



# Computer Aided Diagnosis system for prostatic biopsy guidance and follow-up fusing multi-modal imaging.

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## **Abstract**

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To ...

## Acknowledgements

I would like to acknowledge the thousands of individuals who have coded for the LaTeX project for free. It is due to their efforts that we can generate professionally typeset PDFs now.

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## List of Abbreviations

**ACM** active contour model

**ADC** apparent diffusion coefficient

**AIF** arterial input function

**ASM** active shape model

**BPH** benign prostatic hyperplasia

**CAD** computer-aided detection and diagnosis

**CADe** computer-aided detection

**CADx** computer-aided diagnosis

**CaP** prostate cancer

**CG** central gland

**Chap.** Chapter

**CMI** combined mutual information

**CSE** chemical shift effect

**CZ** central zone

**DCE** dynamic contrast-enhanced

**DW** diffusion weighted

**EES** extravascular-extracellular space

**Eq.** equation

**ERSSPC** European Randomized Study of Screening for Prostate Cancer

**ES** Evolution Strategy

**Fig.** figure

## CONTENTS

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<b>FOV</b>	field of view
<b>FSE</b>	Fast Spin-Echo
<b>GS</b>	Gleason score
<b><i>g-scale</i></b>	generalized scale
<b>ITK</b>	Insight Segmentation and Registration Toolkit
<b>LBP</b>	local binary pattern
<b>LDA</b>	linear discriminant analysis
<b>MANTRA</b>	multi-attribute non-initializing texture reconstruction based active shape model
<b>MAP</b>	maximum <i>a posteriori</i>
<b>MI</b>	mutual information
<b>MRI</b>	magnetic resonance imaging
<b>MRSI</b>	magnetic resonance spectroscopy imaging
<b>MSE</b>	mean squared error
<b>NMR</b>	nuclear magnetic resonance
<b>PCA</b>	principal components analysis
<b>PDF</b>	probability density function
<b>PLCO</b>	Prostate Lung Colorectal and Ovarian
<b>PSA</b>	prostate-specific antigen
<b>PZ</b>	peripheral zone
<b>Sect.</b>	section
<b>SI</b>	signal intensity
<b>SNR</b>	signal-to-noise

**STAPLE** simultaneous truth and performance level estimation

**SVD** singular value decomposition

**T<sub>1</sub>-W** T<sub>1</sub> Weighted

**T<sub>2</sub>-W** T<sub>2</sub> Weighted

**TE** echo time

**TPS** thin plate spline

**TR** repetition time

**TRUS** transrectal ultrasound

**TZ** transitional zone

**US** ultrasound

**WERITAS** weighted ensemble of regional image textures for active shape model segmentation

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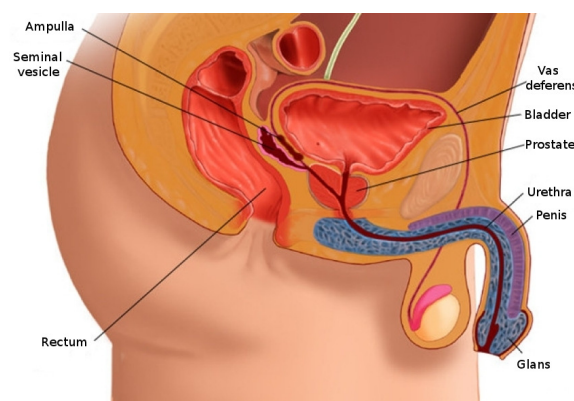
# Chapter 1

## Introduction

### 1.1 Prostate anatomy

The prostate is an exocrine gland of the male reproductive system having an inverted pyramidal shape, which is located below the bladder and in front of the rectum (see Fig. 1.1). It measures approximately three centimetres in height by two and half centimetres in depth and its weight is estimated to be between seven and sixteen grams for an adult (5). The prostate size increases at two distinct stages during physical development: initially at puberty to reach its normal size, then again after sixty years of age leading to benign prostatic hyperplasia (BPH) (6).

