MULTISPECTRAL CO-OCCURRENCE ANALYSIS FOR MEDICAL IMAGE PROCESSING

DISSERTATION

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By

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* * * * *

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ABSTRACT

Presented is a new computer aided multispectral image processing method which is used in 3 spatial dimensions and 1 spectral dimension where the parametric dynamic contrast enhanced magnetic resonance breast maps derived from voxelwise model-fitting represent the spectral dimension. The method is based on co-occurrence analysis using a 3-dimensional window of observation which introduces an automated identification of suspicious lesions. The co-occurrence analysis defines 21 different statistical features, a subset of which were inputted to a neural network classifier where the assessments of voxelwise majority of a group of radiologist readings were used as the gold standard. The voxelwise true positive fraction ($TPF$) and false positive fraction ($FPF$) results of the computer classifier were statistically indistinguishable from the $TPF$ and $FPF$ results of the readers using a one sample paired t-test. In order to observe the generality of the method, two different groups of studies were used with widely different image acquisition specifications.
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CHAPTER 1

INTRODUCTION

1.1 Multispectral Image Processing

Multispectral image processing is a developing analysis method which is based on information from different types of content that relate to the same spatial location of an object. One example of multispectral image processing applications is weather radars which uses a train of $M$ such pulses, each with different frequency. The pulse train produces $M$ virtually independent echoes which after averaging will give improved reflectivity estimates for the same dwell time [1]. The aim of this method is to decrease the acquisition time. Another example of multispectral image processing is multisensor registration using synthetic aperture radar (SAR) and Landsat thematic mapper. The data from each sensor can be geocoded into a common projection and grid spacing [2]. Multispectral image processing is also used in aerial target detection by observing radar carrier frequency diversity which results in a variation in correlation coefficients. Shirman described the recognition of three different types of flying objects (F15, B1B, and ALCM type missile) by using frequency diversity [3].
The multispectral image processing tool we use is based on image classification defined by Haralick et al. [4] who investigated the co-occurrence properties of neighboring points in spatial directions. Our approach focuses on the co-occurrence properties of the neighboring points in spectral direction by investigating the statistical features of different types of data at the same spatial locations.

In this dissertation, we describe the implementations of multispectral image processing co-occurrence analysis using dynamic contrast enhanced magnetic resonance (DCE-MR) images of breast cancer. In this study, we computed 21 features, 6 of which were developed by the author.

1.2 Spectral Data Used

The dataset we have used were dynamic contrast enhanced magnetic resonance (DCE-MR) breast images. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is the acquisition of sequential images during the passage of a contrast agent within a tissue of interest [5]. State of the art research studies in DCE-MRI involve the use of large datasets, which consist of multidimensional collections of data from multiple imaging snapshots.

DCE-MRI has the potential to become a very effective method in the detection and classification of cancer. Currently the primary drawback is the bottleneck caused by manually outlining lesions. A computer assisted method to interpret DCE-MRI may help radiologists by allowing better data throughput and more consistent results. The datasets are based on two compartment model contrast delivery and include local maps of amplitude $A$, redistribution rate constant $k_{ep}$ and elimination rate constant $k_{el}$ that can be treated as images [5]. Spatial maps of $A$, $k_{ep}$, and $k_{el}$ are treated as
color planes in image data to form a multispectral image set. The concept of using 3 DCE-MR parameter color planes is analogous to RGB or HSV color planes in image studies. For example in RGB, the color information is conveyed by three parameters, red, green, and blue. Using the definition of a voxel as a volume element which represents a pixel in 3-dimensional (3-D) space, in our study we classify whether a tissue voxel is malignant or benign by analyzing three parameters, $A$, $k_{ep}$, and $k_{el}$, which characterize vascularization of lesion tissues. Two groups of anonymous subjects were analyzed in order to show the generality of this method.

Previous studies concerning the classification of cancerous lesions can be divided into three categories: Manual methods, semi-automated methods, and automated methods. Manual methods are the classifications done by radiologist without any help of computerized tools [6], [7], [8], [9]. Semi-automated methods can be considered where manual reading is aided by an automated tool [10], [11], [12], [13]. Automated tools can be considered where a computer assisted tool diagnoses the malignancy of a lesion [14], [15], [16]. In Chapter 2, a review of published semi-automated and automated tools is presented.

The solution described in this dissertation focuses on a particular implementation of an automated computing framework and its feasibility toward the multispectral image processing for medical data by using a distributed statistical co-occurrence analysis for 3-random variables (3-rv’s) e.g. $A$, $k_{ep}$, and $k_{el}$ at matched spatial positions. In this sense, we apply co-occurrence statistics commonly used for texture analysis but rather than performing analysis in spatial directions, we apply the approach to multispectral parametric data.
We use 3 spatial \((x, y, z)\) dimensions and 1 spectral \((s)\) dimension in our research. The data sample sizes are \((x, y, z, s) = (256, 256, 30, 3)\) for group 1 subjects and \((x, y, z, s) = (256, 256, 64, 3)\) for group 2 subjects where the spectral samples are \(A, k_{ep},\) and \(k_{el}.\)

1.3 Multispectral Co-occurrence Analysis of Three Variables on Distributed and Parallel Environments

Performing 3 rv co-occurrence analysis among color planes is a computationally expensive method. The data sets we have used are 256x256 images which are contained in arrays having 30 image slices in group 1 and 64 image slices in group 2 for three parameter multispectral analysis. As a consequence of the size of the datasets and the number of computations, the operation takes considerable execution time. In order to solve this problem, distributed and parallel computing environments were used for the work in this dissertation.

1.4 Neural Networks

In order to combine the information supplied by the statistical features obtained by the multispectral co-occurrence analysis we have used an artificial neural network (ANN), one of the most widely used classifiers. The neural network is trained with the multispectral co-occurrence statistical features where the regions to be segmented are marked by a voxelwise majority of radiologists in order to build a classifier and detection network.
1.5 The Statement of the Problem

The organization of our research is depicted in Figure 1.1. First, $A$, $k_{ep}$, and $k_{el}$

![Figure 1.1: The block diagram of the research.](image)

color planes are obtained from the DCE-MR breast images. Second, several statistical features based on multispectral co-occurrence analysis of these color planes are computed. Third, these statistical features are classified by voxelwise combination using an ANN classification tool. Finally, hypothesis testing is applied for the output of the ANN classifier.
The overlying goal for this dissertation is to show that using a co-occurrence approach in the spectral color plane direction is useful for segmenting multispectral medical data. The example explored for demonstration is to show a robust computer assisted tool for the segmentation and detection of breast cancer using DCE-MR parameters $A$, $k_{ep}$, and $k_{el}$. An extension of this dissertation would be to provide a distributed multispectral co-occurrence analysis framework for three variables $A$, $k_{ep}$, and $k_{el}$ associated with the same spatial position and at the neighboring points so there would be 6 random variables in total.

1.6 Organization

In this dissertation, first background of DCE-MRI is reviewed in the Chapter 2. In Chapter 3, multispectral co-occurrence analysis, the main objective of our research, is described. In Chapter 4, the classification of the statistical features from the multispectral co-occurrence analysis are described. In Chapter 5, the results obtained are shown and discussed. In the last chapter, conclusions are given and open problems are discussed.
CHAPTER 2

BACKGROUND FOR BREAST DCE-MRI

In this chapter, the basis of DCE-MRI is described. MRI is a powerful noninvasive imaging technique that continues to have an important role in the medical community [17]. For diagnosis and presurgical planning, it aids physicians with limited risk to the patient.

2.1 Some MRI Basics

This section is a brief description of MRI. Extensive information can be obtained in the following literature [17], [18], [19], [20]. The goal of MRI is to correlate a series of signal measurements with the spatial locations of the various sources [19]. We now utilize the fact that the addition of a spatially changing magnetic field with a radio frequency (rf) electromagnetic wave across the sample produces a signal with spatially varying frequency components according to

\[ \omega(r) = \gamma B(r) \]  \hspace{1cm} (2.1)

where \( \omega \) is the radial frequency of spins, \( \gamma \) is the gyromagnetic ratio, \( B \) is the magnetic field and \( r \) denotes the spatial coordinate along the direction of the gradient of the
magnetic field [19]. Thus, the spectral components now represent spatial information and, in turn, lead to mapping the locations of structures in a physical object (imaging) [19].

MRI signal intensity is based on two types of signal relaxation that occur, longitudinal ($T_1$) and transverse ($T_2$) relaxations [17]. $T_1$ relaxation is the longitudinal or spin-lattice relaxation of spinning protons which characterizes the return to equilibrium and $T_2$ relaxation is the transverse or spin-spin relaxation of the spinning protons that causes the signal loss due to dephasing [18]. Both these relaxations and the respective relaxation times depend on the molecular structures, the environments surrounding the tissue and the magnetic field strength [18]. Also, $T_1$ depends on the temperature and phase (solid, liquid, gel, gas) [21]. In fat regions, at body temperature, $T_1$ is in the range from a hundred milliseconds to seconds. In water ($H_2O$), $T_1$ is in the range of seconds [21]. Most disease states are characterized by an elevated $T_2$ relaxation [19]. Since the $T_2$ values are on the order of milliseconds whereas $T_1$ values are typically on the order of a second, a small increase in $T_2$ corresponds to a larger percentage increase than the same increase in $T_1$ [19].

The transverse components of the spinning protons start to spread and cancel out each other because of their different spinning frequencies. This process is called dephasing. Two types of dephasing occur. Doppler shift from randomly moving protons and random frequency pullings cause the random dephasing. Nonuniform $B$ field and the gradient field changes cause controllable dephasing by changing the frequency and phase of the spins [21]. Controllable dephasing protons can be recovered by flipping the spins to invert their phase order (spin-echo sequence method) or by speeding up the slower spinning protons and slowing down the faster spinning protons (gradient
echo method). This process is called rephasing. The amplitude of the recovered transverse components is called an echo and $T_2$ or $T_2^*$ determine the strength of the echo peak for spin echo and gradient echo methods respectively.

In order to image a whole volume, the three dimensional imaging technique can be used [19]. However, the challenge of 3-D imaging is the long image acquisition time. An alternative to 3-D imaging is to acquire a sequence of 2-D planar image acquisitions (slices) that can also cover all three dimensions. For example, 2-D axial imaging in $x$-$y$ plane can be described as

$$\rho(k_x, k_y) = \int \int dxdy s(x, y) e^{-i2\pi(k_xx + k_yy)}$$  \hspace{1cm} (2.2)

where $k_x$ and $k_y$ are the $x$- and $y$-components of the 2-D frequency domain, also called $k$-space. In order to cover a full volume, image acquisition is repeated for each image slice in a stack of slices. The two implicitly time dependent components of $k$ are the respective gradient-component integrals which define the dimensions of the $k$-space.

$$k_x(t) = \gamma \int^t G_x(\tau) d\tau$$

$$k_y(t) = \gamma \int^t G_y(\tau) d\tau$$  \hspace{1cm} (2.3)

The inverse Fourier transform of the data in the $k$-space gives the image. The example shown in Equations 2.2-2.3 represents axial slices, where in-plane directions are $x$ and $y$, and through-plane direction is $z$. Slice thickness determines image resolution in the through-plane direction while in-plane resolution is

$$\text{Resolution} = \frac{\text{Field of View}}{\text{Matrix size of the image}}$$  \hspace{1cm} (2.4)
where matrix size of the image heavily depends on the size of the $k$-space matrix. Thus, the resolution of the image also depends on the dimensions of the $k$-space which are defined by the gradients, in our example, $G_x$ and $G_y$. This implies there is a trade off between the in-plane resolution and the acquisition time. The through-plane resolution (slice thickness) is defined by $G_z$ (for axial imaging). Thicker slices cover the whole 3-D using fewer number of slices which would decrease acquisition time. On the other hand, a larger number of thinner slices covering the same volume would increase the acquisition time. Therefore, fast acquisitions often requires anisotropic voxel sizes (larger dimension for slice thickness).

Sagittal slice imaging can be performed by changing through-plane and in-plane directions so that

$$
\rho(k_y, k_z) = \int \int dx dy s(y, z)e^{-i2\pi(k_y y + k_z z)}
$$

where

$$
\begin{align*}
  k_y(t) &= \gamma \int_0^t G_y(\tau) d\tau \\
  k_z(t) &= \gamma \int_0^t G_z(\tau) d\tau
\end{align*}
$$

(2.5)

Similarly, coronal slice imaging can be performed using

$$
\rho(k_x, k_z) = \int \int dx dz s(x, z)e^{-i2\pi(k_x x + k_z z)}
$$

where

$$
\begin{align*}
  k_x(t) &= \gamma \int_0^t G_x(\tau) d\tau \\
  k_z(t) &= \gamma \int_0^t G_z(\tau) d\tau
\end{align*}
$$

(2.6)

The direction of acquisition usually depends on the part of the body that is to be observed. For instance in breast imaging, coronal or axial imaging are preferred.
Coronal imaging is done when cardiac motion is not desired to be observed because in coronal image slices, cardiac tissue will not be visible, only breast tissue is visible. If the reader wants to observe cardiac motion as well, axial imaging is preferred because in axial image slices, the cardiac tissue is present together with the breast tissue. In this dissertation, two groups of subjects are analyzed. The images of the first group of subjects are axial slices, on the other hand, the images of the second group subjects are coronal slices. In brain imaging, axial or sagital imaging techniques are preferred depending on the position and shape of the lesion. Most of the studies concerning abdomen are done with axial imaging because the other techniques will not give good in-plane resolution for the organs.

The gradient vector $\mathbf{G}$ is used to define an arbitrary coordinate direction along the $z$-component of the associated applied magnetic field $\mathbf{B}^g$ [19]. The superscript $g$ is used to remind the readers that an applied gradient is being considered [19].

$$\mathbf{G}(t) = \nabla B^g_z(r)$$

$$= \hat{x} \frac{\partial}{\partial x} B^g_z + \hat{y} \frac{\partial}{\partial y} B^g_z + \hat{z} \frac{\partial}{\partial z} B^g_z$$

$$= G_x(t) \hat{x} + G_y(t) \hat{y} + G_z(t) \hat{z}$$ (2.7)

Figure 2.1 shows how $k$-space is filled in 2-D imaging on an $x$-$y$ plane. In the figure, $z=0$. For 2-D axial imaging, $G_z$ defines the position and thickness of the slice. The $G_x$ gradient controls the filling of $k$-space in $k_x$-direction and $G_y$ controls the $k_y$-direction filling of $k$-space. Each line is filled sequentially with a repetition time $T_R$ between the lines. In the figure, $k$-space is filled by raster scanning horizontal lines, but it is also possible to fill the $k$-space plane by scanning vertical lines. The direction filled within each line is called the readout direction, and the other is called
the phase encode direction. In summary, the use of these gradient coils defines the direction of acquisition and 2-D imaging resolution.

![Diagram of k-space filling](image)

Figure 2.1: The filling of $k$-space on $x$-$y$ plane. First phase encoding gradient $G_y$ selects a line in the $k$-space, then the readout gradient $G_x$ fills that line [19].

