using three-dimensional Doppler reconstruction programs, but they are still in a prototype stage.

**2.4.4 DYNAMIC STUDIES WITH MRI**

Current MRI contrast agents are based on gadolinium chelates and pass from the intravascular space to the interstitium, thereby causing parenchymal enhancement. Malignant tumours frequently reveal higher enhancement with these extracellular contrast agents than does the normal surrounding parenchyma. Whereas this feature has been the diagnostic basis for the use of contrast agents, the involved pathophysiological processes and their potential diagnostic information have been largely neglected. With the introduction of fast sequential imaging techniques in MRI, the necessary tools to assess the kinetic enhancement patterns in tumours have become available [37]. For reliable assessment by MRI, an optimised sequence is required in order to use the relative changes of signal intensity as a parameter of contrast enhancement [38]. Furthermore, the temporal resolution of a dynamic sequence as well as the speed of contrast media infusion is relevant for detecting characteristic changes in the enhancement pattern. If those aspects are addressed, tumours with an active neoangiogenesis enhance rapidly, with an early peak followed by a subsequent washout (Fig. 28). Dynamic multislice studies allow a detailed analysis of tumour enhancement but generate a vast number of images. To facilitate diagnostic assessment, data reduction techniques should be implemented for visualisation such as the use of pharmacokinetic parametrisation. Dynamic imaging based on T2* effects can also be used for assessment of microcirculation. Analysing the changes in signal intensity with respect to an input function obtained from a major supplying vessel enables a quantitative assessment of absolute blood circulation [39]. Compared with T1-based sequences, this method directly measures relative blood volume. However, its use is restricted to the brain with its intact blood-brain barrier until purely intravascular contrast agents become available.
Non-enhanced MR angiographic techniques have been established as valid diagnostic methods to assess vascular changes caused by tumours. Over the last years the molecular mechanism controlling angiogenesis so as to match oxygen supply and demand was revealed. The basic element of this regulation is a specific hypoxia inducible transcription factor (HIF-1) [28] that controls the expression of vascular endothelial growth factor (VEGF) [29]. Saturation kinetics of the vascularization of tumors implanted in nude mice, revealed by MRI suggest that this physiological regulatory mechanism that is present in each and every cell in the body, is the dominant signal inducing vascularization of solid tumors [30]. Thus, tumors deficient in HIF-1 showed reduced vascular functionality, as measured by Blood Oxygenation Level Depended (BOLD) contrast MRI [31].

Already in clinical use is the dynamic assessment of contrast enhancement [40]. Evaluation of breast cancer and other lesions have greatly improved our understanding. Correlative MRI studies and histopathological analysis (e.g. breast tumours, brain tumours, cervical cancer) [41-44] have established that the main factors determining the enhancement pattern of tumours are:

1. The vessel density within a tumour
2. The permeability for micro- and macromolecules
3. The extent of the extracellular space.

Analysing those features has led to a new pathophysiological concept of enhancement in tumours demonstrated in breast lesions. The vascular density in malignant tumours is higher than in normal parenchyma, but there is a great overlap with benign lesions. Inflammatory and proliferative processes as well as epithelial hyperplasia also lead to increased vascular density. Although vascular density is the major factor contributing to the overall intensity of enhancement, the latter does not help for differential diagnosis. However, significant differences with regard to the transcapillary exchange rate of the contrast agent (according to pharmacokinetic models) was noted not only between malignant and benign lesions, but also between invasive ductal and lobular carcinomas, or subtypes of fibroadenomas, respectively (Fig. 29) [45]. Unfortunately, in situ carcinoma (DCIS) frequently escapes detection by MR mammography. This is not surprising considering that detectable neoangiogenesis begins when in situ carcinomas progress to invasive cancers. Thus far, dynamic MRI allows a non-invasive assessment of microcirculation. The detectable enhancement patterns are directly influenced by the vascular density and permeability. These features can be used to assess changes in microcirculation during therapy [46]. Therapy monitoring with MRI has been done during chemotherapy in breast cancer, osteosarcomas and brain tumours. Changes in contrast enhancement were observed prior to changes in tumour volume (Fig. 30). Currently, no data
are available as to whether changes during therapy occur first in the metabolism (detectable by FDG PET or MR spectroscopy), in the microcirculation, or whether they are both interdependent. According to the available data, alterations of the transcapillary exchange rate seem to be more indicative of therapy response than are changes in absolute intensity [47]. Under therapy, a decline in vascular permeability appears to occur before regression of vessel density. These findings are important to understand potential differences between the accessible diagnostic information from Doppler sonography compared with dynamic MRI.

Figure 29. Patient with proliferative mastopathy and a large, invasive ductal carcinoma in the left upper outer quadrant (arrow). The time intensity curves reveal characteristic features, a continuous, moderate rise in intensity over time in the proliferative mastopathy, whereas the carcinoma present a rapid, intense rise with a maximum and a subsequent decrease

Figure 30: Patient with invasive ductal carcinoma receiving neoadjuvant chemotherapy monitored by functional MR mammography. a During therapy, a decrease in volume can be readily recognised. b The pharmacokinetic maps and the time-intensity curves reveal a slower enhancement coinciding with response to therapy
2.4.5 MRM EXAMINATION ANALYSIS AND INTERPRETATION

According to Heywang-Köbrunner and Beck [68], a typical evaluation of a DCE-MRI study consists of:

1. Search for or exclusion of an area of enhancement.
2. Analysis of the enhancement characteristics, which are:
   • Presence, speed and amount of enhancement
   • Presence and speed of washout
   • Morphology

![Image of DCE-MRI slice](image_url)

**Figure 31:** Axial slice of an image volume. The upper left image depicts the extent of the ROI (white box) which content is displayed with a zoom factor of 2.5 in the remaining three images. The white circle encloses the lesion whose segmentation is reflected by white pixels. The upper right image depicts the ROI with intensity values reflecting the precontrast signal. The intensity values of the two images in the bottom row reflect signal values in the first and last postcontrast image, respectively. In particular the margin of the lesion exposes a clear signal enhancement in the postcontrast period.