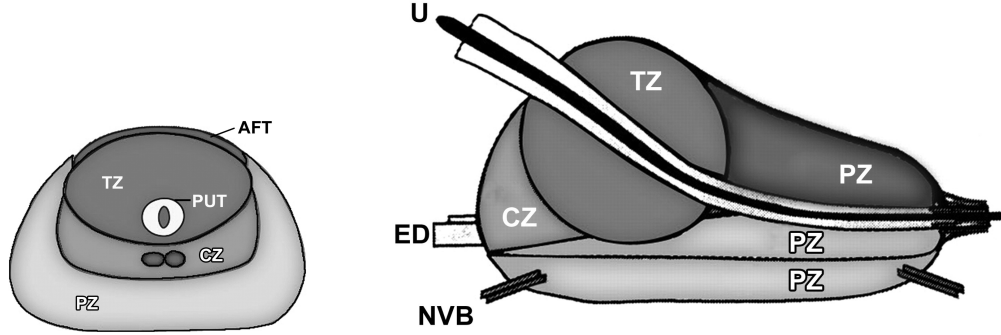
A zonal classification of the prostate, depicted in Fig. 1.2, was suggested by McNeal (7). Subsequently, this categorization was widely accepted in the literature (cf., (6,



**Figure 1.1:** Sagittal anatomy scheme of the male reproductive system.

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(a) Transverse anatomy of the prostate.

(b) Sagittal anatomy of the prostate.

**Figure 1.2:** Prostate anatomy with division in different zones. *AFT*: anterior fibromuscular tissue, *CZ*: central zone, *ED*: ejaculatory duct, *NVB*: neurovascular bundle, *PUT*: tissue, *PZ*: peripheral zone, *U*: urethra, *TZ*: transitional zone, *B*: base, *M*: median, *A*: apex (copyright by (4)).

8, 9, 10)) and is used in all medical examinations (e.g., biopsy, MRI screening. The classification is based on dividing the gland into three distinct regions: (i) central zone (CZ) accounting for 20-25% of the whole prostate gland, (ii) transitional zone (TZ) standing for 5% and (iii) peripheral zone (PZ) representing the 70%. In MRI images, tissues of CZ and TZ are difficult to distinguish and are usually merged into a common region, denominated central gland (CG). As part of this classification, the prostate can be divided in three longitudinal portions depicted in Fig. 1.2(b): (i) base, (ii) median gland and (iii) apex.

### 1.2 Prostate carcinoma

Prostate cancer (CaP) has been reported on a worldwide scale to be the second most frequently diagnosed cancer of men accounting for 13.6% (11). Statistically, in 2008, the number of new diagnosed cases was estimated to be 899,000 with no less than 258,100 deaths (11). In United States, aside from skin cancer, CaP was declared to be the most commonly diagnosed cancer among men, implying that approximately one in six men will be diagnosed with CaP during their lifetime and one in thirty-six will die from this disease causing CaP to be the second most common cause of cancer death among men

(12), (13).

Despite active research to determine the causes of prostate cancer, a fuzzy list of risk factors has arisen (14). The etiology was linked to the following factors (14): (i) family history (15, 16), (ii) genetic factors (17, 18, 19), (iii) race-ethnicity (15, 20), (iv) diet (15, 21, 22), and (v) obesity (15, 23). This list of risk factors alone cannot be used to diagnose CaP and in this way, screening enables early detection and treatment.

CaP growth is characterized by two main types of evolution (24): slow-growing tumours, accounting for up to 85 % of all CaPs (25), progress slowly and usually stay confined to the prostate gland. For such cases, treatment can be substituted with active surveillance. In contrast, the second variant of CaPs develops rapidly and metastasises from prostate gland to others organs, primarily the bones (26). Bone metastases, being an incurable disease, significantly affects the morbidity and mortality rate (27). Hence, the results of the surveillance have to be trustworthy in order to distinguish aggressive from slow-growing CaP.

CaP is more likely to come into being in specific regions of the prostate. In that respect, around 70-80 % of CaPs originate in PZ whereas 10-20 % in TZ (28, 29, 30). Only about 5 % of CaPs occur in CZ (29, 31). However, those cancers appear to be more aggressive and more likely to invade other organs due to their location (31).