### 2.2 Gradient-Echo Imaging

The gradient-echo images can be generated with $T_1$, $T_1/T_2$, $T_2$, $T_2^*$ and spin density weighted contrast with a reasonable selection of the sequence repetition time ($T_R$),
the echo time ($T_E$) and the flip angle ($\alpha$) which is the angle of precessing magnetic moment at the end of excitation. For example if $\alpha=90^\circ$, the pulse is called a $90^\circ$ pulse. Lower angle flips give faster acquisition, but lower signal to noise ratio (SNR).

Consider the axial gradient echo sequence shown in Figure 2.2 for 2-D imaging where the $(n-1)st$ line of $k$-space is acquired. A constant slice selection gradient is applied in the $z$-direction during $rf$ excitation defining axial slices (blue lobe) and then reversed immediately following the pulse in order to recover the dephasing caused by the slice selection gradient (turquoise lobe) [19]. In the example shown, phase encoding is performed in $k_y$ direction by using a different value of $G_y$ for each line in $k$-space (grey lobe). Readout (sampling) is taken in the $k_x$ direction during use of $G_x$ as shown in Figure 2.2. When the slice selection gradient is switched to the rephasing lobe (turquoise lobe), a phase encoding gradient ($G_y$) which selects a line value of $k_y$ is started and the readout gradient ($G_x$) is engaged to intentionally dephase (dark green lobe) and then reversed for rephasing (light green lobe) to sample the signal and to fill that line of $k_y$ in the $k_x$ direction. It is the reversal of the gradients from the dark green to light green lobes that rephases the signal to form the echo. The resulting sampled echo signal data is the $(n-1)st$ line of the $k$-space. The $(n-1)st$ sampling window is centered at a echo time $T_E$ from the center point of the $(n-1)st$ pulse. After a time $T_R$ passes since the $(n-1)st$ pulse, the sequence is repeated for the $n$th line in $k$-space [20]. The image of the slice is the inverse 2-D Fourier Transform of the collected data in $k$-space.

In order to show $T_1$ and $T_2^*$ effects on the signal, consider the $n$th excitation for data collection within a slice. The prepulse transverse magnetization of the $n$th pulse
Figure 2.2: A timing diagram for a 2-D gradient-echo sequence [19], [20].
is defined as

\[ S_{xy}(0_{-}) = 0 \tag{2.8} \]

This indicates that transverse magnetization from the preceding pulse is totally dephased just before we apply a new rf excitation pulse [20].

The longitudinal magnetization is defined as

\[ S_z(t) = S_z^0(1 - e^{-t/T_1(x,y,z)}) + S_z(0_{+})e^{-t/T_1(x,y,z)} \tag{2.9} \]

where \( S_z^0 \) is the longitudinal magnetization of the 0th pulse and \( S_z(0_{+}) \) is the longitudinal magnetization immediately after the rf excitation pulse [20]. From Equation 2.9, we can conclude that

\[ S_z^{(n)}(0_{-}) = S_z^0(1 - e^{-TR/T_1(x,y,z)}) + S_z^{(n-1)}(0_{+})e^{-TR/T_1(x,y,z)} \tag{2.10} \]

where \( S_z^{(n)}(0_{-}) \) and \( S_z^{(n-1)}(0_{+}) \) denote the longitudinal magnetization before the nth pulse and after the (n-1)st pulse, respectively [20].

The relationship between the prepulse and the postpulse longitudinal magnetization for the nth pulse is defined as [20]

\[ S_z^{(n)}(0_{+}) = S_z^{(n)}(0_{-}) \cos(\alpha) \tag{2.11} \]

so that the Equation 2.10 can be written as [20]

\[ S_z^{(n)}(0_{-}) = S_z^0(1 - e^{-TR/T_1(x,y,z)}) + S_z^{(n-1)}(0_{-})e^{-TR/T_1(x,y,z)} \cos(\alpha) \tag{2.12} \]

Under the dynamic equilibrium condition [20]
\[ S_z^{ss}(0-) = S_z^{(n)}(0-) = S_z^{(n-1)}(0-) \] (2.13)

Equation 2.12 can be rewritten as \[ S_z^{ss}(0-) = \frac{S_z^0(1 - e^{-T_R/T_1(x,y,z)})}{1 - e^{-T_R/T_1(x,y,z)} \cos(\alpha)} \] (2.14)

The relationship between the postpulse transverse magnetization and the prepulse longitudinal magnetization is defined as \[ S_{xy}^{ss}(t) = S_z^{ss}(0-) \sin(\alpha e^{-t/T_2^*(x,y,z)}) \] (2.15)

thus \[ S_{xy}^{ss}(t) = \frac{S_z^0(1 - e^{-T_R/T_1(x,y,z)})}{1 - e^{-T_R/T_1(x,y,z)} \cos(\alpha)} \sin(\alpha e^{-t/T_2^*(x,y,z)}) \] (2.16)

and the peak echo amplitude is \[ S_E = \frac{S_z^0(1 - e^{-T_R/T_1(x,y,z)})}{1 - e^{-T_R/T_1(x,y,z)} \cos(\alpha)} \sin(\alpha e^{-T_E/T_2^*(x,y,z)}) \] (2.17)

The image is a function of \( T_1(x,y,z) \) and \( T_2^*(x,y,z) \) weightings. The \( T_2^*(x,y,z) \) weighting is an important factor for the gradient-echo sequence and is controllable by adjusting the echo time, \( T_E \) [20]. Using a short echo time \( T_E \), the \( T_2^*(x,y,z) \)-dependent exponential component in Equation 2.17 will be close to unity; thus Equation 2.17 becomes

\[ S_E \approx \frac{S_z^0(1 - e^{-T_R/T_1(x,y,z)})}{1 - e^{-T_R/T_1(x,y,z)} \cos(\alpha)} \sin(\alpha), \text{ for } T_E \ll T_2^*(x,y,z) \] (2.18)
This mode makes the imaging contrast $T_1(x, y, z)$-dependent. The significance of the $T_1(x, y, z)$ weighting factor depends on the flip angle, $\alpha$. When $\alpha$ is small, $\cos(\alpha) \approx 1$ so that small $\alpha$ eliminates the $T_1(x, y, z)$ factor. As $\alpha$ increases, the $T_1(x, y, z)$ factor becomes more significant [20].

Picking a small $\alpha$ and long $T_R$ makes the imaging contrast primarily $T_2^*(x, y, z)$-dependent.

$$S_E \approx S_z^0 \sin(\alpha e^{-T_E/T_2^*(x,y,z)})$$

for $T_R \gg T_1(x, y, z)$ and $\alpha \approx 0$ \hspace{1cm} (2.19)

A small flip angle $\alpha$, long $T_R$, and a short echo time $T_E$ results in the elimination of both $T_1(x, y, z)$ and $T_2^*(x, y, z)$ weighting factors

$$S_E \approx S_z^0$$

for $T_R \gg T_1(x, y, z)$, $T_E \ll T_2^*(x, y, z)$, and $\alpha \approx 0$ \hspace{1cm} (2.20)

and this is called the proton density imaging.

In many of the clinical applications $T_1(x, y, z)$-weighted imaging is used in order to obtain fast sequences because imaging time for a slice is approximately $N \cdot T_R$ and $T_1$-weighted imaging has short $T_R$. The snapshot images used in this dissertation are obtained using $T_1(x, y, z)$-weighted imaging.

### 2.3 Contrast Agents in MRI

Contrast agents are used in MRI for several purposes, mostly providing physiological information. Unlike nuclear medicine and x-ray studies, variations in MR signal in biological systems rarely provide a direct measure of contrast agent concentration. Instead, variations in MR image intensity depend on the effect that the contrast agent has on the magnetization of the water in the tissue. There are two ways to affect
magnetization by contrast agents. The first method is through direct changes to how relaxation occurs, and the second method is through indirect susceptibility effects. In both methods, the movement of water plays a significant role for the determination of the effect of the contrast agent in changing the water magnetization [22].

An MRI contrast agent must be a biocompatible pharmaceutical and magnetization probe [23]. Three required general characteristics of an MRI contrast agent are relaxivity (sensitivity), tissue specificity, and excretability and lack of toxicity [24]. Relaxivity is the relaxation rate of the proton in the water. The enhanced relaxivity due the contrast agent must be sufficient to increase the relaxivity of the target tissue by at least 10%-20% to be detectable by MRI and the contrast agent should only enhance the targeted tissue. [23]. The dose of the contrast agent must be nontoxic to the patient.

Gadolinium (Gd), a paramagnetic metal ion, improves the MRI signal intensity by increasing the relaxivity of the tissue, but the toxicity of Gd limits its usage to chelated binding for safe excretion from the patient [23]. A heterocyclic compound having a metal ion can be used to remove the excess of metal which may increase the toxicity in the bloodstream [25]. The parental organic compound of chelate is known as a chelating agent (DTPA: diethylenetriaminepentaacetic acid) used for its capability of preventing the accumulation of metal in the body [23]. Gd-DTPA was introduced as the first ionic paramagnetic MRI contrast agent in 1981.

Gadobenate dimeglumine (Gd-BOPTA) is a paramagnetic MRI contrast agent (small molecular weight Gd-chelate) with 0.5 and 0.25 molar concentration. The
advantage for Gd-BOPTA over Gd-DTPA and other gadolinium agents is its albumin-mediated relaxation enhancement in poorly vascularized, small, low enhanced and high albumin concentrated lesions [25].

The contrast agents used in this dissertation are Gd-DTPA and Gd-BOPTA.

MRI methods using contrast enhancement can be divided into two categories, static contrast enhanced MRI and dynamic contrast enhanced MRI. Static contrast enhancement can be achieved with two consecutive $T_1$-weighted imaging sessions, the first imaging before injecting the contrast agent and the second imaging is done after a certain time when the contrast agent is dispersed to the region under study. DCE-MRI is done with the acquisition of a sequence of multiple images after the contrast agent is effective in the tissue of interest. The sequence of imaging snapshots is used to infer the flow and diffusion properties in tissue being studied.

2.4 DCE-MRI

DCE-MRI is the acquisition of sequential images during the passage of a contrast agent within a tissue of interest [5]. DCE-MRI is one of the most used perfusion imaging methods.

DCE-MRI provides noninvasive characterization of angiogenic response of a tumor before and during therapeutic intervention to monitor treatment and predict response [5]. The contrast agent travels through the vascular system and reaches the neoplastic tissue. After the agent reaches the neoplastic tissue, it immediately starts to leak from the tumor vasculature, accumulates in this tissue, rediffuses back into the vascular system and finally leaves the body mostly via the urinary system [5].
Several observations by Knopp et al. [26] and Stomper et al. [27] have concluded that the intensity of enhancement is related to the vascular density within the tissue.

The rate of enhancement is related to angiogenic factors. Differences in the contrast enhancement pattern are related to specific histopathological properties of the tumor [5]. An example can be a more aggressive tumor, invasive ductal carcinomas (IDC). These tumors reveal an intense and rapid enhancement and washout. On the other hand invasive lobular carcinoma (ILC) presents moderate uptake, reflecting a lower vascular density and lower expression of vascular endothelial growth factor [5]. In addition to these basic properties, the signal intensity heavily depends on the type and dose amount of the contrast agent because of its $T_1$-relaxation effect.

DCE-MRI can be performed on most clinical MRI systems with a field strength of at least 1 T [5]. In DCE-MRI, there is a trade off between spatial and temporal resolution. Patient motion, incorrect timing and incorrect dosage are common difficulties encountered in DCE-MRI clinical applications. The large number of images to be analyzed is a limitation for DCE-MRI [5]. DCE-MRI is performed using $T_1$-weighted imaging because the contrast enhances the $T_1$-effect and $T_1$-weighted imaging is fast. For DCE-MRI, the parameters $T_R$ and $T_E$ should be chosen as small as possible to guarantee an adequate time resolution and an acceptable signal to noise ratio, respectively [28].

The basic properties of DCE-MRI are similar to MRI. The in-plane resolution depends on the phase and readout gradients. The slice thickness can be adjusted by slice gradient. There is a trade off between the slice thickness and the image quality. A thin slice might result in insufficient number of spins which would lower the image quality by reducing the signal strength. This fact along with timing constrains
causes the anisotropy of the dimensions of voxels where the in-plane dimensions of
a voxel are smaller than through-plane dimension (slice thickness). The direction of
acquisition depends on the slice selection gradient which is generally determined by
the anatomical structures to be imaged. In DCE-MRI there is a compromise between
spatial resolution and temporal resolution. Decreasing the time spacing between the
snapshots can also decrease the image resolution because the voxel dimensions are
adjusted to compensate.

2.4.1 Two Compartment Pharmacokinetic Modeling

The dynamics of the contrast agent can be observed with its exchange rates be-
tween vascular and extravascular space and these two spaces can be treated as com-
partments, and the dynamics of the contrast agent can be best described with a
two compartment model. The two compartment model is composed of a primary
compartment, plasma (blood vessel) and a secondary compartment, extravascular
(extracellular) space [28]. The peripheral compartment is connected to the plasma
by bilinear exchange process as shown in Figure 2.3.

The mass models for two compartment model can be expressed by the following
two differential equations

\[
\frac{dM_1}{dt} = k_{in} - (k_{pe} + k_{el})M_1 + k_{ep}M_2
\]

(2.21)

\[
\frac{dM_2}{dt} = k_{pe}M_1 - k_{ep}M_2
\]

(2.22)

where \(M_1\) is the mass amount of the contrast agent in the blood vessel (plasma), \(M_2\) is
the mass amount of the contrast agent in the extracellular space, \(k_{pe}\) is the first-order
rate constant for the transfer from the plasma (blood vessel) to the extracellular space, $k_{ep}$ is the rate constant for the transfer from the extracellular space to the plasma (blood vessel), $k_{el}$ is the rate constant for the elimination from the blood vessel, and $k_{in}$ is the zero order rate constant which is equal to the infusion rate [28]. The infusion rate, $k_{in}$, is a function of time and it can usually be described as

$$k_{in}(t) = K[u(t) - u(t - \tau)] \quad (2.23)$$
where \( u(t) \) is the unit step function and \( \tau \) is the contrast injection duration. We can consider Equation 2.1 and 2.2 as the state space equations of a control system where \( M_1 \) and \( M_2 \) are the states of the system, \( k_{in} \) is the input of the system. The state space equation can be described as:

\[
\begin{bmatrix}
\dot{M}_1 \\
\dot{M}_2 \\
\end{bmatrix} = \begin{bmatrix}
-(k_{pe} + k_{el}) & k_{ep} \\
k_{pe} & -k_{ep} \\
\end{bmatrix} \begin{bmatrix}
M_1 \\
M_2 \\
\end{bmatrix} + \begin{bmatrix}
k_{in} \\
0 \\
\end{bmatrix}
\]

(2.24)

Following the acquisition of gradient echo sequences with DCE-MRI, using sequences of MR images a time-intensity curve was constructed for each voxel in a DCE-MRI dataset and was matched to the two compartment exchange model parameters \( A \), \( k_{ep} \), and \( k_{el} \) by the best-fit time-intensity curve for the voxel for the method developed by Hoffmann et al. using Equation 2.25 [29].

\[
\tilde{S}(A, k_{ep}, k_{el}) = \frac{S_{CM}}{S_0} = 1 + \frac{A}{\tau} \left\{ a(e^{k_{el}t'} - 1)e^{-k_{el}t} - b(e^{k_{ep}t'} - 1)e^{-k_{ep}t} \right\}
\]

(2.25)

where

\[
a = \frac{k_{ep}}{k_{el}(k_{ep} - k_{el})}
\]

and

\[
b = \frac{1}{(k_{ep} - k_{el})}
\]

(2.26)

In Equation 2.25, \( A \) is the amplitude which could be best understood as the asymptotic degree of relative signal enhancement if there were no CM elimination. During the infusion \((0 < t < \tau)\), the identity \( t' = t \) is used, and afterwards the identity \( t' = \tau \) [29]. In this equation \( S_0 \) denotes the static precontrast MR signal intensity and \( S_{CM} \) denotes the dynamic signal intensity with the contrast agent. Several example
time-intensity curves can be seen in Figure 2.4. In the figure, the images in the left hand column are the breast images on which the $A$ and $k_{ep}$ parameters are color-coded and overlayed using the color map shown in Figure 2.5. The blue outline in Figure 2.4 shows the region of interest (ROI). In the right hand column, the averaged time-intensity curves can be seen for the corresponding ROIs. In the first and the second row, the ROI was picked among malignant tissues. In the third row, the ROI was selected within nonmalignant tissue.