Due to its physiological features, breast tissue affected by benign or malignant disorders tends to accumulate significantly more contrast agent molecules than healthy tissue. Therefore, suspicious tissue masses expose temporal kinetic signals which exhibit signal enhancements in the postcontrast period (Fig. 31). A standard approach for detecting such enhancing tissue regions is the examination of subtraction images. A subtraction image is computed by subtracting the precontrast image from one of the postcontrast images. The image displays non-enhancing tissue with low grey values whereas strong enhancing tissue such as carcinoma appears with high intensities.
Figure 32: Three main types of temporal kinetic patterns can be observed for breast lesions. Signals of type Ia/IIb exhibiting a steady uptake over the entire postcontrast period are likely to be measured for benign tissue. Malignant tissue typically exhibits kinetic signals with a strong uptake followed by a wash-out in the late postcontrast period (Type III). Signals of type II are rated as suspicious for malignancy according to the strong signal uptake followed by a course with indistinct characteristics in the late postcontrast period [69].

However, typically a number of tissue regions exists which exhibit a certain signal enhancement, although they are not affected by a pathological disorder. For a thorough evaluation, several subtraction images based on different postcontrast images should be examined. It is proposed, [68] that at least the subtraction images based on one early and one late postcontrast image have to be considered in addition to the original images of the DCE-MRI sequence.

Subsequent to the localisation and delineation of the extent of lesions, they have to be examined with respect to signs which are indicative for benign or malignant disorders of the local tissue. For this purpose, the radiologist evaluates the enhancement patterns of different lesion voxels and the morphology of the entire tissue mass.

The temporal kinetic signals enable experienced radiologists to infer qualitative information about the physiological parameters of the local tissue. As these physiological parameters are strongly influenced by the type and state of the tissue, distinct temporal kinetic patterns can be observed for different types of tissue. Temporal kinetic signals can either be measured for single voxels or for a larger, manually marked region-of-interest (ROI). The examination of signals associated with single voxels provides the most detailed information about the lesion. Nevertheless, the examination of all voxels of a lesion is extremely time-consuming and becomes quickly impracticable for lesions of middle or large size. Further more, the assessments of individual temporal kinetic signals have to be correlated with those of the neighbouring voxels, because isolated signals with a suspicious temporal course are frequently caused by e.g. a larger vessel and not by a disorder of the tissue. Thus, lesions are typically analysed by displaying the average kinetic signals of all voxels inside manually placed ROIs. Evaluation of entire lesions by means of average kinetic signals of a small number of manually placed ROIs substantially reduces the expenditure of time. However, the ROIs have to be placed very carefully in order to avoid an effect which is comparable to the partial-volume effect: Averaging the kinetic signals of a ROI which covers a larger number of
voxels of healthy and cancerous tissue may lead to an indistinct time course signal which misleadingly indicates unsuspicious tissue.

Three major types of temporal kinetic signals can be distinguished for lesion tissue [69]. The first type of signal exhibits a CA concentration that either continuously increases (Type Ia, Fig. 28) or flattens in the intermediate and late postcontrast period (Type Ib, Fig. 28). The second type of signal (Type II, Fig. 28,) shows an initial uptake of CA concentration in the early postcontrast period followed by constant CA concentration in the intermediate and late postcontrast period. Finally, signals of type III (Type III, Fig.28) expose a clear wash-out of CA concentration in the intermediate and late postcontrast period after a significant signal uptake in the early postcontrast period. Non-lesion tissue such as fat or muscles typically exhibits temporal kinetic signals which do not show any or only weak enhancements over the entire considered period of time. For the categorisation of the signal time curves, the short-time series are plotted as relative enhancement curves as calculated by

\[ spt = (spt - sp1/spt) \cdot 100, \quad t = 1, \ldots, nt \]  

with \( sp1 \) as the signal intensity at position \( p \) in the precontrast image.

Kuhl et al [69] showed that type Ia/Ib signals are likely to be yielded from benign lesions such as fibroadenoma (fibrocystic changes). Type III signals are rated as indicative for malignant tissue, whereas type II signals are rated as suggestive for malignancy. The provided experiments considering a cohort of 266 cases indicate a sensitivity of 91% and a specificity of 83% (diagnostic accuracy 86%), if lesions are classified using the described categorisation scheme.

Additional information can be obtained from the morphological structure of the entire lesion. Properties such as characteristics of the margin (smooth, lobulated, irregular or spiculated), internal spatial homogeneity of the lesion (homogeneous, intermediate, heterogeneous), presence of peripheral enhancements (rim enhancement) or internal non-enhancing septation give rise to a malignant or benign state of lesions [70]. For a reliable assessment of morphological characteristics of lesions, MR images need to have high spatial resolution. On the other hand, the assessment of temporal kinetic signals demands a high temporal resolution, which is achieved at the expense of spatial resolution. In practice, the optimal diagnostic performance is achieved by the combined assessment of the lesion’s morphology and its temporal kinetic signals [71]. The combination of both types of diagnostic criteria is also suggested by the experiments of Szabo et al. [70], who evaluated the impact of the different diagnostic criteria on the diagnostic performance of a proposed scoring scheme. The following table shows a brief summary of the major characteristics of benign, suspicious and malignant lesions. Morphological properties describe spatial patterns of entire lesion masses. The temporal kinetic patterns reflect characteristics of the course of temporal kinetic signals which either refer to single voxels or to ROIs consisting of several voxels.

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Morphology</th>
<th>Temporal Kinetic Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Smooth margin, homogenous tissue</td>
<td>Steadily increasing signal, decreasing slope in the late postcontrast period</td>
</tr>
<tr>
<td>Suspicious</td>
<td>Poorly defined margin</td>
<td>Strong uptake, plateau in the late postcontrast period</td>
</tr>
<tr>
<td>Malignant</td>
<td>Irregular or spiculated margin, heterogeneous tissue, rim enhancement</td>
<td>Strong uptake, washout</td>
</tr>
</tbody>
</table>
2.4.6 CHALLENGES OF DCE-MRI DATA INTERPRETATION. THE DIAGNOSTIC PROBLEM.