### 1.3 CaP screening and imaging techniques

Current CaP screening consists of three different stages. First, prostate-specific antigen (PSA) control is performed to distinguish between low and high risk CaP. Then, for confirmation, samples are taken during prostate biopsy and finally analysed to evaluate the prognosis and the stage of CaP. In this section, we present a detailed description of the current screening as well as its drawbacks.

Since its introduction in mid-1980s, PSA is widely used for CaP screening (32). A higher-than-normal level of PSA can indicate an abnormality of the prostate either as a BPH or a cancer (33). However, other factors can lead to an increased PSA level such as prostate infections, irritations, a recent ejaculation or a recent rectal examination (6). PSA can be found in the bloodstream in two different forms: free PSA (about 10%), and linked to another protein (about 90%). A level of PSA higher than  $10 \text{ ng.mL}^{-1}$  is considered to be at risk (6). If the PSA level is between  $10 \text{ ng.mL}^{-1}$  and  $4 \text{ ng.mL}^{-1}$ ,

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the patient is considered as suspicious (34). In that case, the ratio of free PSA to total PSA is computed; if the ratio is higher than 15%, the case is considered as pathological (6).

A transrectal ultrasound (TRUS) biopsy is carried out for cases which are considered as pathological. At least six different samples are taken randomly from the right and left parts of three different zones: apex, median and base. These samples are further evaluated using the Gleason grading system (35). The scoring scheme to characterize the biopsy sample is composed of five different patterns which correspond to grades ranging from 1 to 5. Higher grades are associated with poor prognosis (36). Then, in the Gleason system, two scores are assigned corresponding to (i) the grade of the most present tumour pattern, and (ii) the grade of the second most present tumour pattern (36). A higher GS indicates a more aggressive tumour (36). Also, it should be noted that biopsy is an invasive procedure which can result in serious infection or urine retention (37, 38).

Although PSA screening has been shown to improve early detection of CaP (38), its lack of reliability motivates further investigations using MRI-CAD. Two reliable studies, carried out in the United States (39) and in Europe (40, 41), have attempted to assess the impact of early detection of CaP, with diverging outcomes (38, 42). The study carried out in Europe<sup>1</sup> concluded that PSA screening reduces CaP-related mortality by 21-44% (40, 41), while the American<sup>2</sup> trial found no such effect (39). However, both studies agree that PSA screening suffers from low specificity, with an estimated rate of 36 % (43). Both studies also agree that over-treatment is an issue: decision making regarding treatment is further complicated by difficulties in evaluating the aggressiveness and progression of CaP (44).

Hence, new screening methods should be developed with improved specificity of detection as well as more accurate risk assessment (aggressiveness and progression). Current research is focused on identifying new biological markers to replace PSA-based screening (45, 46, 47). Until such research comes to fruition, these needs can be met through active-surveillance strategy using multi-parametric MRI techniques (33, 48).

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<sup>1</sup>The European Randomized Study of Screening for Prostate Cancer (ERSPC) started in the 1990s in order to evaluate the effect of PSA screening on mortality rate.

<sup>2</sup>The Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial is carried out in the United States and intends to ascertain the effects of screening on mortality rate.

An MRI-CAD system, which is an area of active research and forms the focus of this thesis, can be incorporated into this screening strategy allowing a more systematic and rigorous follow-up.

Another weakness of the current screening strategy lies in the fact that TRUS biopsy does not provide trustworthy results. Due to its “blind” nature, there is a chance of missing aggressive tumours or detecting microfocal “cancers”, which influences the aggressiveness-assessment procedure (49). As a consequence, over-diagnosis is estimated at up to 30 % (50), while missing clinically significant CaP is estimated at up to 35 % (51). In an effort to solve both issues, alternative biopsy approaches have been explored. MRI/ultrasound (US)-guided biopsy has been shown to outperform standard TRUS biopsy (52). There, multimodal MRI images are fused with US images in order to improve localization and aggressiveness assessment to carry out biopsies. Human interaction plays a major role in biopsy sampling which can lead to low repeatability; by reducing potential human errors at this stage, the CAD framework can be used to improve repeatability of examination. CaP detection and diagnosis benefit from the use of CAD and MRI techniques.