Using a nonlinear least squares method, (Levenberg-Marquardt algorithms), the parameters $A$, $k_{ep}$, and $k_{el}$ are fitted voxelwise by minimizing the sum $Q$ of squared deviations between the experimental time point data $L_i$ and the calculated curve values $\tilde{S}_i$ for $i = 1, 2, \cdots, m$.

\[
Q = \sum_{i=1}^{m} \left( \tilde{S}_i - L_i \right)^2
\] (2.27)

### 2.4.2 Estimation of the Color Planes

The type of the equation we are fitting is a nonlinear equation with a solution $\xi = [A \ k_{ep} \ k_{el}]^T$ denoting the parameter coefficients that we aim to estimate. Because the equation is nonlinear, the parameter coefficients can be estimated with the nonlinear least squares method. The description of nonlinear least squares fitting follows that presented in [30]. For each voxel of the dataset, let us consider a general system of $m$ equations one for each imaging snapshot time point and $3$ unknowns $\xi_j$ which are the parameters to be estimated for $j = 1, 2, 3$. 

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Figure 2.4: The time-intensity curves for malignant and non-malignant ROIs.
Figure 2.5: The $A$ and $k_{ep}$ color map (16 colors). The $x$ axis represents the $k_{ep}$ values with 4 indexed levels 0, 1, 2, and 3. The $y$ axis represents the $A$ values with 4 indexed levels 0, 1, 2, and 3. For example, the pixel having white color has a level of $(A, k_{ep}) = (3,3)$.

\[
\tilde{S}_1(\xi_1, \xi_2, \xi_3) = L_1 \\
\tilde{S}_2(\xi_1, \xi_2, \xi_3) = L_2 \\
\vdots \\
\tilde{S}_m(\xi_1, \xi_2, \xi_3) = L_3
\]

\[\iff \tilde{S}(\xi) = L \]  

Of course, in the presence of noise and measurement error, the equalities in Equation 2.28 are impossible to fit exactly, so the approach is to find a best least squares approximation. In Equation 2.28, $\tilde{S}_i$ is $\tilde{S}(A, k_{ep}, k_{el})$ for $t=t_i$ where $i = 1, 2, \cdots, m$ and the least squares error is

\[
E(\xi) = Q = \left|\left|\tilde{S}(\xi) - L\right|\right|^2 = \sum_{i=1}^{m} (\tilde{S}_i(\xi) - L_i)^2
\]
We can write the Taylor series expansion of the functions $\tilde{S}_i(\xi)$ for $i=1,\ldots,m$ in order to linearize the problem and find a suitable solution which relies on the first-order Taylor expansion of the functions $\tilde{S}_i$ in the neighborhood of point $\xi$ [30], in other words the parameter vector $\xi$ is updated by a new estimate $\xi+\delta\xi$.

$$\tilde{S}_i(\xi + \delta\xi) = \tilde{S}_i(\xi) + \delta\xi_1 \frac{\partial \tilde{S}_i}{\partial \xi_1}(\xi) + \delta\xi_2 \frac{\partial \tilde{S}_i}{\partial \xi_2}(\xi) + \delta\xi_3 \frac{\partial \tilde{S}_i}{\partial \xi_3}(\xi) + O(|\delta\xi|^2)$$  \hspace{1cm} (2.30)

$$\approx \tilde{S}_i(\xi) + \nabla \tilde{S}_i(\xi) \cdot \delta\xi$$

and

$$\tilde{S}(\xi + \delta\xi) \approx \tilde{S}(\xi) + J_\tilde{S}(\xi)\delta\xi$$  \hspace{1cm} (2.31)

where $J_\tilde{S}(\xi)$ is the Jacobian of $\tilde{S}$ which is an $mxn$ matrix defined as

$$J_\tilde{S}(\xi) = \begin{pmatrix} \nabla \tilde{S}_1(\xi) \\
\vdots \\
\nabla \tilde{S}_m(\xi) \end{pmatrix} = \begin{pmatrix} \frac{\partial \tilde{S}_1}{\partial \xi_1}(\xi) & \frac{\partial \tilde{S}_1}{\partial \xi_2}(\xi) & \frac{\partial \tilde{S}_1}{\partial \xi_3}(\xi) \\
\vdots & \ddots & \vdots \\
\frac{\partial \tilde{S}_m}{\partial \xi_1}(\xi) & \frac{\partial \tilde{S}_m}{\partial \xi_2}(\xi) & \frac{\partial \tilde{S}_m}{\partial \xi_3}(\xi) \end{pmatrix}$$  \hspace{1cm} (2.32)

**Levenberg Marquardt Algorithm**

In order to minimize $E$, we use the first order Taylor expansion of $\tilde{S}$, but this time we seek the value of $\delta\xi$ that minimizes $E(\xi+\delta\xi)$ for a given value of $\xi$ where

$$E(\xi + \delta\xi) = \left| \left| \tilde{S}(\xi + \delta\xi) - L \right| \right|^2 \approx \left| \left| \tilde{S}(\xi) - L + J_\tilde{S}(\xi)\delta\xi \right| \right|^2$$  \hspace{1cm} (2.33)

At this point, we are back in the linear least squares setting and the adjustment $\xi$ can be computed as the solution of

$$[J_\tilde{S}(\xi)J_\tilde{S}(\xi) + \mu I] \delta\xi = -J_\tilde{S}(\xi)(\tilde{S}(\xi) - L)$$  \hspace{1cm} (2.34)
where the damping parameter $\mu$ multiplied by an identity matrix $I$ is allowed to vary at each iteration. This method is called the Levenberg-Marquardt algorithm [30]. If the updated parameter vector $\xi + \delta \xi$ with $\delta \xi$ computed from Equation 2.34 leads to a reduction in the error $E$, the update is accepted and the process repeats with a decreased $\mu$. Otherwise, $\mu$ is increased, the augmented normal equations are solved again and the process iterates until a value of $\delta \xi$ that decreases error is found [31].

$\tilde{S}_{max}$, the maximum observed value of the curve is calculated and in each iteration, estimated parameters are stored until $4 \sqrt{Q/(m - 1)} < (\tilde{S}_{max} - 1)$ [28]. When the iterations stop, the last parameter vector $\xi$ is considered to be the solution.

Spatial patterns were saved as pseudo images in a format similar to RGB color planes. In group 1 subjects for each parameter, we constructed a separate 256x256x30 color plane, thus making the datasets to be of size 256x256x30x3. For the second group of subjects, the dimensions of the datasets were 256x256x64x3.

Main possible malfunction concerning the estimation of the parameters can occur with an insufficient number of snapshots. If the number of snapshots do not cover the infusion process of the contrast agent completely, it will be difficult to estimate the parameters accurately. In order to realize the state space dynamics of the system precisely using the time-intensity curve, sufficient number of snapshots are needed to observe the increasing rate of time-intensity curve. To address this problem, the number of snapshots must be increased as much as possible, but not with disregarding the slice thickness and the acquisition time.
2.5 Conventional (Manual) Lesion Segmentation

The parameters $A$ and $k_{ep}$ contain information about the degree of angiogenic activity in the cancerous tissue. Radiologists manually outline the malignant regions on the original DCE-MR images on which the $A$ and $k_{ep}$ parameters are overlayed as colors as shown in Figure 2.4. To identify voxels representing malignant tissues, radiologists rely on the property that microvessels in malignant tissues are more dense and porous than normal. This difference is represented in the local parametric color planes of $A$, $k_{ep}$ and $k_{el}$ [26]. The decisions are made by considering both anatomy and the $A$ and $k_{ep}$ color planes as shown in Figure 2.5.

The two dimensional color table used to represent color plane combinations have 16 levels where each color plane dimension has 4 levels (0, 1, 2, 3) as shown in Figure 2.5. For example, the pixel having white color has a level of $(A, k_{ep}) = (3,3)$ representing highest value of both $A$ and $k_{ep}$. The quantization thresholds that determine the color coding are set by the reader and there is no absolute rule how the color coding range should be picked for best analysis of the cancerous regions [23]. The selected colors are usually in the level 3 of $A$ or $k_{ep}$ color planes which are $(A,k_{ep}) = (1,3), (2,3), (3,1), (3,2), (3,3)$. Some voxels with these colors are neglected because of anatomical location and training of the reader.

The disadvantages of manual segmentation using DCE-MR parameters include the variability in selection of color coding range, tedium and time required. In addition, the amount of information can be enormous for the large sized datasets and the visual perception system can be overwhelmed [23]. While outlining multiple ROIs on each image slice, the reader’s capacity may be overloaded resulting in lowering the
diagnostic performance. The primary goal of the computer assisted diagnosis (CAD) tool described in this dissertation is to address this problem. Since the parameters $A$, $k_{ep}$, and $k_{el}$ are useful for human classification, we concentrate on the multispectral statistics of these three parameters for the co-occurrence analysis in the development of the CAD tool.

The radiologists address three dimensionality by mentally connecting the data in the through-plane direction. Also they observe the data in a video format as a sequence of in-plane image slices; however, neither of these approaches is a true 3-D analysis. The research described in this paper also addresses this problem by focusing on the multispectral analysis using local windows of observations covering both in-plane and through-plane dimensions.

2.6 Previous CAD Tools for Breast Cancer DCE-MR Mammmography

The CAD tools described in this section can be divided into two groups: Semi-automated and automated CAD tools.

2.6.1 Semi-Automated CAD Tools

The semi-automated tools are also divided into two groups which are voxel-based semi-automated CAD tools and lesion-based semi-automated CAD tools. In lesion-based tools, the features are usually morphological parameters of lesions and the gold standard for the lesion is verified by pathology for each lesion. In voxel-based tools, the features are based on individual or local group properties of the voxels in the image. Because pathology/histology data can not be matched to individual voxels in the MRI data, a different gold standard is applied for voxel-based methods.
Vomweg at al. evaluated the capability of an ANN and additional novel training methods in distinguishing between benign and malignant breast lesions in DCE-MRI in 2003 [10]. A total of 604 histologically proven cases of contrast-enhanced lesions of the female breast MRI were analyzed. Manually determined morphological parameters (maximum diameter, shape, boundary and enhancement pattern), dynamic (signal time-intensity at a center of a lesion) and clinical parameters (age of the patient, familial and individual risk factors of getting breast cancer and the reason why the investigation was performed) were collected and stored in a database. The data set was divided into several groups using random or experimental methods to train and test an ANN. For input variable selection, an additional novel computer program was applied. The ANN obtained a lesionwise sensitivity of 93.6% and a specificity of 91.9 % which outperformed the expert who had 92.1% sensitivity and 85.6% specificity [10].

Gibbs and Turnbull applied texture analysis on manually segmented lesions on high-resolution DCE-MRI of the breast to provide a method of lesion discrimination in 2003. They observed significant differences between benign and malignant lesions for a number of textural features. Using a logistic regression analysis (LRA) for classification by initially dividing the patient data into training and test datasets, reasonable model robustness was also established. The classifier resulted a sensitivity of 96%, a specificity of 71%, and a negative predictive value of 92% for suspicious lesions [11].

Chen et al. presented a fuzzy c-means (FCM) clustering-based method for the segmentation of breast lesions in three dimensions with DCE-MRI in 2006. Their lesion segmentation algorithm consisted of six consecutive stages: ROI selection by a
human operator, lesion enhancement within the selected ROI, application of FCM on
the enhanced ROI, binarization of the lesion membership map, connected-component
labeling and object selection, and holefilling on the selected object. They applied the
algorithm on 121 primary mass lesions where manual segmentation of the lesions by
an expert reader served as a gold standard in the evaluation of the CAD tool. Using
voxelwise segmentation, 97% of lesions were segmented correctly; however, positive
agreement was 40% overlap with the manual segmentation which was a very low
ratio [12].

Meinel et al. developed a semi-automated computer assisted segmentation tool
in 2007. After region-growing (semi-automated) segmentation, 42 features based on
lesion shape, texture, and enhancement kinetics were computed. For each of the
six lesion features (radius, perimeter, area, volume, compactness, spiculation, and
enhancement kinetics), seven statistics (minimum, maximum, summation, average,
standard deviation, and root mean square) were calculated [13]. The 13 best features
were selected (average and root mean square of relative intensity; average, standard
deviation, and root mean square of spiculation; average and root mean square of
radius; average and root mean square of perimeter length; average and standard
deviation of compactness; average and root mean square of area) and were used
as inputs to a backpropagation neural network (BNN). The BNN was trained and
tested using the leave-one-out method on 80 BMRI lesions (37 benign, 43 malignant)
where the lesion histopathology was used as the gold standard. Five human readers
classified the 80 lesions first without and then with CAD assistance. The specificity
performance of the human readers was 80.7% when aided by the CAD system while
the specificity of the readers were only 50.5% without using the CAD tool [13].
2.6.2 Automated CAD Tools

The advantage of automated tools over the semi-automated tools is the objectivity of the approach because automated CAD tools are largely human independent. The advantage of using voxel-based classifiers comes with dealing with heterogeneous tumors such as malignant tumors also containing necrotic or benign tissue.

Tzacheva et al. proposed using static region descriptors and a neural network classifier to evaluate a number of parameters that identify important tumor characteristics of DCE-MRI in 2003. The parameters they used were static signal intensity (SI) after contrast enhancement, mass margin descriptors, evaluation of mass shape by calculation of eccentricity, mass size, and mass granularity by texture analysis. As a classification algorithm, they used 10 feed-forward back-propagation neural networks trained with features of the images which were preprocessed by region-oriented segmentation based on intensity threshold and binary image conversion. The dataset was shuffled using a recursive swap algorithm to ensure random order of inputs where it was divided into 10 even folds. Each of the 10 neural networks was trained with the remaining nine fold and tested on one nonoverlapping fold, and the performance was averaged (10-fold cross validation). Using neural networks, they achieved a voxelwise sensitivity of 90.0%, specificity of 90.6%, and accuracy of 91.2%. Using Bayesian classifier, they achieved a voxelwise sensitivity of 91.9%, specificity of 92.5%, and accuracy of 92.3% for the 10-fold cross validation [14].