Due to the lack of standardised protocols for DCE-MR imaging, there are no general guidelines for the interpretation of the image data. The definitions of diagnostic criteria such as strong signal uptake, heterogeneous enhancement or spiculated margin are subjective and strongly depend on the experience of the investigator. As a consequence, a certain inter- and intra-observer variance [72,73], i.e. varying outcomes from different observers or from repeated assessments by the same observer, has been reported in the domain of DCE-MRI [74]. The individual interpretation strategy typically depends on the preferences of the investigator, who has to adapt to the given technical capabilities of the imaging hardware such as the temporal and spatial resolution, but also to the patient population with its prevailing histological features. There has been a variety of attempts to quantify the characteristics of kinetic signals by using measurements such as the slope of enhancement. However, manually chosen parameters such as thresholds, above which certain measurements have to be considered as indicative for malignant or benign tissue, still depend on the investigators experience and may vary with the deployed imaging protocol.

Apart from the varying imaging protocols, the multitemporal nature of the image data turns the interpretation of DCE-MR images into a challenging task for a human investigator. The key-information of the DCE-MRI data, i.e. the temporal kinetic of the signals, is fragmented and distributed over the entire image sequence. To take full advantage of the DCE-MRI data, the investigator has to examine all images of the sequence simultaneously rather than subsequently. For the localisation of enhancing tissue regions, the information of several subtraction images has to be correlated to assure that fast as well as slow enhancing lesions are detected. Following the localisation of suspicious masses, the temporal kinetic signals associated with the lesion voxels have to be examined in order to characterise the lesion as malignant or benign. Due to the heterogenous nature of cancerous tissue, average temporal kinetic signals of whole-lesion ROIs commonly exhibit only indistinct signal characteristics. In fact, reliable results are only obtained if the kinetic signals of individual lesion voxels or averaged signals of ROIs, carefully placed at the most enhancing regions, are examined (Fig. 33). The placement of such ROIs by means of a conventional display of the three-dimensional image data, i.e. two-dimensional slices of the original image volumes and the subtraction images, strongly depends on the expertise of the radiologist and may vary for repeated exami-

---

Figure 33: Two temporal kinetic signals as measured for a case with a histological proven malignant lesion. The green curve reflects the course of the average signal of a whole-lesion ROI, enclosing all lesion voxels as marked by the manual lesion segmentation(orange ROI). The blue curve depicts the average signal of a ROI which was manually placed over a strong enhancing subregion of the lesion (green ROI). Due to the heterogeneity of the cancerous tissue, the average signal of the whole-lesion ROI exposes signal characteristics which are more likely for benign tissue. In contrast, the average signal of the manually placed ROI exhibits signal characteristics which are suggestive for malignancy and, therewith, indicates a lesion classification which is concordant with the outcome of the histological examination.
nation or for examination by different radiologists. The continually growing demands for scanners with an increasing spatial and temporal resolution facilitating the examination of ever smaller anatomical structures is the driving force for the rapidly enhancing capabilities of modern imaging hardware. In this situation, the manual evaluation of the multitemporal data by a radiologist may become a limiting factor for the utilisation of such advanced scanners in clinical practice. Radiologists are faced with an increasing amount of information obtained from various, increasingly powerful imaging modalities. As a consequence, there is a substantial demand for CAD systems to assist radiologists in the examination and interpretation of the information by e.g. optimising the display of DCE-MRI data or providing a semiautomatic placement of ROIs to limit the expenditure of time and to attenuate the inter and intra-observer variability.

**COMPUTER AIDED DIAGNOSIS SYSTEMS**

To avoid that the human investigator becomes a limiting factor in the diagnostic process, an increasing demand for CAD systems assisting the human expert exists. Focussing on breast cancer diagnosis based on DCE-MRI data, the application of CAD systems is motivated by the properties of the complex image data, namely:

- A high spatial resolution of MR images displaying the region of interest as a three-dimensional image consisting of several hundreds two-dimensional image slices. These images provide a large amount of spatial information about tissue and anatomical structures. At the same time, the phenomena under investigation, i.e. pathological disorders of tissue, are typically represented by only a very small fraction of voxels.
- A temporal dimension of data which causes the key-information to be distributed on a large number of three-dimensional images. Subtle differences of certain magnitudes between a very small number of voxels provide evidence to cancerous masses, whereas other signal variations are caused by blood flow or artefacts which mainly stem from respiration and heart beat motions.
- A multiparameter component, which can be introduced by acquisition of images with different T1/T2-weightings. Variation of the influence of the two relaxation processes leads to a varying contrast between different anatomical structures and may facilitate the elimination of tissue regions misleadingly identified as suspicious.
- From these properties and from the conceptional formulation of DCE-MRI data analysis [68], the following three main areas of application of CAD systems in DCE-MRI analysis can be formulated:

I Efficient visualisation of the entire image data in order to provide access to the key information of the DCE-MRI data and to facilitate manual data exploration.
II Localisation of suspicious masses in order to reduce the amount of image information that has to be evaluated by the investigator by guiding the investigator’s attention directly to the spatial locations of suspicious masses.
III Characterisation of suspicious masses in order to assist manual examination or to perform a fully automatic classification of lesion compartments or entire lesions resulting in pathophysiological assessments.

In recent years, different CAD systems for DCE-MRI data have been proposed. The area of application of such tools ranges from software providing a platform for data exploration and manipulation [75,76], to analytical methods evaluating the measured signal in order to provide an assessment of the local tissue or quantitative information about its physiological parameters. Such analytical methods can be subdivided into two groups. The first group are model-based techniques which employ an explicitly formulated mathematical model of the physiological process underlying the recorded signal. The second group consists of data-driven techniques which derive implicit models by a data-driven adaptation to the measured image data.
2.4.7 MODEL-BASED ENHANCEMENT ANALYSIS

Model-based approaches such as pharmacokinetic models or the three-time-points (3TP) method are based on explicitly defined mathematical models describing the physiological process underlying the measured signal or the course of the measured signal itself. Thus, both methods depend on extensive a-priori knowledge about the phenomenon under investigation. Evaluation of the measured temporal kinetic patterns with one of these models allows inferring quantitative information about physiological parameters describing the vascular properties of the local tissue.

Figure 34: Pharmacokinetic models provide mathematical models for the temporal kinetic signals examined in DCE-MR image sequences. The models consider contrast agent concentration in as well as the exchange of contrast agent molecules between tissue compartments. The temporal kinetic patterns as measured by a T1-weighted DCE-MRI protocol reflect the temporal course of contrast agent concentration in the extravascular-extracellular-space compartment.

PHARMACOKINETIC MODELS

Pharmacokinetic models [77-79] are widely used for modelling dispersion profiles of molecules such as drugs or contrast agents in the tissue. Physiologically meaningful parameters are combined in a mathematical model describing the temporal change of molecule concentration in the considered tissue compartments (Fig.34). Fitting these models to a recorded signal such as the DCE-MRI signal describing the change of CA concentration enable physicians to infer quantitative information about the underlying physiologic process. This information can turn be displayed as a parametric map. Parametric maps illustrate spatial variations of physiological parameters by voxels displayed in pseudo-colours reflecting the local parameter values.

DCE-MRI considers the dispersion of contrast agent molecules in the tissue. More precisely, the signal of a T1-weighted imaging sequence is predominately sensitive to the quantity of CA molecules in the extravascular-extracellular-space of tissue. The complexity of the physics behind MRI prohibits a complete and detailed model and certain simplifications are necessary. The most frequently used pharmacokinetic models consider only a limited number of compartments such as the blood plasma compartment and the extravascular-extracellular-space compartment. Furthermore, most models assume [78]:
1. A uniformly distributed CA inside the compartment $C_i, C_j$.
2. A linear inter-compartment flux $k_{ij}$ of CA molecules between two compartments $C_i, C_j$, i.e. a flux which is proportional to the difference between the CA concentration in both compartments.
3. Time invariant and constant parameters describing the compartments during the period of data acquisition.
The mathematical description of all kinetic models used for DCE-MRI analysis can be ascribed to the generalised kinetic model [79]

\[
\frac{dC_t}{dt} = K_{\text{Trans}} \left(C_p(t) - \frac{C_t(t)}{v_e} \right) = K_{\text{Trans}} C_p(t) - k_{ep} C_t(t) \tag{14}
\]

with \(C_t\) as the concentration of CA in the lesion tissue and \(C_p\) being the concentration of CA in the arterial blood plasma. The parameters of interest are the transfer constant \(K_{\text{Trans}}\) and \(k_{ep} = K_{\text{Trans}}/v_e\) with \(v_e\) being the fractional volume of extravascular-extracellular-space. \(K_{\text{Trans}}\) reflects the flux of CA molecules through the vascular endothelium whereas \(k_{ep}\) relates to the flux between the extravascular-extracellular-space compartment and the blood plasma compartment. The combination of both parameters provides information about perfusion and vascular permeability and allows for assessing the 'leakiness' of vasculature, which reflects the angiogenesis within a tumour [80].

In practice, values for \(K_{\text{Trans}}\) and \(k_{ep}\) are estimated by a least-square fit of the model to the temporal kinetic signal \(s_p\) as measured at the spatial position \(p\). A voxel-by-voxel evaluation of the entire lesion using the pharmacokinetic model leads to position dependent tuples \((K_{\text{Trans}}, k_{ep})_p\). These can be displayed as pseudo-colours superimposed on a two-dimensional (Fig. 35) or three-dimensional visualisation of an MR image and provide a physiologically meaningful visualisation of the data depicting the spatial variation of tumour vasculature throughout the lesion [81].

![Parametric map depicting the local value of \(K_{\text{Trans}}\) as pseudo-colours. The image indicates a high microvessel density (high \(K_{\text{Trans}}\)) at the margin of the lesion surrounding a necrotic core. Both properties are indicative for malignancy. (Image provided by David Collins, Cancer Research, UK.)](image)

**THREE-TIME-POINTS METHOD**

Even though the three-time-points (3TP) method [82,83] is literally not a pharmacokinetic model, it provides a pseudo-colouring of lesion voxels which has shown to be related to the tissue parameters \(K_{\text{Trans}}\) and extravascular-extracellular-space fractional volume \(v_e\). A 3TP based voxel-by-voxel colouring of lesions requires DCE-MRI sequences consisting of one precontrast, one early postcontrast and one late postcontrast image as measured at time points \(t_1\), \(t_2\) and \(t_3\), respectively. The strength of the signal uptake in the early postcontrast period is mapped to the intensity of the pseudo colour, whereas the presence of a wash-out is mapped to the colour hue. Both values are obtained from a computational inexpensive model, which allows for a rapid evaluation of lesions.

**Signal Model of 3TP**

Let each voxel with spatial coordinate \(p\) be associated with a temporal signal triple \(s_p = (s_{p1}, s_{p2}, s_{p3})\). Then, each voxel is mapped to a pseudo colour

\[cp = (hp, ip)\] with colour hue \(hp\) and intensity \(ip\).
The colour intensity is calculated by

\[ ip = \frac{(spt2 - spt1)}{(t2 - t1)} \]  

(15)

and displays the strength of the signal uptake between the precontrast and the early postcontrast image. For the purpose of visualisation, the intensity corresponding to the strongest signal uptake observed for a certain lesion is scaled to 255. The colour hue reflects presence or absence of a significant signal wash-out between the two postcontrast images:

\[
\begin{align*}
\text{red} & : \text{if } spt3 < spt2 \land |spt2 - spt3| > \sigma sp t2 \\
\text{blue} & : \text{if } spt3 > spt2 \land |spt2 - spt3| > \sigma sp t2 \\
\text{green} & : \text{else}
\end{align*}
\]

(16)

The parameter \( \sigma \) controls the tolerance for the comparison of the two postcontrast values. Only a signal change of a certain magnitude, e.g. 10% of the early postcontrast value, is rated to be indicative for presence or absence of a significant signal wash-out (see Fig 36-Left).

Figure 36: Left: Illustration of the 3TP pseudo-colouring scheme. The intensity of the pseudo-colour reflects the amount of signal uptake between the precontrast and the early postcontrast image. The colour hue reflects presence or absence of a significant wash-out in the postcontrast period. Right: The 3TP calibration map illustrates the relation between pseudo-colours and values of the \((K_{\text{trans}}, v_e)\) tuple. A typical parameter tuple for malignant (M) and benign (B) tissue is indicated by the white crosses, respectively.