Fleig focused on the spatial neighborhood statistics of the DCE-MR parameters $A$, $k_{ep}$, and $k_{ed}$. Voxelwise texture values were used in a neural network classifier trained on manual segmentations of a radiologist as a gold standard. Each voxel was
assigned as malignant or nonmalignant. For each color plane of the DCE-MR and for each of the three cardinal directions through 3-D space, Fleig’s method computed ten types of statistical properties described by Haralick et al.: angular second moment, correlation, contrast, inverse difference moment, variance, sum average, sum variance, sum entropy, entropy, and difference variance (total of 90 new features). He has reported fairly good sensitivity (80%-85%) and specificity (75%-80%) results for each slice [15]. We have applied Fleig’s method on more data with an improved gold standard using more readers. Results are reported in Chapter 5 to compare with the 3rv method presented for this dissertation.

Woods et al. investigated the use of four-dimensional (4-D) co-occurrence-based texture analysis to distinguish between nonmalignant and malignant tissues in DCE-MRI in 2007. The classification system was a model-free neural network where each voxel was assigned either a nonmalignant or malignant label based on the textural features. The gold standard was the manual lesion segmentation of a primary radiologist and the classifier performance was compared to the performance of a second radiologist manual lesion segmentation. The method achieved a voxelwise sensitivity of 96.22% and a specificity of 99.85% [16].

2.7 Summary

In order to classify such combinations $A, k_{ep}$, and $k_{el}$, we have developed a multispectral image processing technique for 3-rv’s based on the traditional co-occurrence texture matrix analysis. The co-occurrence technique is described in Chapter 3.
CHAPTER 3

MULTISPECTRAL IMAGE PROCESSING USING CO-OCCURRENCE STATISTICS

In our research we have used multispectral statistical co-occurrence analysis for DCE-MR parameter color planes using 3-rv’s each coming from different color plane datasets ($A$, $k_{ep}$, and $k_{el}$). We have expanded the co-occurrence analysis to 3-rv’s in order to span all three color plane spaces. It is important to note that, although they can be the same, the number of dimensions of imaging data has no relation to the number of the random variables of the co-occurrence analysis. For example, Woods et al. focused on the traditional 2-random variable (2-rv) co-occurrence analysis applied on 4-D data. On the other hand, Fleig et al. focused on the traditional 2-rv co-occurrence analysis on 3-D data. The number of rv’s are defined by the number of variables for which we want to observe the statistics.

Traditional co-occurrence texture analysis is based on 2-rv joint conditional probability density functions, $F_{\alpha_1,\alpha_2}(\alpha_1, \alpha_2; d, \theta)$. Each $F_{\alpha_1,\alpha_2}(\alpha_1, \alpha_2; d, \theta)$ is the estimate of the probability of going from gray level $\alpha_1$ to gray level $\alpha_2$ or going from gray level $\alpha_2$ to gray level $\alpha_1$, given that the intersample spatial spacing is $d$ and the direction is given by the angle $\theta$. In other words $F_{\alpha_1,\alpha_2}(\alpha_1, \alpha_2; d, \theta)$ is a measure of the probability reflecting the likelihood that two voxels with gray levels $\alpha_1$ and $\alpha_2$ appear with
a distance of $d$ (chessboard distance measurement) and a direction angle $\theta$. Figure 3.1 shows an example of traditional co-occurrence texture analysis where $d_{spatial} = 1$ and $\theta_{spatial} = 90^\circ$.

![Figure 3.1: Traditional co-occurrence texture analysis which calculates the joint statistics of neighboring points in an image.](image)

We demonstrate the procedure of the computation of the traditional co-occurrence of the scanning window outlined with dashed yellow lines inside the $5 \times 5$ image shown in Figure 3.1. There are no 1’s and 5’s in the scanning window so all co-occurrences where one of the rv values is 1 or 5 are zero. Let’s pick the intersample spatial spacing
$d$ as 1 and direction angle $\theta$ as $90^\circ$ in order to find the co-occurrence of 2 and 2 in the scanning window. As we can see, 2 has no neighbor with gray level 2 with $d=1$ and $\theta = 90^\circ$ so $F(2,2|1,90^\circ)=0$. Observing the co-occurrences of 2 and 3 with $d=1$ and $\theta = 90^\circ$ as outlined by the blue boxes shown in Figure 3.1, we can find 3 co-occurrences as 3 being the neighbor of 2 and another 3 co-occurrences as 2 being the neighbor of 3, thus making the total co-occurrence $F(2,3|1,90^\circ)=6$. The bidirectional property of this traditional method makes the co-occurrence array symmetrical. For a fixed $d=1$, the resulting co-occurrence is shown in Table 3.1 for various direction angles where $\theta=0^\circ$, $45^\circ$, $90^\circ$, and $135^\circ$. All entries are zero except the ones listed in the Table 3.1.

<table>
<thead>
<tr>
<th>$\alpha_1$ value</th>
<th>$\alpha_2$ value</th>
<th>$F_{\theta=0^\circ}$</th>
<th>$F_{\theta=45^\circ}$</th>
<th>$F_{\theta=90^\circ}$</th>
<th>$F_{\theta=135^\circ}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>3</td>
<td>4</td>
<td>0</td>
<td>4</td>
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<td>4</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>6</td>
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</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3.1: Co-occurrence results of the matrix for the scanning window shown in Figure 3.1. All combinations of $\alpha_1$ and $\alpha_2$ not shown have co-occurrences of zero for all directions.

Haralick et al., in their widely cited paper, computed 14 statistical features for traditional co-occurrence analysis using 2-rv’s to achieve textural feature extraction
for image classification [4]. Their statistical features are based on joint moments and joint entropies. Fleig et al. used this approach in order to classify breast lesions [15].

3.1 Multispectral Image Processing for DCE-MRI Color Planes

Using 3 Random Variables

Multispectral co-occurrence analysis used in our research is based on the voxelwise gray level dependence of three different parametric color planes which are $A, k_{ep}$, and $k_{el}$ at the same spatial coordinates ($d=0$). In this manner we focus on the neighboring points in the spectral dimension rather than spatial dimension. We use 3-rv’s to characterize gray level dependence, each representing a color plane ($A, k_{ep}, k_{el}$) in the dataset. Because traditional statistical co-occurrence texture methods use only 2-rv’s with a 2-rv co-occurrence array (matrix), we have redefined the process in the following ways to suit 3-rv statistics using a 3-rv co-occurrence array. Here, $F_{\alpha,\beta,\gamma}(\alpha, \beta, \gamma)$ is the 3-rv co-occurrence array of three color planes, where $\alpha$ represents $A$ color plane, $\beta$ represents $k_{ep}$ color plane, and $\gamma$ represents $k_{el}$ color plane. Note that traditional co-occurrence analysis is usually bidirectional; however, the multispectral co-occurrence analysis is unidirectional. The procedure can be seen in Figure 3.2.

This time, we demonstrate the procedure of the computation of the multispectral co-occurrence array of the three color planes shown in Figure 3.2. For simplicity let us consider each color plane as a $5 \times 5 \times 1$ array and a $3 \times 3 \times 1$ local window of observation shown as a dashed box in Figure 3.2. Again, since no color plane values of 1 or 5 are inside the scanning window for any of the color planes, co-occurrence array entries where any rv is 1 or 5 must be zero here. We describe the procedure
Figure 3.2: Multispectral co-occurrence texture analysis which calculates the joint statistics of three different color planes in corresponding locations.

for computing the co-occurrence of $\alpha=2$, $\beta=3$, and $\gamma=4$ inside the scanning window. The combination of $\alpha=2$, $\beta=3$, and $\gamma=4$ co-occur only in the element outlined by the blue box on each image. Thus, $F_{\alpha,\beta,\gamma}(2, 3, 4)=1$. Table 3.2 shows the multispectral co-occurrence results for the example in Figure 3.2. All entries are zero except the ones listed in the Table 3.2.

In this dissertation, we raster scan a 3-dimensional local spatial window of observation (5x5x2) noting values of $\alpha$, $k_{ep}$, $k_{el}$ and generate a separate 3-rv co-occurrence array $F_{\alpha,\beta,\gamma}(\alpha, \beta, \gamma)$ of 3 color plane values for each location of the window as it is scanned through the data. The in-plane dimensions of the scanning window are 5x5 and the through-plane dimension is 2. Because of the anisotropic voxel dimensions (the slice thickness is much greater than the in-plane dimensions), we chose fewer samples in the through-plane direction for the observation window. Note that
Table 3.2: Multispectral co-occurrence results of the data shown in Figure 3.2. Co-occurrences for all values of $\alpha$, $\beta$, and $\gamma$ not shown are zero.

through-plane direction is different between group 1 and group 2 subjects in the experiments described in Chapter 5.

After the formation of the 3-rv joint co-occurrence array for each raster step in the scanning operation, we compute 21 statistical features we have modified from Haralick’s studies [4].

Using a normalized 3-rv co-occurrence form

$$f_{\alpha,\beta,\gamma}(\alpha, \beta, \gamma) = \frac{F_{\alpha,\beta,\gamma}(\alpha, \beta, \gamma)}{\sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} F_{\alpha,\beta,\gamma}(i, j, k)}$$

we also calculated 1-rv and 2-rv distributions as projections of the 3-rv co-occurrence array:
\[ f_\alpha(\alpha) = \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} f_{\alpha,\beta,\gamma}(\alpha, j, k) \]
\[ f_\beta(\beta) = \sum_{i=0}^{N_G-1} \sum_{k=0}^{N_G-1} f_{\alpha,\beta,\gamma}(i, \beta, k) \]
\[ f_\gamma(\gamma) = \sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} f_{\alpha,\beta,\gamma}(i, j, \gamma) \]

\[ f_{\alpha,\beta}(\alpha, \beta) = \sum_{k=0}^{N_G-1} f_{\alpha,\beta,\gamma}(\alpha, \beta, k) \]
\[ f_{\beta,\gamma}(\beta, \gamma) = \sum_{i=0}^{N_G-1} f_{\alpha,\beta,\gamma}(i, \beta, \gamma) \]
\[ f_{\alpha,\gamma}(\alpha, \gamma) = \sum_{j=0}^{N_G-1} f_{\alpha,\beta,\gamma}(\alpha, j, \gamma) \]

where \( N_G \) is the number of distinct gray levels in a given color plane. For this study, \( N_G = 32 \). \( A, k_{ep}, \) and \( k_{el} \) images were rescaled to 32 levels in order to avoid extremely sparse computations in the co-occurrence analysis.

Other co-occurrence arrays which are useful are the sum variable co-occurrence array and the difference variable co-occurrence arrays we define as

\[ f_{\alpha+\beta+\gamma}(l) = \sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} f_{\alpha,\beta,\gamma}(i, j, k), l = i + j + k \]
\[ f_{\alpha-\beta}(l) = \sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} f_{\alpha,\beta}(i, j), l = |i - j| \]
\[ f_{\beta-\gamma}(l) = \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} f_{\beta,\gamma}(j, k), l = |j - k| \]
\[ f_{\gamma-\alpha}(l) = \sum_{i=0}^{N_G-1} \sum_{k=0}^{N_G-1} f_{\alpha,\gamma}(i, j), l = |i - k| \]

In order to observe the co-occurrence properties of color plane values, we have derived 21 statistics which are based on the Haralick features [4]. These features can
be divided into two groups: 3-rv and 2-rv features. The 3-rv features are expanded from the 2-rv Haralick features and introduced for the first time in this research. These features are defined as

1) Angular Second Moment:

$$\psi_1(\alpha, \beta, \gamma) = \sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} [f_{\alpha,\beta,\gamma}(i,j,k)]^2$$  \hspace{1cm} (3.4)

2) Central Moment:

$$\psi_2(\alpha, \beta, \gamma) = \sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} (i - \mu_\alpha)(j - \mu_\beta)(k - \mu_\gamma)f_{\alpha,\beta,\gamma}(i,j,k)$$

where

$$\mu_\alpha = \sum_{i=0}^{N_G-1} if_\alpha(i)$$ \hspace{1cm} (3.5)

$$\mu_\beta = \sum_{j=0}^{N_G-1} jf_\beta(j)$$

$$\mu_\gamma = \sum_{k=0}^{N_G-1} kf_\gamma(k)$$

3) Sum average:

$$\psi_3(\alpha, \beta, \gamma) = \sum_{l=0}^{3N_G-3} (l + 3)f_{\alpha+\beta+\gamma}(l)$$ \hspace{1cm} (3.6)

4) Sum Central Moment:

$$\psi_4(\alpha, \beta, \gamma) = \sum_{l=0}^{3N_G-3} (l + 3 - \psi_3)^2 f_{\alpha+\beta+\gamma}(l)$$ \hspace{1cm} (3.7)

5) Sum Entropy:

$$\psi_5(\alpha, \beta, \gamma) = - \sum_{l=0}^{3N_G-3} f_{\alpha+\beta+\gamma}(l) \log\{f_{\alpha+\beta+\gamma}(l)\}$$ \hspace{1cm} (3.8)

6) Entropy:

$$\psi_6(\alpha, \beta, \gamma) = - \sum_{i=0}^{N_G-1} \sum_{j=0}^{N_G-1} \sum_{k=0}^{N_G-1} f_{\alpha,\beta,\gamma}(i,j,k) \log\{f_{\alpha,\beta,\gamma}(i,j,k)\}$$ \hspace{1cm} (3.9)
Difference operators in the remaining Haralick features cannot be extended to 3-rv. It is, however, useful to consider some statistics that use joint statistics of pairs of rv's for this work. For the reconstruction of 2-rv Haralick features, co-occurrence matrices were constructed from the dual combinations of the three color planes such as $\alpha$-$\beta$, $\beta$-$\gamma$, and $\alpha$-$\gamma$.