Pathophysiological Interpretation and Model Calibration

The pathophysiological interpretation of the 3TP outcome is given by a calibration map which illustrates the relation between pseudo-colours \( c \) and tuples of physiological parameters \((K_{\text{trans}}, v_e)\) [Weinstein et al., 1999]. Artificial temporal kinetic patterns are generated for tuples \((K_{\text{trans}}, v_e)\) with \(K_{\text{trans}}, v_e \in [0, 1]\) using the pharmacokinetic model of Tofts and Kermode [77] and are mapped to pseudo-colours by 3TP. These pseudo-colours are displayed at the corresponding positions \((K_{\text{trans}}, v_e)\) leading to a 2-dimensional calibration map (Fig. 36, right). The \((K_{\text{trans}}, v_e)\) parameter space is subdivided by 3TP into three regions. Tissue with high microvessel density and permeability (high \(K_{\text{trans}}\)) and high cell density (low \(v_e\)), which in combination is indicative for cancerous tissue, is displayed intense red. A low cell density (high \(v_e\)) and a low microvessel density and permeability (low \(K_{\text{trans}}\)) is indicative for benign tissue and is displayed blue. Both regions are separated by a green region marking parameter tuples with indistinct pathological interpretations.
The relation between \((K_{\text{trans}}, v_e)\) tuples and associated pseudo-colours depends on the tolerance parameter \(\sigma\) and the design of the MRI protocol (time points of image acquisition, T1/T2 weighting, etc.). All parameters have to be faithfully selected in order to obtain an optimal pixel mapping function. In practice, the time points of image acquisition as well as \(\sigma\) are chosen for a certain imaging protocol by evaluating the corresponding calibration maps. Thereby, the pseudocolour at two positions \(B = (0.3\text{min}^{-1}, 0.5)\) and \(M = (0.95\text{min}^{-1}, 0.5)\) in the \((K_{\text{trans}}, v_e)\)-space are regarded particularly. The corresponding parameter tuples have shown to be typical for benign and malignant tissue, respectively. The pixel-mapping function is well calibrated, if the positions \(M\) and \(B\) are simultaneously located in the red and blue region, and a green corridor of adequate width separates both regions. If lesions are examined with the 3TP technique, Kelcz et al [82] suggest regarding lesions exposing more than 15% red voxels as being malignant whereas lesions exposing more than 50% blue voxels and low intensities are likely to be benign.
3. MATERIALS AND METHODS

3.1. CASE SAMPLE

The case sample consists of 57 breast lesions from 55 patients. All patients were referred for magnetic resonance mammography following mammographic findings. Histological examination of these lesions verified 30 of them as malignant and 27 as benign.

3.2. IMAGING PROTOCOL

The MRI examinations were carried out on a 1.5T system (Magnetom Vision; Siemens, Erlangen, Germany) with a bilateral dedicated phased-array breast coil. MRI examinations for all premenopausal patients were done in the second week of the menstrual cycle to minimize glandular tissue enhancement. The patient was in a prone position. The imaging protocol consisted of an initial scout view that provided axial, coronal and sagittal images of the right and left breast, in order to localize the spatial distribution of the parenchymal volume in both breasts. Transverse TURBO SPIN-ECHO T2-weighted sequences (TR 4200, TE 90, flip angle 180°, matrix 252x256, FOV 350 mm, section thickness 5 mm, number of slices 25, acquisition time 2min and 35sec) and TIRM sequences (Turbo inversion recovery magnitude sequence (TR 9128, TE 60, TI 150msec, flip angle 180°, matrix 242x256, FOV 380 mm, section thickness 3 mm, number of slices 28, acquisition time 3min and 29sec) were acquired. A coronal three-dimensional T1-weighted spoiled gradient echo volume acquisition (TR 8.1, TE 4, flip angle 20°, matrix 105x256, FOV 320 mm, section thickness 160 mm, number of slices 64, acquisition time 1min) was then performed both prior to and then five times over a period of 5-8 min after the intravenous injection of 0.2mmol/kg of gadopenate dimeglumine (Omniscan, Magnevist) followed by a 10-ml saline solution flush. Over the whole dynamic series the system’s receiver adjustment remained unchanged. After the dynamic series, image subtraction was performed to suppress the signal from fat in order enhancing lesions to be identified on the subtracted images. The enhancing lesions on the subtracted images were also identified on the non-subtracted images in order to exclude subtraction artifacts or other normal enhancing structures such as dilated vessels.

3.3. GENERATION OF IMAGE KINETIC FEATURE MAPS

The dynamic image sequence that is a basic part of any MR Mammographic examination procedure can provide a variety of features which quantify different aspects of the kinetic behavior of the contrast agent that is injected to the patient just before the acquisition of the images. As it is already noted, this kinetic behavior reflects the way a certain tissue is supplied with blood which in turn indicates the geometry and state of the vessels. In their effort to quantify this kinetic behavior many authors have proposed a variety of metrics that are calculated from the intensity-time curve of an either manually or automatically placed ROI that circumscribes the tissue under investigation, which are generally referred to as empirical or semi-quantitive kinetic parameters or features. [69, 110-115].

Some of these proposed features are:

**Strength of lesion enhancement**

Heywang et al [110] quantified a normalized (to the signal of fatty tissue) enhancement ratio and classified the lesions as malignant ($S_n>300NU$), borderline ($300NU>S_n>250NU$) and non
significant (250NU>S$_a$) with a sensitivity of 100% and specificity of 27% in a series of 144 patients.

**Velocity of lesion enhancement**
Kaiser et al [111] quantified a normalized (to the baseline lesion signal intensity) enhancement ratio and used the velocity of this measurement as a classification criterion as they found that malignant lesions reveal an enhancement rate over a threshold of 100%. They reported a sensitivity of 99% and a specificity of 98% but they did not validate their results in a large series of patients. Stomper et al in mid 90’s [112] via the same technique and again in a small series of patients reported a sensitivity of 92% and a specificity of 61%.

A different enhancement velocity quantification approach was proposed by Kneeshaw et al in 2005 [113]. They calculated the ratio of the peak signal enhancement normalized to the precontrast signal to the actual time that peak enhancement occurs, at manually placed ROIs and called this ratio normalized Maximum Intensity Time Ratio or nMITR. In a series of 88 patients with clinically occult lesions that were associated with microcalcifications they reported 75% sensitivity and 88.2% specificity.