7) Contrast for ($\alpha$, $\beta$):

$$
\psi_7(\alpha, \beta) = \sum_{n=0}^{N_G-1} n^2 \left\{ \sum_{i=1}^{N_G} \sum_{j=1}^{N_G} f_{\alpha,\beta}(i, j) \right\}, |i - j| = n
$$

(3.10)

8) Contrast for ($\beta$, $\gamma$):

$$
\psi_8(\beta, \gamma) = \sum_{n=0}^{N_G-1} n^2 \left\{ \sum_{j=1}^{N_G} \sum_{k=1}^{N_G} f_{\beta,\gamma}(j, k) \right\}, |j - k| = n
$$

(3.11)

9) Contrast for ($\alpha$, $\gamma$):

$$
\psi_9(\alpha, \gamma) = \sum_{n=0}^{N_G-1} n^2 \left\{ \sum_{i=1}^{N_G} \sum_{k=1}^{N_G} f_{\alpha,\gamma}(i, k) \right\}, |i - k| = n
$$

(3.12)

10) Inverse Difference Moment for ($\alpha$, $\beta$):

$$
\psi_{10}(\alpha, \beta) = \sum_{i=1}^{N_G} \sum_{j=1}^{N_G} \frac{1}{1 + (i - j)^2} f_{\alpha,\beta}(i, j)
$$

(3.13)

11) Inverse Difference Moment for ($\beta$, $\gamma$):

$$
\psi_{11}(\beta, \gamma) = \sum_{j=1}^{N_G} \sum_{k=1}^{N_G} \frac{1}{1 + (j - k)^2} f_{\beta,\gamma}(j, k)
$$

(3.14)

12) Inverse Difference Moment for ($\alpha$, $\beta$):

$$
\psi_{12}(\alpha, \gamma) = \sum_{i=1}^{N_G} \sum_{k=1}^{N_G} \frac{1}{1 + (i - k)^2} f_{\alpha,\gamma}(i, k)
$$

(3.15)

13) Correlation for ($\alpha$, $\beta$):

$$
\psi_{13}(\alpha, \beta) = \sum_{i=1}^{N_G} \sum_{j=1}^{N_G} ij f_{\alpha,\beta}(i, j) - \mu_{\alpha} \mu_{\beta} \over \sigma_{\alpha} \sigma_{\beta}
$$

(3.16)
14) Correlation for \((\beta, \gamma)\): 
\[
\psi_{14}(\beta, \gamma) = \frac{\sum_{j=1}^{N_G} \sum_{k=1}^{N_G} jk f_{\beta,\gamma}(j, k) - \mu_\beta \mu_\gamma}{\beta \sigma_\gamma} 
\] (3.17)

15) Correlation for \((\alpha, \gamma)\): 
\[
\psi_{15}(\alpha, \gamma) = \frac{\sum_{i=1}^{N_G} \sum_{k=1}^{N_G} ik f_{\alpha,\gamma}(i, k) - \mu_\alpha \mu_\gamma}{\alpha \sigma_\gamma} 
\] (3.18)

16) Difference Variance for \((\alpha, \beta)\):
\[
\psi_{16}(\alpha, \beta) = \sum_{i=0}^{N_G-1} [i - \{ \sum_{i=0}^{N_G-1} f_{\alpha-\beta}(i) \}]^2 f_{\alpha-\beta}(i) 
\] (3.19)

17) Difference Variance for \((\beta, \gamma)\):
\[
\psi_{17}(\beta, \gamma) = \sum_{j=0}^{N_G-1} [j - \{ \sum_{j=0}^{N_G-1} f_{\beta-\gamma}(j) \}]^2 f_{\beta-\gamma}(j) 
\] (3.20)

18) Difference Variance for \((\alpha, \gamma)\):
\[
\psi_{18}(\alpha, \gamma) = \sum_{k=0}^{N_G-1} [k - \{ \sum_{k=0}^{N_G-1} f_{\gamma-\alpha}(k) \}]^2 f_{\gamma-\alpha}(k) 
\] (3.21)

19) Difference Entropy for \((\alpha, \beta)\):
\[
\psi_{19}(\alpha, \beta) = - \sum_{i=0}^{N_G-1} f_{\alpha-\beta}(i) \log\{ f_{\alpha-\beta}(i) \} 
\] (3.22)

20) Difference Entropy for \((\beta, \gamma)\):
\[
\psi_{20}(\beta, \gamma) = - \sum_{j=0}^{N_G-1} f_{\beta-\gamma}(j) \log\{ f_{\beta-\gamma}(j) \} 
\] (3.23)

21) Difference Entropy for \((\alpha, \gamma)\):
\[
\psi_{21}(\alpha, \gamma) = - \sum_{k=0}^{N_G-1} f_{\gamma-\alpha}(k) \log\{ f_{\gamma-\alpha}(k) \} 
\] (3.24)

Each voxel associated has a vector of 21 features derived from the co-occurrence array determined from the neighborhood spanned by the scanning window.
3.2 Summary

In this chapter, the theory of the multispectral statistical analysis methods we use has been briefly described, including a major innovation of this research, i.e. the 3-rv multispectral co-occurrence features. In the next chapter, the classification method is presented. The results of the experiments are shown and discussed in Chapter 5.
CHAPTER 4

CLASSIFICATION OF MULTISPECTRAL
CO-OCCURRENCE STATISTICAL FEATURES USING
NEURAL NETWORKS

Multispectral co-occurrence analysis using 3-rv’s outputs 21 types of statistical features which are combined with an artificial feedforward neural network. We have used artificial neural networks (ANN) because they are easy to use and widely regarded to be accurate in combinatorial applications.

4.1 Feedforward Neural Network Classifier

In our research we use feedforward neural networks. The feedforward neural networks are divided into two categories, single layer feedforward neural networks and multilayer feedforward neural networks [32]. To explain feedforward neural networks, we start with describing the simplest case, the single layer feedforward neural networks and expand to the multilayer feedforward neural networks used for this dissertation.

4.2 Single Layer Feedforward Neural Networks

The neural networks are organized in the form of layers [32]. In the simplest form of a layered neural network, there are source nodes which project onto an output layer
of neurons, but not into the reverse direction. Figure 4.1 shows the structure of the single layer feedforward neural network. The source nodes are not usually regarded as a layer because no computation is done in these nodes. Note that the example shown in Figure 4.1 has a single output for simplicity, but multiple outputs are also possible.

Figure 4.1: Single layer feedforward neural network with a single output node.
4.3 Training with Single Layer Feedforward Neural Network

Training data for a single layer ANN includes a collection vectors of input examples \( \psi_i(j) \), each with a corresponding output value \( y_i \). The training process determines the optimum set of weights \( w_j \) that best match inputs to outputs. Continuing with the simplest example of a simple output node, the description of finding the weights \( w_j \) follows that presented in [33]. In Figure 4.1, the information from the different resulting feature voxels are weighted and added as shown in the Equation 4.1.

\[
y_i = g \left( \sum_j \psi_i(j) w_j \right)
\]

(4.1)

where \( \psi_i(j) \) is the \( j \)th feature of the \( i \)th voxel, \( w_j \) is the weighting factor of the same feature, \( y_i \) is the \( i \)th voxel value of the output image of the classifier, and \( g(.) \) is the function of a neuron, in this example the output node. Here, \( \psi_i(j) \) and \( y_i \) form the training set. In simple cases, \( g(.) \) is preferred to be a linear function.

Using linear neuron functions, we can write the Equation 4.1 for all of the voxels picked for the training set.

\[
\begin{align*}
y_1 &= \psi_1(1)w_1 + \psi_1(2)w_2 + \cdots + \psi_1(n)w_n \\
y_2 &= \psi_2(1)w_1 + \psi_2(2)w_2 + \cdots + \psi_2(n)w_n \\
\vdots &= \vdots \\
y_m &= \psi_m(1)w_1 + \psi_m(2)w_2 + \cdots + \psi_m(n)w_n
\end{align*}
\]

(4.2)

Here \( n=21 \) for 3-rv multispectral co-occurrence analysis for DCE-MR parameter breast data. The number of voxels we have included in our training set is \( m \). Representing Equation 4.2 as a matrix vector product, we get

\[
\begin{pmatrix}
y_1 \\
y_2 \\
\vdots \\
y_m
\end{pmatrix} =
\begin{pmatrix}
\psi_1(1) & \psi_1(2) & \cdots & \psi_1(n) \\
\psi_2(1) & \psi_2(2) & \cdots & \psi_2(n) \\
\vdots & \vdots & \ddots & \vdots \\
\psi_m(1) & \psi_m(2) & \cdots & \psi_m(n)
\end{pmatrix}
\begin{pmatrix}
w_1 \\
w_2 \\
\vdots \\
w_n
\end{pmatrix}
\]

(4.3)
where

\[ y(m) = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_m \end{pmatrix} \]

\[ \Psi(m) = \begin{pmatrix} \psi_1 \\ \psi_2 \\ \ldots \\ \psi_m \end{pmatrix} = \begin{pmatrix} \psi_1(1) & \psi_1(2) & \ldots & \psi_1(n) \\ \psi_2(1) & \psi_2(2) & \ldots & \psi_2(n) \\ \vdots & \vdots & \ddots & \vdots \\ \psi_m(1) & \psi_m(2) & \ldots & \psi_m(n) \end{pmatrix} \] (4.4)

\[ w(m) = \begin{pmatrix} w_1 \\ w_2 \\ \vdots \\ w_n \end{pmatrix} \]

We can estimate the weighting factors vector \( w(m) \) by picking a sample combination of tissue voxels to be segmented (cancerous tissue) and to be excluded from the segmentation (noncancerous tissue) and forming the vector \( y(m) \) of output image voxel values (100% if to be segmented, 0% if to be excluded from segmentation). This procedure is called the training of the classifier. We already have the values of the matrix \( \Psi(m) \) which contains the voxel values of the statistical features. Given \( y(m) \) and \( \Psi(m) \) we can estimate \( w(m) \) by linear least squares method [30].

\[ w(m) = (\Psi^T(m)\Psi(m))^{-1}\Psi^T(m)y(m) \] (4.5)

where matrix \( \Psi(m) \) must be of rank \( n \) so that the solution exists and minimizes the error \( E \) defined as

\[ E = \Psi(m)w(m) - y(m) \] (4.6)

and the sum-of-squared-error criterion function

\[ \epsilon(w) = \|\Psi(m)w(m) - y(m)\|^2 = \sum_{i=1}^{m} (\psi_iw(m) - y_i)^2 \] (4.7)
Linear least squares method can be computationally expensive while working on large number of data samples. Also, statistical variation due to noise and measurement error make it unlikely that Equation 4.3 can be solved for $w(m)$ directly. $\Psi(m)$ may not be of rank $n$ which results in the nonexistence of the pseudoinverse of $\Psi(m)$ which is $(\Psi^T(m)\Psi(m))^{-1}\Psi^T(m)$ so a recursive method to find the best least square value of $w(m)$ is used. Considering Equation 4.3, a recursive linear least squares estimation method can be derived. Let’s first derive the least squares estimation by using $y_1, \ldots, y_p$ where $2 \leq p \leq m$.

\[
\begin{pmatrix}
y_1 \\
y_2 \\
\vdots \\
y_p
\end{pmatrix} =
\begin{pmatrix}
\psi_1(1) & \psi_1(2) & \cdots & \psi_1(n) \\
\psi_2(1) & \psi_2(2) & \cdots & \psi_2(n) \\
\vdots & \vdots & \ddots & \vdots \\
\psi_p(1) & \psi_p(2) & \cdots & \psi_p(n)
\end{pmatrix}
\begin{pmatrix}
w_1 \\
w_2 \\
\vdots \\
w_n
\end{pmatrix}
\]

(4.8)

where

\[
y(p) =
\begin{pmatrix}
y_1 \\
y_2 \\
\vdots \\
y_p
\end{pmatrix}
\]

\[
\Psi(p) =
\begin{pmatrix}
\psi_1 \\
\psi_2 \\
\vdots \\
\psi_p
\end{pmatrix}
= 
\begin{pmatrix}
\psi_1(1) & \psi_1(2) & \cdots & \psi_1(n) \\
\psi_2(1) & \psi_2(2) & \cdots & \psi_2(n) \\
\vdots & \vdots & \ddots & \vdots \\
\psi_p(1) & \psi_p(2) & \cdots & \psi_p(n)
\end{pmatrix}
\]

(4.9)

\[
w(p) =
\begin{pmatrix}
w_1 \\
w_2 \\
\vdots \\
w_n
\end{pmatrix}
\]

thus,

\[
w(p) = (\Psi^T(p)\Psi(p))^{-1}\Psi^T(p)y(p)
\]

(4.10)

We can find $w(p + 1)$ with $w(p)$, $\Psi(p)$, and $y(p)$ using Widrow-Hoff (also called least squares or LMS) method described in Equation 4.11 [33].
\[ w(p + 1) = w(p) + \eta(p)[y_p - w^T(p)\psi_p]\psi_p \] (4.11)

where \( \eta(p) = \eta(1)/p \) and \( \eta(1) \) is any positive constant resulting the decrease of \( \eta(p) \) for convergence of the solution. Equation 4.11 shows that first a linear least squares estimation can be done by using \( y_1 \). Then, using \( y_2 \) through \( y_m \) iteratively, the estimation will converge minimizing the mean square error. The initial weighting constants vector \( w(0) \) is chosen arbitrarily.

### 4.4 Multilayer Feedforward Neural Networks

Multilayer neural networks distinguish themselves with the presence of one or more hidden layers of which the computation nodes are called as hidden neurons or hidden units [32]. The function of hidden neurons is to intervene between the external input and the network output in an appropriate manner. Using hidden layers allows the network to extract higher order statistics.

Figure 4.2 shows a multilayer feedforward neural network using one hidden layer and a single output node for simplicity. In multilayer neural networks, multiple hidden layers and multiple output nodes are also possible. The source nodes of the network supply respective elements of the activation pattern (input vector), which constitute the input signals applied to the neurons (computation nodes) in the second layer (hidden layer). The output signals of the second layer are used as inputs to the third layer, and for the rest of the neural network [32]. The neural network shown in Figure 4.2 is a 4-4-1 neural network because it has 4 source nodes, 4 hidden neurons, and 1 output neuron. As another example, a feedforward neural network with \( m \) source
nodes, a first hidden layer with \( h_1 \) neurons, a second hidden layer with \( h_2 \) neurons, and \( q \) neurons in the output layer is referred to as \( m-h_1-h_2-q \) neural network [32].

The neural network shown in Figure 4.2 is a fully connected network because every node in each layer is connected to every other node in the adjacent forward layer [32]. If some of the connections are missing from the network, the network is

Figure 4.2: Multilayer feedforward neural network with one hidden layer, one output layer, and a single output node.
called partially connected. In our research we have used a fully connected feedforward neural network having 2 layers: one for hidden layer and one for output layer.

4.5 Training with Multilayer Feedforward Neural Network

In Figure 4.2, there are summations in each layer of the system. First the training set voxels are linearly combined in the hidden layer as shown in Equation 4.12.

\[ \phi_i(k) = g \left( \sum_j \psi_i(j) w_{kj}^{(2)} \right) \]  

(4.12)

where \( \psi_i(j) \) is the \( j \)th feature of the \( i \)th voxel, \( w_{kj}^{(2)} \) is the weighting factor of the same feature, and \( \phi_i(k) \) is the \( k \)th neuron of the hidden layer for the \( i \)th voxel features.

The hidden layers are also linearly combined by a network to the output neuron as shown in Equation 4.13.

\[ y_i = g \left( \sum_k \phi_i(k) w_{1k}^{(1)} \right) \]  

(4.13)

where \( w_{1k}^{(1)} \) is the weighting factor of the corresponding neuron of the hidden layer and \( y_i \) is the \( i \)th voxel value of the output image of the classifier. Here, \( \psi_i(j) \) and \( y_i \) form the training set as well. If linear functions are used in the neurons, combining Equations 4.12 and 4.13, we get

\[ y_i = \sum_k \sum_j x_i(j) w_{kj}^{(2)} w_{1k}^{(1)} \]

\[ = \sum_j x_i(j) \sum_k w_{kj}^{(2)} w_{1k}^{(1)} \]  

(4.14)

where

\[ w_j = \sum_k w_{kj}^{(2)} w_{1k}^{(1)} \]  

(4.15)
Equation 4.15 shows that the basic training idea using iterative linear least squares theory for the single layer neural networks can also apply here for the estimation of \( w_j \) if linear functions are used in the layers. The advantage of using a hidden layer is the benefit of backpropagation by first estimating the weighting factors \( w_{1k}^{(1)} \) (from hidden layer to output layer), then by estimating the weighting factors \( w_{kj}^{(2)} \) (from source nodes to the hidden layer) [32].

### 4.5.1 Backpropagation Algorithm

Backpropagation, an extension of least squares method, is the simplest and most general method for supervised training of multilayer neural networks [33]. The power of backpropagation is its ability of calculating the effective error of each hidden unit and deriving a learning rule for the input-to-hidden weights [33]. The basic approach in backpropagation is to start with an untrained network, present a training pattern to the input layer, pass the signals through the net, and determine the output at the output layer where these outputs are compared to the desired output values. The training error is considered as the squared difference between the desired output \( y \) and the actual output \( \hat{y} \):

\[
\epsilon(w) \equiv \frac{1}{2} (\hat{y} - y)^2
\]  

(4.16)

The backpropagation rule is based on gradient descent where weights are initialized with random values, and then they are changed in a direction that will reduce the error as

\[
\Delta w = -\eta \frac{\partial \epsilon(w)}{\partial w}
\]  

(4.17)
or in component form

\[ \Delta w_{ab} = -\eta \frac{\partial \epsilon(w)}{\partial w_{ab}} \] (4.18)

Here \( w_{ab} \) is the weight from neuron \( b \) to neuron \( a \) and \( \eta \) is the learning rate [33]. This iterative algorithm requires taking the weight vector at iteration \( p \) and updating as

\[ w(p+1) = w(p) + \Delta w(p) \] (4.19)

Let’s focus on the two layer neural network described in Figure 4.2. Consider the hidden-to-output weights \( w^{(1)}_{1k} \). Because the error is explicitly dependent upon \( w^{(1)}_{1k} \), we must use the chain rule for differentiation [33]:

\[ \frac{\partial \epsilon(w)}{\partial w_{1k}} = \frac{\partial \epsilon(w)}{\partial \text{net}} \frac{\partial \text{net}}{\partial w_{ab}} \] (4.20)

where \( \text{net} \) is the weighted sums of the inputs of output and sensitivity unit \( \delta_s \) is defined as

\[ \delta_s = -\frac{\partial \epsilon(w)}{\partial \text{net}} = (\hat{y} - y) g'(\text{net}) \] (4.21)

where \( g'(\text{net}) \) is the first order derivative of \( g(\text{net}) \).

Taken together Equations 4.18- 4.21, the weight update or learning rule for the hidden-to-output weights becomes

\[ \Delta w_{1k} = \eta(\hat{y} - y) g'(\text{net}) y \] (4.22)
In our research, we have used linear neuron functions, i.e. \( g(\text{net}) = \text{net} \) and \( g'(\text{net}) = 1 \), thus Equation 4.22 becomes the recursive least squares approach we have covered in the Section 4.3.

The idea of the backpropagation learning algorithm is the repeated application of the chain rule to compute the influence of each weight in the network with respect to an arbitrary error function as [34]:

\[
\frac{\partial \epsilon(w)}{\partial w_{ab}} = \frac{\partial \epsilon(w)}{\partial y} \frac{\partial y}{\partial \text{net}_a} \frac{\partial \text{net}_a}{\partial w_{ab}}
\] (4.23)

where \( \text{net}_a \) is the weighted sums of the inputs of neuron \( a \).

The choice of learning rate \( \eta \) has an important effect on the time of convergence. While a small \( \eta \) results in too many steps to reach an acceptable solution, a large \( \eta \) results an oscillation, preventing the error from falling below a certain value. In order to address this problem, a momentum term \( \lambda \) is sometimes introduced as [34]:

\[
\Delta w_{ab}(p + 1) = -\eta \frac{\partial \epsilon(w)}{\partial w_{ab}}(p) + \lambda \Delta w_{ab}(p)
\] (4.24)

However, as practical experience has shown, \( \lambda \) is equally problem-dependent as \( \eta \) and no general improvement can be accomplished [34]. A better solution can be obtained using resilient propagation.

### 4.5.2 Resilient Propagation (RPROP)

Resilient propagation performs a direct adaptation of the weight step based on local gradient information by introducing an update value \( \Delta_{ab} \) for each weight as [34]:

56
\[ \Delta_{ab}(p + 1) = \begin{cases} 
\rho^+ \cdot \Delta_{ab}(p), & \text{if } \frac{\partial\epsilon(w)}{\partial w_{ab}}(p) \cdot \frac{\partial\epsilon(w)}{\partial w_{ab}}(p + 1) > 0 \\
\rho^- \cdot \Delta_{ab}(p), & \text{if } \frac{\partial\epsilon(w)}{\partial w_{ab}}(p) \cdot \frac{\partial\epsilon(w)}{\partial w_{ab}}(p + 1) < 0 \\
\Delta_{ab}(p), & \text{else} 
\end{cases} \tag{4.25} \]

Once the update value for each weight is adopted, the weight update is defined as [34]:

\[ \Delta w_{ab}(p + 1) = \begin{cases} 
\rho^+ \cdot \Delta_{ab}(p + 1), & \text{if } \frac{\partial\epsilon(w)}{\partial w_{ab}}(p + 1) > 0 \\
\rho^- \cdot \Delta_{ab}(p + 1), & \text{if } \frac{\partial\epsilon(w)}{\partial w_{ab}}(p + 1) < 0 \\
0, & \text{else} 
\end{cases} \tag{4.26} \]

where \( w_{ab}(p + 1) = w_{ab}(p) + \Delta w_{ab}(t) \)

If the partial derivative changes sign, i.e. the previous step was too large and the minimum was missed, hence the operation resets to the previous weight update [34].

\[ \Delta w_{ab}(p + 1) = -\Delta w_{ab}(p), \text{ if } \frac{\partial\epsilon(w)}{\partial w_{ab}}(p) \cdot \frac{\partial\epsilon(w)}{\partial w_{ab}}(p + 1) < 0 \tag{4.27} \]

The update values and the weights are changed every time the whole pattern set has been presented once to the network (learning by epoch) [34].

The following pseudocode shows how the RPROP algorithm works. The operators minimum and maximum deliver the minimum and maximum of two numbers, respectively. The operator sign returns +1 if the argument is positive, -1 if the argument is negative, and 0 otherwise. In the beginning, all update values are set as \( \Delta_{ab} = \Delta_0 \) The range of the update values are limited in between an upper limit of \( \Delta_{max} \) and a lower limit of \( \Delta_{min} \) [34].
For all weights and biases

\[
\begin{align*}
&\text{if } \left( \frac{\partial \ell(w)}{\partial w_{ab}}(p) \right. \\
&\quad \left. \times \frac{\partial \ell(w)}{\partial w_{ab}}(p + 1) > 0 \right) \text{then} \{ \\\n&\quad \Delta_{ab}(p + 1) = \min \left( \rho^+ \times \Delta_{ab}(p), \Delta_{max} \right) \\\n&\quad \Delta w_{ab}(p + 1) = -\text{sign} \left( \frac{\partial \ell(w)}{\partial w_{ab}}(p + 1) \right) \times \Delta_{ab}(p + 1) \\\n&\quad w_{ab}(p + 2) = w_{ab}(p + 1) + \Delta w_{ab}(p + 1) \} \\
&\text{else if } \left( \frac{\partial \ell(w)}{\partial w_{ab}}(p) \right. \\
&\quad \left. \times \frac{\partial \ell(w)}{\partial w_{ab}}(p + 1) < 0 \right) \text{then} \{ \\\n&\quad \Delta_{ab}(p + 1) = \max \left( \rho^- \times \Delta_{ab}(p), \Delta_{min} \right) \\\n&\quad w_{ab}(p + 2) = w_{ab}(p + 1) - \Delta w_{ab}(p) \\\n&\quad \frac{\partial \ell(w)}{\partial w_{ab}}(p + 1) = 0 \} \\
&\text{else if } \left( \frac{\partial \ell(w)}{\partial w_{ab}}(p) \right. \\
&\quad \left. \times \frac{\partial \ell(w)}{\partial w_{ab}}(p + 1) = 0 \right) \text{then} \{ \\\n&\quad \Delta_{ab}(p + 1) = -\text{sign}(\Delta_{ab}(p)) \times \Delta_{ab}(p + 1) \\\n&\quad w_{ab}(p + 2) = w_{ab}(p + 1) - \Delta w_{ab}(p + 1) \} \\
&\} \\
\end{align*}
\]

4.6 Summary

In this chapter, classification of the statistical features using a feedforward neural network is described. In the following chapter, the results of the experiments will be displayed and discussed. The final chapter will introduce the open problems about the research described in this dissertation.
CHAPTER 5

TESTING, RESULTS AND DISCUSSIONS

5.1 DCE-MRI Acquisition for Breast Cancer

Two groups of anonymous datasets having IDC type of breast cancer were used in this research in order to show the generality of this method. In the first group, there are 8 axial subjects with 26 time points at 28 second intervals and in the second group, there are 6 coronal subjects with 6 time points at 120 second intervals.

Images in group 1 were acquired as a set of thicker transaxial slices with shorter time separation between snap shots using 1.5-T MRI system (Genesis Signa; GE Medical Systems) with Gd-DTPA contrast agent (MAGNEVIST; Berlex Laboratories, Wayne, New Jersey, USA) with a 0.2 ml/kg bodyweight dosage. Using dynamic $T_1$-weighted 2-D gradient echo sequence ($T_R = 7.8$-ms, $T_E = 4.2$-ms), 30 transaxial slices were produced where each slice consisted of $256 \times 256$ voxels with a field of view of $300 \times 300$-mm$^2$ and a slice thickness of 5-mm. Using time sequences of MR images, a time-intensity curve was constructed for each voxel in a given DCE-MRI dataset and matched to the two compartment exchange model parameters $A$, $k_{ep}$, and $k_{el}$ by the best-fit time intensity curve for the voxel using the method developed by Hoffmann et al. based on Levenberg-Marquardt fitting [29]. Spatial patterns were
saved as pseudo-images in a format similar to RGB color planes. For each subject, we constructed three separate 256x256x30 pseudo-image sets, one for $A$, one for $k_{ep}$, and one for $k_{el}$. The 8 subjects of this dataset were labeled 1-A, 2-A, 3-A, 4-A, 5-A, 6-A, 7-A, and 8-A where $A$ denotes axial imaging.

In the second group of datasets, images were acquired as a set of thinner coronal slices with longer time separation between snapshots using 1.5-T MRI system (Magnetom Vision; Siemens, Erlangen, Germany) with extravascular Gd-BOPTA contrast agent (Multihance; Bracco Group, Milano, Italy) with a dosage of 0.2-ml/kg body-weight. Using a dynamic $T_1$-weighted 2-D gradient echo sequence ($T_R = 8.1$-ms, $T_E = 4.0$-ms), 64 coronal slices were produced where each slice consisted of 256x256 voxels with an effective slice thickness of 2.5-mm and a field of view (FOV) of 320x320-mm$^2$. Again, a time-intensity curve was constructed for each voxel in a given DCE-MRI dataset and matched to the two compartment exchange model parameters $A$, $k_{ep}$, and $k_{el}$ using the curve fitting method developed by Hoffmann et al. At the end, three separate 256x256x64 pseudo-image sets, one for $A$, one for $k_{ep}$, and one for $k_{el}$ were reconstructed. The subjects of this dataset were labeled 1-C, 2-C, 3-C, 4-C, 5-C, and 6-C where $C$ denotes coronal imaging.

**Radiologist Diagnosis**

The datasets of the first group were reviewed by three independent readers (radiologists) who manually outlined suspicious lesions twice with a two-week-time interval between sessions using the techniques described in Section 2.4. The voxelwise majority of the decisions of the readers for this study was used as the gold standard. In the second group, the cancerous lesions of the datasets were manually outlined by
four independent readers (radiologists) where one of the readers manually outlined the lesions 2 times with an interval of one week between sessions, thus resulting a total of 5 readings for each subject. The gold standard for this group of datasets was computed in a similar manner used for the first group by considering the voxelwise majority of the decisions of the readers.

Images for both groups were manually marked using pharmacokinetic two compartment model-based analysis software implemented in IDL (Interactive Data Language, Boulder, Colorado, USA). Using the curve fitting algorithm described by Hoffmann et al., the pharmacokinetic parameters $A$ and $k_{ep}$ were color-coded and superimposed on the precontrast MR image [29]. The radiologists then manually drew a ROI using the computer mouse interface. Each lesion was assigned IDC label by the radiologists. The radiologist reading times varied in the range of 15-35 minutes per subject in both groups.

5.2 Co-Occurrence Analysis Computing Framework

Rather than using adaptive rebinning based on image data from individual subjects independently, we used the same set of rebinning values for all subjects because in axial slices, the strong enhancement in the cardiovascular tissues caused by high perfusion would rebin cancerous and noncancerous tissues in the same level or very close levels, if rebinning values were case dependent.

Statistical co-occurrence analysis on 3 color planes of 3-D DCE-MR parameter pseudo-image data is a computationally expensive method. The datasets we used were 256 by 256 image arrays and these arrays contained 30 image slices in the first group and 64 image slices in the second group. As a consequence of the size of the
datasets and the number of calculations, computation of the co-occurrence arrays and features for all of the scanning windows takes considerable execution time. In order to address this problem, a distributed and parallel computing environment, IP4G (Department of Biomedical Informatics, The Ohio State University, Columbus, OH) was used for the work described in this dissertation [35]. IP4G is a middleware framework for developing image analysis applications in a grid environment. We have observed an approximately linear speed up with the increase of the number of processors up to 8 (The maximum number of processors available).

In our multispectral approach, total execution time per subject for the computation of 21 features and their classification was only 10 minutes for the first group of datasets and 22 minutes for the second group of datasets by using 8 computer nodes each having dual hyperthreaded Xeon 2.4-GHz processors with 2-GB of ram, 300-GB storage. The operating system is Redhat 8 and Kernel version is 2.4.18. [36]. The radiologist reading times varied in a range of 15-35 minutes per subject in both groups.

5.3 Training the Feedforward ANN Classifier

We have used a voxelwise feedforward ANN classifier with linear transfer functions using the co-occurrence features as input data. The ANN classifier was implemented in Matlab (Mathworks, Inc., Natick, MA). In this study, 14 subjects (1-A, 2-A, 3-A, 4-A, 5-A, 6-A, 7-A, 8-A, 1-C, 2-C, 3-C, 4-C, 5-C, 6-C) having IDC breast tumor verified by pathology were used. The ANN had one hidden layer having 15 neurons and an output layer having 1 neuron. The ANN system structure is based on the weighted combination of the feature vector elements of voxels picked for the training
set. The training set is composed of an individual central in-plane slice through tumor from each of 3 randomly picked subjects from group 1 (1-A, 6-A, 7-A). All subjects from group 2 and remaining subjects and slices from group 1 were reserved for hypothesis testing. By using an ANN trained on group 1 data and hypothesis testing on group 2, we demonstrate ability of classifier to generalize.