**Time point of lesion enhancement initiation**
Gilles et al in mid 90’s [114] using a similar technique of high temporal resolution based the lesion classification on the determination the time point of lesion enhancement relative to arterial enhancement and suggested that every lesion that enhances in the first 94secs (first image) is to be considered malignant. They reported a sensitivity of 95% and a specificity of 53% in a series of 134 patients.

**Time point of lesion enhancement initiation and spatial onset of enhancement within the lesion**
Boetes et al in mid 90’s [115] using an ultrafast imaging technique (turboGRE-single section (low coverage)-temporal resolution of 2.3sec) observed that malignant lesions start to enhance 11.5secs after bolus arrival in the descending aorta, and that in malignant lesions enhancement starts in the periphery and progresses in a centripetal manner while benign lesions enhance centrifugally. They reported a sensitivity of 95% and a specificity of 86% in a series of 87 lesions.

**Shape of enhancement time curve**
Kuhl et al in late 90’s [69] suggested that in addition to early post contrast period intermediate an late post contrast phases also yield diagnostically useful information. After qualitative evaluation of the time intensity curves and their classification in one of four general types (continuous enhancement and continuous enhancement with slower rate at late phase – probably benign, plateau after the early increase and washout after the early increase – probably malignant) in a series of 266 enhancing lesions they achieved a sensitivity of 91% and a specificity of 83% (fig 37).

Instead of creating a tool able only to measure such empirical kinetic features we preferred to generate feature maps for each slice of the dynamic imaging sequence and perform all measurements by manually placed ROIs directly on these maps. Such an approach has the advantage of allowing a visual inspection of distribution of the values of each feature over the whole area of the breasts allowing for a more precise identification of the suspicious lesions.

The features we chose represent all the categories that were previously described except from the ‘time point of lesion enhancement initiation and spatial onset of enhancement within the lesion’ described by Boetes et al since this estimation requires a temporal resolution which is much higher than the one provided by our imaging protocol. These are:

**Wash-in period**
- $\text{nMITR} = (1/S_{I0})(S_{I\text{max}}-S_{I0})/T$,
- $\text{SAT} = S_{I1}/S_{I\text{max}}$, (ie Saturation: the signal intensity reached during the 1st postcontrast frame with respect to the peak signal intensity reached after contrast injection)
- Time to Peak (t2p) signal
- $\text{ENH1} = (S_{I1}-S_{I0})/S_{I0}$ (ie Enhancement Ratio 1)
- ENH2=(SI2-SI0)/SI0 (ie Enhancement Ratio 2)
- MSLP=Max{ENH1,ENH2-1} (ie Maximum Slope: relative signal increase from the precontrast frame to the 1st postcontrast frame or from the 1st to the 2nd postcontrast frame, whichever value is higher)

**Wash-out period**
- WASH1=ENH2-ENHlast (ie Washout Ratio between last an 2nd postcontrast frame)
- WASH2=ENH3-ENHlast (ie Washout Ratio between last an 3rd postcontrast frame)

where Sn, n=0,1 is the Signal Intensity value of the precontrast and first postcontrast image frame respectively.

Figure 36: An ENH1 feature map generated by The MRM Kinetic Feature Extraction and Visualization Tool developed for this thesis. Note the highly inhomogeneous lesion of high ENH1 values (up to 4.5) on the right breast as opposed to the ENH1 values of the normal parenchyma (< 1).

### 3.4. GENERATION OF VISUALIZATION KINETIC MAP IMAGES

Based on the visualization technique proposed by Mehnert et. al. [116] we generated an image for the group of the temporal frames of each slice of the dCE image sequence that maps the basic kinetic behavior of each pixel. This kinetic behavior is described by Kuhl et. al. [69]. In their study they identified three basic types of enhancement curves as shown in figure 37. Type I (persistent signal enhancement) curves are strongly related to benignity whereas type II (late phase plateau) and III (late phase wash-out) curves relate with increasing probability to malignancy.

It is generally accepted that the general enhancement curve pattern of malignant kinetic behavior consists of a strong signal enhancement that reaches its peak in a short time period and is followed by a plateau or wash-out. This kinetic curve categorization scheme is used by most radiologists in their effort to characterize enhancing areas that appear in dCE MRM studies.
This kinetic curve categorization suggests a simple model of enhancement based on two line segments, the early post-contrast rise first line segment and the continued uptake (positive slope), plateau (zero slope) or wash-out (negative slope) second line segment. This model, known as the linear-slope model in the plant and soil sciences [117], is described by three parameters (p1, p2, p3) and has the form:

\[ E[Y_i] = \begin{cases} 
  p2 \cdot t_i & \text{if } t_i \leq p1 \\
  p2 \cdot p1 + p3(t_i - p1) & \text{if } t_i > p1 
\end{cases} \quad (17) \]

where in a random sample of \( i = 1, \ldots, n \) observations of the intensity response \( Y_i \) at a corresponding time \( t_i \) of a given pixel, the expected value of the random variable \( Y_i \) is \( E[Y_i] \), \( p2 \) is the slope of the first line segment, \( p1 \) is the time point at which the two line segments meet and \( p3 \) is the slope of the second line segment, as is schematically presented in figure 38. The first line segment is set to begin at zero by subtracting each slice frame of the time series of the dynamic sequence from the first pre-contrast one. Since the model is not linear in its parameters, the fitting algorithm of choice is the non-linear least squares of Levenberg-Marquardt implemented in MATLAB (The MathWorks, Inc., Natick, MA, USA).
The initial parameter values where set as listed in the following table.

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Initial Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>p1 t1</td>
<td>t2</td>
<td>first post-contrast time point</td>
</tr>
<tr>
<td>p2 Y/(t_2)</td>
<td>slope of 1st segment from origin to 1st post-contrast time point</td>
<td></td>
</tr>
<tr>
<td>p3 0</td>
<td>zero slope for the 2nd line segment</td>
<td></td>
</tr>
</tbody>
</table>

Experimental Signal Intensity – Time curves and the corresponding model prediction can be seen in figure 39.

![Figure 39: Experimental (dotted lines) and corresponding model generated (solid lines) Signal Intensity – Time curves. The model prediction simplifies the experimental curve by splitting it to the two line segments that follow the general scheme that is proposed by Kuhl et al. [69] which is generally adopted by most radiologists.](image)

For the generation of the map image these parameters where used to extract triplets of coordinates of the HSV three-dimensional color space (fig. 40). This color-space has the advantage of coding colors in a way similar to the one the human eye perceives them. The goal of this visualization scheme is to create an image that provides the necessary kinetic information in a simple to interpret form.

![Figure 40: The HSV three-dimensional colorspace](image)
All images of the dCE sequence were filtered using a 3x3 order statistic filter to attenuate noise and in plane small motion artifacts, whereas sustaining the ability to recognize small enhancing pixel groups. These images were then passed in the fitting process. The model described has two variables $Y_i$ and $t_i$. As $Y_i$ we used the enhancement ratios of each post-contrast frame for each slice of the dynamic sequence on a pixel basis. This approach has the advantage of rendering $Y_i$ a clear number making the final visualization map image independent of differences in signal intensity between different types of imaging sequences or hardware components. The $t_i$ variable is the experimental time point when each slice frame is acquired. Three parametric maps are extracted from the fitting process each corresponding to one of the model’s parameters p1, p2 and p3.

The p1 map which relates to the time point when the signal of a pixel reaches its peak value is assigned to represent the saturation of each pixel. The outcome of this process is that the sooner a pixel reaches its peak signal value the more saturated its color will appear. The p2 map which is the early phase signal increase ratio, scaled to [0,1], is assigned to represent the value of each pixel. Thus the stronger a pixel enhances the brighter its color will appear in the visualization map image.

Finally the p3 map which relates to the 2nd phase kinetic behavior of each enhancing pixel, ie the slope of the 2nd line segment of the model and the existence of a persistent uptake, plateau or wash-out kinetic behavior, is assigned to represent the hue of each pixel. To make a better use of the HSV colormap this parameter is scaled to [0,0.7]. In this way the visible color scale on our visualization map image will expand from red (high negative slope) to blue (high positive slope) avoiding misinterpretation problems that would be generated if purple and upper peak red colors were imaged. This color-scale is then calibrated in such a way that high positive slope region appears blue, relatively small positive slope region appears cyan, zero slope region green, relatively small negative slope yellow and high negative slope red as is presented in figure 41.

![Figure 41: Hue encoding of different value regions of the slope of the intermediate and late phase (2nd line segment) kinetic pixel behavior. The strong persistent enhancement (slope>25%) behavior is encoded as blue, moderate persistent enhancement (5%<slope<25%), as cyan, plateau (-5%<slope<5%) as green, moderate washout (-25%<slope<-5%), as yellow and strong washout (slope<-25%) behavior as red.](image-url)
Not all pixels are allowed to appear with this color coding. If a pixel with a very small signal increase was to appear, it would make the interpretation of the image obscure thus all such pixels appear unsaturated.

Figure 42: The Visualisation Kinetic Map images generated by the MRM Kinetic Feature Extraction and Visualisation Tool. The map image (left) can be laid over the precontrast frame forming an image where only voxels of significant behavior are imaged. Note the formation of bright highly saturated yellow to red voxels on the right breast which indicates a lesion of high and rapid initial enhancement followed by strong washout, a behavior highly suggestive of malignancy.
4. RESULTS

The dynamic series of the MRM examinations of the 55 patients were analyzed for this study. In collaboration with the supervising radiologist we identified all suspicious lesions and generated empirical feature and visualization maps. All examinations where then assessed only with the use of the MRM Kinetic Feature Extraction and Visualisation Tool (fig. 42) by two independent observers. The two observers were asked to evaluate the identified lesions on the colormaps that were generated in terms of Hue (washout), Saturation (time to peak), Value (washin) and Heterogeneity. They graded each feature on a three grade scale and a sum was calculated. The following table summarizes the grading system.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hue (washout)</td>
<td>blue</td>
<td>green</td>
<td>red</td>
</tr>
<tr>
<td>Saturation (time to peak)</td>
<td>low</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>Value (washin)</td>
<td>low</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>low</td>
<td>intermediate</td>
<td>high</td>
</tr>
</tbody>
</table>

All grades were then summed to correspond to the 5-grade BIRADS scale. Grade 1 is not included since the case sample was referred for magnetic resonance mammography after they had identified lesions by conventional mammography and clinical examination. The correspondence of our rating scheme with the BIRADS scale is illustrated in the next table.

<table>
<thead>
<tr>
<th>Rating Sum (RS)</th>
<th>BIRADS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS ≤ 2</td>
<td>2</td>
<td>benign finding</td>
</tr>
<tr>
<td>2 &lt; RS ≤ 4</td>
<td>3</td>
<td>Probably benign finding</td>
</tr>
<tr>
<td>4 &lt; RS ≤ 6</td>
<td>4</td>
<td>Suspicious abnormality</td>
</tr>
<tr>
<td>6 &lt; RS ≤ 8</td>
<td>5</td>
<td>Highly suggestive of malignancy</td>
</tr>
</tbody>
</table>

Figure 42: A benign lesion (left) and a malignant one (right) as identified by the Kinetic Feature Extraction and Visualisation Tool. The identification of the lesions as well as the difference in their contrast enhancement kinetic behavior is obvious.
We evaluated the performance of this diagnostic scheme as opposed to the grading system which is generally used by the majority of the radiologists. The features that are evaluated in this diagnostic scheme are presented in this table:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Enhancement Pattern</th>
<th>Washin</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Homogeneous</td>
<td>&lt;50%</td>
<td>Persistent</td>
</tr>
<tr>
<td>1</td>
<td>Inhomogeneous</td>
<td>50-100%</td>
<td>Plateau</td>
</tr>
<tr>
<td>2</td>
<td>Rim Enhancement</td>
<td>&gt;100%</td>
<td>Washout</td>
</tr>
</tbody>
</table>

This diagnostic procedure which will be referred to as “classical”, is the one that is used by the radiologists that supported this work in their clinical routine. The evaluation of the haemodynamic properties of the lesions is done by hand drawn ROIs, extraction of dynamic curves, measurement of the signal increase at the washin period and classification of the shape of the curve according to the Kuhl system [69]. The results of the two methods were then compared to the histological data and their corresponding ROC curves are presented in figure 43. The classification performance of the two diagnostic approaches in terms of Area Under the Curve ($A_z$) and the corresponding standard error (SE) are presented in this table:

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>$A_z \pm SE$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>0.86 ± 0.05</td>
</tr>
<tr>
<td>Colormap</td>
<td>0.88 ± 0.05</td>
</tr>
</tbody>
</table>

The difference in performance of the two approaches is thus proven to be of no statistical significance (p-value > 0.05, Student’s t-test).