For the training set, first, all of the voxels of the malignant tissues in the selected 3 slices meeting the majority gold standard were picked and assigned to the training set. Then three times this number of voxels were picked randomly from the parenchymal tissue and were added to the training set, bringing the total number of voxels to 3920. This method helps the classifier to understand the malignant and nonmalignant voxels of a training set while selecting the best weighted combination of the resulting features. At the end, this weighted combination is applied for the hypothesis testing. Outcome voxels of the ANN classifier ranged between 0 and 1. Thresholds were observed at several levels such as 2% (only for group 1 subjects), 10%, 20%, 30%, 40%, 50%, 60%, 70%, 71%, 73%, 75%, 77%, 78%, 82%, and 90% in order to classify voxels as nonmalignant or malignant.

5.4 Labeling the Resulting Images

Resulting images of the computer classifier are displayed with a color definition using the voxelwise majority of the readings as the gold standard. Yellow regions represent true positive \((TP)\) locations where the classifier and the gold standard agree the tissue is malignant. The red regions indicate false negatives \((FN)\) where the classifier misses a malignant tissue identified by the gold standard. The green regions are false positives \((FP)\), where the classifier states a tissue is malignant but
the gold standard labels it as nonmalignant. Black or grey regions are true negatives (TN), where the classifier and the gold standard agree there is no malignancy.

To demonstrate the feasibility of using a multispectral co-occurrence approach, we statistically compared the computer assisted tool true positive fraction (TPF) and false positive fraction (FPF) with the performance of the manual segmentations of the individual readers. TPF and FPF are defined as

\[
TPF = \frac{TP}{TP + FN} 
\]

\[
FPF = \frac{FP}{FP + TN} 
\]

where TPF would give information of the correctly classified malignant tissue and FPF would give information of the correctly classified benign tissue.

### 5.5 Hypothesis Test

The statistical comparison of the results of the classifier and the readers was done by using one sample paired \(t\)-test described by Rosner [37]. The pairs were formed by taking the difference TPF and FPF between the classifier and an individual manual reader segmentation for each subject. The paired \(t\)-test procedure was repeated for each threshold level used in classifier and for each reading. The null hypothesis is that a reader has a TPF and FPF performance statistically different than the computer classifier. This null hypothesis allows us to observe if the computer classifier TPF and FPF values are statistically distinguishable from the TPF and FPF values of
the individual readers. The hypothesis test was applied on the group 1 and group 2 subjects excluding the slices picked from group 1 subjects for the training set.

5.6 Results

The experiments were implemented on 14 subjects in two groups who have IDC breast tumors as described earlier. Using one hidden layer in the ANN classifier provided the best results. We used 5 of the 3-rv features (angular second moment, entropy, sum entropy, sum average, sum variance) and 10 of the 2-rv statistical features (contrast for \( (\alpha,\beta) \), contrast for \( (\beta,\gamma) \), contrast for \( (\alpha,\gamma) \), correlation for \( (\alpha,\beta) \), difference entropy for \( (\alpha,\beta) \), difference entropy for \( (\beta,\gamma) \), difference entropy for \( (\alpha,\gamma) \), difference variance for \( (\alpha,\beta) \), difference variance for \( (\beta,\gamma) \), and inverse difference moment for \( (\alpha,\beta) \)). We also used the DCE-MR parameter local voxel values \( A, k_{ep}, \) and \( k_{el} \), thus making a total of 18 voxelwise inputs to the classifier. The other statistical features were not used because they did not improve the results of the ANN classifier.

Figures 5.1 and 5.2 show typical images of the computer classifier. The other image slices can be found in Appendix A. For the first group of subjects, the classifier TPF and FPF results are shown in Tables B.1 and B.2 respectively in Appendix B. The reader TPF and FPF results are displayed in Tables B.3 and B.4 respectively. The receiver operator characteristics (ROC) are shown in Figure 5.3. The area under the ROC curve is 0.9660. The classifier TPF and FPF results for the second group of subjects are shown in Tables B.5 and B.6 respectively. The reader TPF and FPF results are displayed in Tables B.7 and B.8 respectively. ROC are also shown in Figure 5.4. The area under the ROC curve is 0.8830.
Figure 5.1: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the first group patients using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN

The null hypothesis was rejected for both $TPF$ and $FPF$ using a threshold level range of 40%-50% where $\alpha=0.05$, indicating computer classifier performs within the 95% confidence interval of the individual readers using threshold levels in a range of 40%-50% for both groups of subjects. This test result is especially interesting for group 2, because the ANN was trained using a completely different MRI acquisition, including time resolution and through-plane direction. Because of using DCE-MR
Figure 5.2: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the second group patients using threshold level 50%. Yellow=TP, Green=FP, Black/Gray=TN, Red=FN
Figure 5.3: 3-rv multispectral co-occurrence based classifier: ROC for the first group of patients. Area under the curve = 0.9660.
Figure 5.4: 3-rv multispectral co-occurrence based classifier: ROC for the second group of patients. Area under the curve = 0.8830.
parameters calculated from model-fitting, our method can be generalized for different types of acquisitions.

5.7 Results of the Experiments of David Fleig’s Method

David Fleig, as mentioned in Section 2.6.2., developed a traditional texture method based ANN classifier using DCE-MR color planes $A$, $k_{vp}$, and $k_{el}$ in 2003. Because his method was based on traditional texture analysis, he used 2-rv Haralick features which were angular second moment, central moment, sum average, sum central moment, sum entropy, entropy, contrast, inverse difference moment, correlation, and difference variance. In the beginning, there were some shortcomings including the quantization levels. In the parallel and distributed texture analysis process, each computing node determined its own local minima and maxima values for quantization. This would be a problem especially for the generality of the training of the ANN classifier. We have solved this problem by fixing the quantization levels to general values for all subjects of the color planes for each computing node.

David Fleig tested his method on only Group 2 subjects. Group 1 subjects were acquired after his graduation and in this research we have applied his method on Group 1 studies for the first time. Another contribution of this dissertation to Fleig’s method was to increase in the number of readers for development of the gold standard. For Group 2, David Fleig had only one reading for a gold standard while now we have 5 readings for group 2 subjects and 6 readings for group 1 subjects.

In training the classifier using David Fleig’s method, we have followed the same manner with the 3-rv multispectral co-occurrence based classifier. The same image slices from 3 subjects of group 1 (1-A, 6-A, 7-A) were picked for the training set.
and the neural network was tested on the remaining group 1 subjects and slices and all group 2 subjects. The same color labeling and threshold levels were used with both the multispectral co-occurrence based classifier and for over investigation of Fleig’s approach. The resulting images of the Fleig’s modified classifier can be seen in Figure 5.5 for group 1 subjects and Figure 5.6 for group 2 subjects.

![Images](a) Subject 1-A (b) Subject 2-A (c) Subject 3-A (d) Subject 4-A (e) Subject 6-A (f) Subject 7-A

Figure 5.5: Fleig’s texture analysis based classifier: Resulting images of the experiments on the first group patients using threshold level 20%. Yellow=TP, Green=FP, Red=FN, Black=TN

The $TPF$ and $FPF$ results of David Fleig’s approach applied on group 1 subjects can be seen in Tables B.9 and B.10 respectively. The receiver operator characteristic
Figure 5.6: Fleig’s texture analysis based classifier: Resulting images of the experiments on the second group patients using threshold level 20%. Yellow=TP, Green=FP, Black/Gray=TN, Red=FN
(roc) is shown in Figure 5.7. The area under the ROC curve is 0.9256. For group 2 subjects, the $TPF$ and $FPF$ performances can be seen in Tables B.11 and B.12 respectively. ROC is also shown in Figure 5.8. The area under the ROC curve is 0.8593.
Figure 5.7: Fleig’s texture analysis based classifier: ROC for the first group of patients. Area under the curve = 0.9256.
Figure 5.8: Fleig’s texture analysis based classifier: ROC for the second group of patients. Area under the curve = 0.8593.
5.8 Discussions

In all of the subjects, the 3-rv multispectral co-occurrence based computer assisted diagnostic tool presented in this dissertation never missed detecting a cancerous lesion selected by the majority gold standard. In manual segmentation using a computer mouse, tissue classification around the boundaries of lesions is often difficult. The disagreement between the classifier and the gold standard occurred primarily in the boundaries of the cancerous lesions. The disagreements were also present for inter- and intra-reader assessments. Our observation of reader variations are consistent with reports in literature [38]. One of the main contributions of this classifier would be the development of an objective standardized decision base for the reading radiologist with more consistent segmentations in the lesion boundaries.

Most of the literature published on CAD tools for DCE-MRI begin with an isolated ROI either manually selected or semi-automatically segmented and the classifier determines the malignancy for the entire mass [10], [11], [12], [13]. Our approach is a more detailed voxel based automated method which allows users to investigate heterogeneous tumors by classifying the benign and necrotic tissues within a lesion having malignancy.

The ANN of Vomweg has obtained a lesionwise sensitivity of 0.936 and a specificity of 0.919 [10]. Gibbs and Turnbull achieved a lesionwise sensitivity of 0.96 and a specificity of 0.71 [11]. Chen’s method had a very low positive agreement which was 40% overlap with the manual segmentation [12]. Meinel’s method aided the readers to improve their lesionwise specificity performance to 0.807 [13]. Specificity and sensitivity can be related to $TPF$ and $FPF$ as
Sensitivity = $TPF$ \hspace{1cm} (5.3)

Specificity = $1 - FPF$ \hspace{1cm} (5.4)

For both group subjects, the lesionwise sensitivity of our method was 1 because we have correctly classified all of the malignant lesions using all threshold levels. Using threshold levels 60%-90%, our method obtained a lesionwise specificity of 1 for both group subjects. This shows that our method has a better lesionwise classification performance than the methods listed above.

Among the voxel-based automated tools, Tzacheva et al. focused on breast cancer detection using static region descriptors and neural networks [14]. The statistical performance evaluation indicated 0.90 $TPF$ and 0.09 $FPF$. Using a threshold range of 10%-20%, our method obtained higher $TPF$ results together with a lower $FPF$ results than those computed by Tzacheva et al.

Using fixed quantization levels with more data and more readers as gold standard improved the accuracy of Fleig’s method. His method did not pass the hypothesis test for a fixed threshold level for both groups but he has achieved better results compared to the research projects cited above. Also, Figures 5.3, 5.4, 5.7, and 5.8 show that the ROC performance of Fleig’s method is very close to our method.

Woods et al. developed a voxel-based model-free neural network classification tool using 4-D texture analysis performed on DCE-MRI datasets of breast lesions [16]. The classifier provided a $TPF$ value of 0.96 for a given $FPF$ value of 0.0015; however, their method strongly depends on MRI acquisition, and therefore the classifier must
be trained for each new acquisition type. Classification performance presented here
does not simultaneously match $TPF$ and $FPF$ of Woods et al., but it can be more
readily generalized without retraining.

The results reported in this dissertation are very preliminary but promising. The
purpose of this research has been to show the feasibility of the multispectral co-
ocurrence based classification method. A wider study, with more subjects, more
types of acquisitions, more readers for inter- and intra-reader comparisons, and per-
haps a 75% gold standard is recommended. Furthermore, input features were selected
on an ad hoc basis in the current study. The encouraging results shown here suggest
that a carefully optimized input set might even provide better results.

5.9 Summary

After describing the acquisition methods of the spectral data used, we have de-
scribed the multispectral co-occurrence analysis approach used in this research. Fol-
lowing these chapters, the classification methods to convey the information out of the
resulting multispectral statistical features are described. In this chapter, the results
of the experiments were displayed and discussed. In the next chapter, the future
works concerning multispectral co-occurrence analysis will be described.
CHAPTER 6

CONCLUSION AND OPEN PROBLEMS

6.1 Summary and Conclusion

In Chapter 2, we first briefly described MRI including relaxation, gradient echo sequences, contrast agents, DCE-MRI, two compartment modeling, and the estimation of the color planes $A$, $k_{ep}$, and $k_{el}$. Chapter 3 described the first stage of our pattern recognition, feature extraction. In the chapter, after a brief introduction to traditional co-occurrence technique, the multispectral co-occurrence technique and features used in this dissertation are described. Chapter 4 described the second stage of the pattern recognition, classification using a feedforward ANN. In Chapter 5, the results of our method and David Fleig’s method applied on more data with better gold standards were displayed and discussed together with a comparison of the previous studies.

Our method performs voxelwise malignancy detection in a manner statistically consistent with manual segmentation. Also our CAD tool extracts and classifies the features faster than manual segmentation.

Traditional co-occurrence texture analysis focuses on the statistics of spatially neighboring voxels. Using this idea we have introduced a new way of observing the
joint statistics in the spectral neighborhood. To accommodate 3-rv’s in a multispectral co-occurrence approach, we have expanded the 2-rv traditional texture analysis method and statistical features into 3-rv’s. This approach is promising to advance voxelwise computer based lesion detection and characterization.

Most of the previous literature published in tumor classification of DCE-MRI are semi-automated tools. In semi-automated tools there is a ROI either manually or semi-automatically segmented and the classification is done for the malignancy for the entire mass. Our research is a more detailed automated method which analyzes the malignancy of each voxel in the dataset providing the advantage of assessing heterogenous lesions.

The advantage of the method described in this dissertation over the previously developed automated tools is the use of DCE-MR parametric images and advanced 3-rv multispectral statistical features. Using parametric images allows us to generalize our method for different types of acquisitions and the advanced 3-rv multispectral statistical features provide a more precise analysis.

### 6.2 Possible Applications and Open Problems

The multispectral co-occurrence technique described in this dissertation focuses on 3 rv’s each coming from different color planes. The same approach can be applied on the weather and air search radars using color planes as data obtained with an individual carrier frequency. Our method can also be trained and possibly applied to other multispectral medical image processing applications such as PET-MRI, PET-CT or combined $T_1$- and $T_2$-weighted MRI.
Rather than spatial statistics, our method focuses on spectral statistics. The results of David Fleig's method described in Section 5.7. shows that spatial statistics are also useful for pattern recognition. A possibly better solution could be developed using both spatial and spectral statistics with statistical features of different types of data at the same spatial locations together with the spatial neighboring locations.
APPENDIX A

RESULTING IMAGES OF THE CLASSIFIER
Figure A.1: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 1-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.2: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 2-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.3: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 3-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.4: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 4-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.5: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 5-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.6: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 6-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.7: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 7-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.8: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 8-A using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.9: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 1-C using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.10: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 2-C using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.11: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 2-C using threshold level 50%, continued. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.12: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 3-C using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.13: 3-ry multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 3-C using threshold level 50%, continued. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.14: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 4-C using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.15: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 5-C using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.16: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 5-C using threshold level 50%, continued. Yellow=TP, Green=FP, Red=FN, Black=TN.
Figure A.17: 3-rv multispectral co-occurrence based classifier: Resulting images of the experiments on the patient 6-C using threshold level 50%. Yellow=TP, Green=FP, Red=FN, Black=TN.
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<th>4-A</th>
<th>5-A</th>
<th>6-A⁺</th>
<th>7-A⁺</th>
<th>8-A</th>
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<td>1.0000</td>
<td>1.0000</td>
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<td>0.2670</td>
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<td>0.3813</td>
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</tr>
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<td>0.3200</td>
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Table B.1: TPF results of 3-rv multispectral co-occurrence based classifier: First group patients (* Excluding training slices).
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<th>3-A</th>
<th>4-A</th>
<th>5-A</th>
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<th>7-A*</th>
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<td>0.1464</td>
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<tr>
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<tr>
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<td>0.0009</td>
</tr>
<tr>
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<td>0.0007</td>
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Table B.2: *FPF* results of 3-rv multispectral co-occurrence based classifier: First group patients (*Excluding training slices*).
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<tbody>
<tr>
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<td>0.9128</td>
<td>0.9990</td>
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<td>Reader 1, Time 2</td>
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<tr>
<td>Reader 2, Time 1</td>
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<td>0.5073</td>
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Table B.3: TPF results of readers: First group patients.
### Table B.4: FPF results of readers: First group patients.