![Figure 43: The Receiver Operator Characteristic analysis curves of the two diagnostic approaches that were used for this study.](image-url)
5. DISCUSSION

As it is stated previously, magnetic resonance mammography is a promising technique that has started to earn its position as a diagnostic tool. Since it provides high resolution breast imaging with no use of ionising radiation and with inherently good soft tissue discrimination, there has been a great effort to explore its capabilities and boundaries in the breast examination arena. The addition of dynamic contrast enhanced study of the breast upgraded the method to a great extend because of the fact that malignant lesions are in most cases highly differentiated from benign ones haemodynamically, due to the angiogenetic properties of cancerous cells.

Being a relatively new method magnetic resonance mammography has been approached with a plethora of different protocols both in technique and diagnostic procedures which are being evaluated in the everyday clinical practice. Although this continuous effort has not concluded definitively to a single approach there is a general agreement on the technique as well as the clinical diagnostic procedure. All breast MR Mammographies include T1 and T2 weighted imaging of the breast with and / or without saturation of the signal of fat and a dynamic contrast enhanced T1 weighted study of both breasts. The lesions identified are evaluated both morphologically and haemodynamically.

The amount of data gathered for one such exam is enormous making the diagnostic procedure a difficult task. Both this and the fact that the inherent diagnostic capabilities of MRM are extremely wide, many researchers have worked on post processing methods to make diagnosis both easier and more accurate.

For this work we tried to study the different approaches to assess the haemodynamic data that are proposed as simple diagnostic assistance, quantifiable diagnostic feature extraction as well as CAD systems. These are generally categorized in three basic classes. There are tools that extract quantifiable features directly from the curve extracted from a ROI on the dynamic study, others that generate continuous data by fitting the experimental data of the dynamic series to simple mathematical models thus providing more features and finally tools that extract directly pharmacokinetic parameters of the lesions, fitting the experimental data to compartmental models that reflect the pathophysiology of the lesions. All tools provide colormap images extracted from the dynamic series in an effort to shrink the big amount of data of the study to one set of images to make the diagnostic process faster and more robust.

The straightforward pharmacokinetic approach appears more promising. The main reason for this is that the fitting method describes the underlying pathophysiology of the lesion by use of simpler or more complex compartmental models. Although some of the CAD systems that are now available implement such methods (mainly 3TP algorithm), there is a general understanding that straightforward pharmacokinetic analysis requires a very demanding imaging protocol in order to be able to measure such parameters accurately. The protocol should implement T1 mapping of the breast, sampling of the signal of a feeding vessel (AIF) every second and a sampling of the Tissue Residue Function at most every 16 seconds in order to be able to make measurements with an accuracy of 10% [118]. These requirements even with the most modern equipment would diminish the screening capabilities of the exam since the whole breast (or both breasts) cannot be imaged in such temporal resolution while maintaining a minimum required spatial resolution.
This, and the fact that the imaging protocol we could use for this study was a standard one, were the basic reasons that lead us to implement in our ‘Kinetic Feature Extraction and Visualization Tool’ methods for the calculation of simple semi-quantitative feature maps of the breast as well as a bilinear fitting algorithm of the dynamic data. This and all such software although they cannot extract measurable parameters that directly correspond to different aspects of the underlying pathology and can be compared to biopsy results, provide the means to evaluate all aspects of the magnetic resonance mammography examination that should be evaluated in the clinical routine [68], in a faster and more robust manner.

The basic difficulty of the evaluation process that this tool addresses is that it lessens the data volume that should be processed by the radiologist since it condenses the dynamic series to one set of images. This set of colormap images gives information of the overall haemodynamic behaviour of the breast and proves to be quite useful in assessing the haemodynamic heterogeneity of the identified lesions, which is a strong indicator of malignancy. This assessment without the colormap representation image set would normally require an examination of at least 3 sets of the imaging volume at different time points of the dynamic series.

In advance the use of this software enables us to avoid the inter and intra-observer variability of the method caused by the manual placement of ROIs where signal vs time curves are extracted and evaluated.

During the evaluation of the colormap representation of the dynamic behaviour of the lesions, the radiologists noted that they could not assess the periphery of the lesions (well- or ill-circumscribed lesions). This is expected with the use of such colormap images since the use of colors enhances the definition of all enhancing lesions. For this reason the definition of the lesion boundaries was not chosen as a diagnostic feature in our study.

In our algorithm we did not use any image registration techniques. We tried to overcome small movement issues by the use of filters. This is a major drawback of all mapping techniques of the breast because the large imaging time (6 to 15 mins) makes it almost impossible to avoid patient movement. This can make the fitting algorithms to fail and produce false color-coding, which may in turn lead to a false evaluation of a lesion (fig 44).

Figure 44: Example of wrong fitting result. Due to relative movement the value of the pixel changed to a much lower value at the last time point. This would lead to a bright red color coding indicative of malignant behaviour.
This is a major issue with both classical and colormap evaluation methods of MRM. Patient movement makes it impossible to subtract the pre-enhancement image set from the subsequent contrast enhanced dynamic image sets in order to identify enhancement lesions as well as to place a ROI to extract signal-time curves. Our model had the same performance with the standard classical evaluation protocol by assessing only the colormap images ($A_{zClassical}=0.86 \pm 0.05$, $A_{zColormap}= 0.88 \pm 0.05$). These results state that such techniques offer a reliable method to evaluate MR mammography exams by assessing a fraction of the total data set produced by the scanner. The fact that there is no need of manual ROI placement should improve the inter- and intra-observer variability. Instead of implementing image registration techniques a simpler confidence interval estimation of the fitting algorithm and rejection of pixels with poor fitting accuracy would improve our post processing software. This addition could be used as means to estimate the existence of patient motion between the different time point data sets of the dynamic imaging series, which is considered to be the main reason for the fitting algorithm to fail.
6. REFERENCES


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