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<td>0.9368</td>
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<tr>
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<td>0.6513</td>
<td>0.9670</td>
<td>0.9773</td>
<td>0.8934</td>
<td>0.8875</td>
<td>0.9462</td>
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<tr>
<td>Threshold 30%</td>
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<td>0.9224</td>
<td>0.9407</td>
<td>0.8368</td>
<td>0.8140</td>
<td>0.8919</td>
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</tr>
<tr>
<td>Threshold 40%</td>
<td>0.4445</td>
<td>0.8456</td>
<td>0.8835</td>
<td>0.7592</td>
<td>0.7366</td>
<td>0.8178</td>
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<tr>
<td>Threshold 50%</td>
<td>0.3515</td>
<td>0.7378</td>
<td>0.8132</td>
<td>0.6934</td>
<td>0.6447</td>
<td>0.7291</td>
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<tr>
<td>Threshold 60%</td>
<td>0.2543</td>
<td>0.6116</td>
<td>0.7260</td>
<td>0.6276</td>
<td>0.5551</td>
<td>0.6049</td>
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</tr>
<tr>
<td>Threshold 70%</td>
<td>0.2372</td>
<td>0.5850</td>
<td>0.7068</td>
<td>0.6079</td>
<td>0.5395</td>
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<tr>
<td>Threshold 71%</td>
<td>0.2201</td>
<td>0.5567</td>
<td>0.6875</td>
<td>0.5961</td>
<td>0.5218</td>
<td>0.5441</td>
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<tr>
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<td>0.2002</td>
<td>0.5225</td>
<td>0.6676</td>
<td>0.5868</td>
<td>0.5023</td>
<td>0.5105</td>
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</tr>
<tr>
<td>Threshold 75%</td>
<td>0.1632</td>
<td>0.4497</td>
<td>0.6260</td>
<td>0.5500</td>
<td>0.4664</td>
<td>0.4364</td>
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<td></td>
</tr>
<tr>
<td>Threshold 77%</td>
<td>0.1276</td>
<td>0.3816</td>
<td>0.5770</td>
<td>0.5211</td>
<td>0.4260</td>
<td>0.3640</td>
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<td></td>
</tr>
<tr>
<td>Threshold 78%</td>
<td>0.1143</td>
<td>0.3470</td>
<td>0.5522</td>
<td>0.5066</td>
<td>0.4031</td>
<td>0.3381</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold 82%</td>
<td>0.0987</td>
<td>0.3120</td>
<td>0.5296</td>
<td>0.4895</td>
<td>0.3816</td>
<td>0.3004</td>
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<tr>
<td>Threshold 90%</td>
<td>0.0840</td>
<td>0.2869</td>
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<td>0.4737</td>
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<td>0.2567</td>
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</table>

Table B.5: TPF results of 3-rv multispectral co-occurrence based classifier: Second group patients.
<table>
<thead>
<tr>
<th>Subject</th>
<th>1-C</th>
<th>2-C</th>
<th>3-C</th>
<th>4-C</th>
<th>5-C</th>
<th>6-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold 10%</td>
<td>0.0234</td>
<td>0.0545</td>
<td>0.0978</td>
<td>0.0607</td>
<td>0.0450</td>
<td>0.0588</td>
</tr>
<tr>
<td>Threshold 20%</td>
<td>0.0077</td>
<td>0.0268</td>
<td>0.0439</td>
<td>0.0198</td>
<td>0.0302</td>
<td>0.0332</td>
</tr>
<tr>
<td>Threshold 30%</td>
<td>0.0028</td>
<td>0.0137</td>
<td>0.0169</td>
<td>0.0071</td>
<td>0.0218</td>
<td>0.0202</td>
</tr>
<tr>
<td>Threshold 40%</td>
<td>0.0011</td>
<td>0.0068</td>
<td>0.0056</td>
<td>0.0028</td>
<td>0.0162</td>
<td>0.0125</td>
</tr>
<tr>
<td>Threshold 50%</td>
<td>0.0004</td>
<td>0.0033</td>
<td>0.0018</td>
<td>0.0012</td>
<td>0.0119</td>
<td>0.0076</td>
</tr>
<tr>
<td>Threshold 60%</td>
<td>0.0002</td>
<td>0.0016</td>
<td>0.0007</td>
<td>0.0005</td>
<td>0.0081</td>
<td>0.0044</td>
</tr>
<tr>
<td>Threshold 70%</td>
<td>0.0002</td>
<td>0.0014</td>
<td>0.0005</td>
<td>0.0004</td>
<td>0.0074</td>
<td>0.0039</td>
</tr>
<tr>
<td>Threshold 71%</td>
<td>0.0001</td>
<td>0.0012</td>
<td>0.0005</td>
<td>0.0004</td>
<td>0.0067</td>
<td>0.0034</td>
</tr>
<tr>
<td>Threshold 73%</td>
<td>0.0001</td>
<td>0.0010</td>
<td>0.0004</td>
<td>0.0003</td>
<td>0.0061</td>
<td>0.0029</td>
</tr>
<tr>
<td>Threshold 75%</td>
<td>0.0001</td>
<td>0.0007</td>
<td>0.0003</td>
<td>0.0002</td>
<td>0.0048</td>
<td>0.0021</td>
</tr>
<tr>
<td>Threshold 77%</td>
<td>0.0001</td>
<td>0.0005</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0037</td>
<td>0.0015</td>
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<td>Threshold 78%</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0032</td>
<td>0.0013</td>
</tr>
<tr>
<td>Threshold 82%</td>
<td>0.0000</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0028</td>
<td>0.0011</td>
</tr>
<tr>
<td>Threshold 90%</td>
<td>0.0000</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0024</td>
<td>0.0009</td>
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Table B.6: FPF results of 3-rv multispectral co-occurrence based classifier: Second group patients.
<table>
<thead>
<tr>
<th>Subject</th>
<th>1-C</th>
<th>2-C</th>
<th>3-C</th>
<th>4-C</th>
<th>5-C</th>
<th>6-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>0.8904</td>
<td>0.9327</td>
<td>0.8848</td>
<td>0.9132</td>
<td>0.8117</td>
<td>0.9498</td>
</tr>
<tr>
<td>Reader 2</td>
<td>0.9103</td>
<td>0.8826</td>
<td>0.9470</td>
<td>0.8671</td>
<td>0.7788</td>
<td>0.9316</td>
</tr>
<tr>
<td>Reader 3</td>
<td>0.9488</td>
<td>0.9005</td>
<td>0.9708</td>
<td>0.9855</td>
<td>0.9260</td>
<td>0.9170</td>
</tr>
<tr>
<td>Reader 4 Time 1</td>
<td>0.7135</td>
<td>0.6622</td>
<td>0.9072</td>
<td>0.9553</td>
<td>0.6005</td>
<td>0.9421</td>
</tr>
<tr>
<td>Reader 4 Time 2</td>
<td>0.9203</td>
<td>0.8544</td>
<td>0.9108</td>
<td>0.1145</td>
<td>0.9516</td>
<td>0.9474</td>
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Table B.7: TPF results of readers: Second group patients.
<table>
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<th>Subject</th>
<th>1-C</th>
<th>2-C</th>
<th>3-C</th>
<th>4-C</th>
<th>5-C</th>
<th>6-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>0.0003</td>
<td>0.0037</td>
<td>0.0018</td>
<td>0.0002</td>
<td>0.0027</td>
<td>0.0007</td>
</tr>
<tr>
<td>Reader 2</td>
<td>0.0005</td>
<td>0.0007</td>
<td>0.0035</td>
<td>0.0001</td>
<td>0.0018</td>
<td>0.0003</td>
</tr>
<tr>
<td>Reader 3</td>
<td>0.0096</td>
<td>0.0083</td>
<td>0.0145</td>
<td>0.0022</td>
<td>0.0181</td>
<td>0.0013</td>
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<tr>
<td>Reader 4 Time 1</td>
<td>0.0004</td>
<td>0.0003</td>
<td>0.0007</td>
<td>0.0004</td>
<td>0.0018</td>
<td>0.0004</td>
</tr>
<tr>
<td>Reader 4 Time 2</td>
<td>0.0011</td>
<td>0.0013</td>
<td>0.0010</td>
<td>0.0022</td>
<td>0.0035</td>
<td>0.0004</td>
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Table B.8: *FPF* results of readers: Second group patients.
Table B.9: TPF results of Fleig’s texture analysis based classifier: First group patients (* Excluding training slices).

<table>
<thead>
<tr>
<th>Subject</th>
<th>1-A*</th>
<th>2-A</th>
<th>3-A</th>
<th>4-A</th>
<th>5-A</th>
<th>6-A*</th>
<th>7-A*</th>
<th>8-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold 2%</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Threshold 10%</td>
<td>0.9619</td>
<td>0.9521</td>
<td>0.9816</td>
<td>0.8605</td>
<td>0.9194</td>
<td>0.9964</td>
<td>0.9969</td>
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<td>0.9180</td>
<td>0.8788</td>
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<td>0.7215</td>
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<td>0.9900</td>
<td>0.9886</td>
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<td>Threshold 30%</td>
<td>0.8541</td>
<td>0.7792</td>
<td>0.8612</td>
<td>0.6411</td>
<td>0.5000</td>
<td>0.9618</td>
<td>0.9665</td>
<td>0.8800</td>
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<tr>
<td>Threshold 40%</td>
<td>0.8008</td>
<td>0.7006</td>
<td>0.7951</td>
<td>0.5843</td>
<td>0.3871</td>
<td>0.9145</td>
<td>0.9364</td>
<td>0.7400</td>
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<tr>
<td>Threshold 50%</td>
<td>0.7283</td>
<td>0.6117</td>
<td>0.7155</td>
<td>0.5215</td>
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<td>0.8350</td>
<td>0.9001</td>
<td>0.5200</td>
</tr>
<tr>
<td>Threshold 60%</td>
<td>0.6215</td>
<td>0.5148</td>
<td>0.6311</td>
<td>0.4630</td>
<td>0.1452</td>
<td>0.7364</td>
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<tr>
<td>Threshold 70%</td>
<td>0.5167</td>
<td>0.4023</td>
<td>0.5029</td>
<td>0.3949</td>
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<td>0.5986</td>
<td>0.7670</td>
<td>0.1200</td>
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<tr>
<td>Threshold 71%</td>
<td>0.4919</td>
<td>0.3759</td>
<td>0.4767</td>
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<td>0</td>
<td>0.5714</td>
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<tr>
<td>Threshold 73%</td>
<td>0.4576</td>
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<td>0</td>
<td>0.5386</td>
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<tr>
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<td>0.4223</td>
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<td>0.5109</td>
<td>0.7062</td>
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<tr>
<td>Threshold 77%</td>
<td>0.4013</td>
<td>0.2994</td>
<td>0.3922</td>
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<td>0.4850</td>
<td>0.6799</td>
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<td>Threshold 90%</td>
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<td>0.2227</td>
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</tr>
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<td>1-A*</td>
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<td>3-A</td>
<td>4-A</td>
<td>5-A</td>
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<tr>
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<td>Threshold 10%</td>
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<tr>
<td>Threshold 20%</td>
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<td>0.0044</td>
<td>0.0093</td>
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<tr>
<td>Threshold 30%</td>
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<td>0.0039</td>
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<td>0.0036</td>
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<tr>
<td>Threshold 40%</td>
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<td>0.0019</td>
<td>0.0020</td>
<td>0.0017</td>
<td>0.0008</td>
<td>0.0019</td>
<td>0.0017</td>
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</tr>
<tr>
<td>Threshold 50%</td>
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<td>0.0011</td>
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<td>0.0011</td>
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<tr>
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<td>0.0007</td>
<td>0.0008</td>
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</tr>
<tr>
<td>Threshold 70%</td>
<td>0.0002</td>
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<td>0.0003</td>
<td>0.0003</td>
<td>0.0002</td>
<td>0.0004</td>
<td>0.0005</td>
<td>0.0000</td>
</tr>
<tr>
<td>Threshold 71%</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0004</td>
<td>0.0005</td>
<td>0.0000</td>
</tr>
<tr>
<td>Threshold 73%</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.0005</td>
<td>0.0000</td>
</tr>
<tr>
<td>Threshold 75%</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.0005</td>
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</tr>
<tr>
<td>Threshold 77%</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.0004</td>
<td>0.0000</td>
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<tr>
<td>Threshold 78%</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0004</td>
<td>0.0000</td>
</tr>
<tr>
<td>Threshold 82%</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0003</td>
<td>0.0000</td>
</tr>
<tr>
<td>Threshold 90%</td>
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<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Table B.10: FPF results of Fleig’s texture analysis based classifier: First group patients (* Excluding training slices).
<table>
<thead>
<tr>
<th>Subject</th>
<th>1-C</th>
<th>2-C</th>
<th>3-C</th>
<th>4-C</th>
<th>5-C</th>
<th>6-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold 10%</td>
<td>0.8553</td>
<td>0.9419</td>
<td>0.9732</td>
<td>0.8276</td>
<td>0.9514</td>
<td>0.9599</td>
</tr>
<tr>
<td>Threshold 20%</td>
<td>0.7600</td>
<td>0.8663</td>
<td>0.9473</td>
<td>0.6632</td>
<td>0.8925</td>
<td>0.9247</td>
</tr>
<tr>
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<td>0.2704</td>
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<td>0.2478</td>
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<tr>
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<td>0</td>
<td>0.2260</td>
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</tr>
<tr>
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<td>0.2032</td>
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<td>0.1795</td>
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<tr>
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<td>0.1377</td>
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Table B.11: TPF results of Fleig’s texture analysis based classifier: Second group patients.
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<th>Subject</th>
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<th>2-C</th>
<th>3-C</th>
<th>4-C</th>
<th>5-C</th>
<th>6-C</th>
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<td>0.0001</td>
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<tr>
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</table>

Table B.12: $FPF$ results of Fleig's texture analysis based classifier: Second group patients.
BIBLIOGRAPHY


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