In an effort to improve the current state of CaP diagnosis and detection, this thesis is intended to provide a multiparametric MRI CAD system. MRI principles and its different modalities are presented in Chapter (Chap.) 2.

## 1.4 Computer-aided systems for CaP

During the last century, physicists have focused on constantly innovating in terms of imaging techniques assisting radiologists to improve cancer detection and diagnosis. However, human diagnosis still suffers from low repeatability, synonymous with erroneous detection or interpretations of abnormalities throughout clinical decisions (53, 54). These errors are driven by two major causes (53): observer limitations (e.g., constrained human visual perception, fatigue or distraction) and the complexity of the clinical cases themselves, for instance due to unbalanced data (number of healthy cases more abundant than malignant cases) or overlapping structures.

Computer vision has given rise to many promising solutions, but, instead of focusing on fully automatic computerized systems, researchers have aimed at providing computer image analysis techniques to aid radiologists in their clinical decisions (53). In fact,

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these investigations brought about both concepts of computer-aided detection (CAdE) and computer-aided diagnosis (CAdx) grouped under the acronym CAD. Since those first steps, evidence has shown that CAD systems enhance the diagnosis performance of radiologists. Chan *et al.* reported a significant 4 % improvement in breast cancer detection (55), which has been confirmed in later studies (56). Similar conclusions were drawn in the case of lung nodule detection (57), colon cancer (58) and CaP as well (54). Chan *et al.* (55) also hypothesized that CAD systems will be even more efficient assisting inexperienced radiologists than senior radiologists. That hypothesis was tested by Hambrock *et al.* (54) and was confirmed in case of CaP detection. In this particular study, inexperienced radiologists obtained equivalent performance to senior radiologists, both using CAD whereas the accuracy of their diagnosis was significantly poorer without CAD's help.

In contradiction with the aforementioned statement, CAD for CaP is a young technology due to the fact that it is based on MRI (59). Four distinct MRI modalities are employed in CaP diagnosis which were mainly developed after the mid-1990s: (i) T<sub>2</sub>-W MRI (60), (ii) DCE MRI (61), (iii) MRSI (62) and (iv) DW MRI (63). In addition, the increase of magnetic field strength (from 1.5 to 3 Tesla) and the development of endorectal coils, both improved image spatial resolution (64) needed to perform more accurate diagnosis. It is for this matter that the development of CAD for CaP is still lagging behind fields stated above.

This research is aimed at first, to provide an overview of the current state-of-the-art of CAD for CaP and later, according to the drawn conclusions, to propose a CAD which takes advantage of multiparametric MRI modalities. A review of the current proposed CAD for CaP is presented in Chap. 3.

### 1.5 Research motivation

### 1.6 Thesis outline

## Chapter 2

# MRI Principles and Imaging Techniques

### 2.1 MRI principles

### 2.2 MRI imaging techniques

MRI provides promising imaging techniques to overcome the previous mentioned drawbacks. Unlike TRUS biopsy, MRI examination is a non-invasive protocol and has been shown to be the most acute and harmless technique available currently (65). In this section, we review different MRI techniques developed for CaP detection and diagnosis. Features strengthening each modality, will receive particular attention together with their drawbacks. Commonly, these features form the basis for developing analytic tools and automatic algorithms. However, we refer the reader to Sect.. ?? for more details on automatic feature detection methods since they are part and parcel of the CAD framework. Table 2.1 provides an overview of the following discussion.

#### 2.2.1 $T_2$ -W MRI

$T_2$ -W MRI was the first MRI-modality used to perform CaP diagnosis using MRI (60). Nowadays, radiologists make use of it for CaP detection, localization and staging purposes. This imaging technique is well suited to render zonal anatomy of the prostate (34).

## 2. MRI PRINCIPLES AND IMAGING TECHNIQUES

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**Table 2.1:** Overview of the features associated with each MRI modality. Acronyms: prostate cancer (CaP) - signal intensity (SI) - Gleason score (GS).

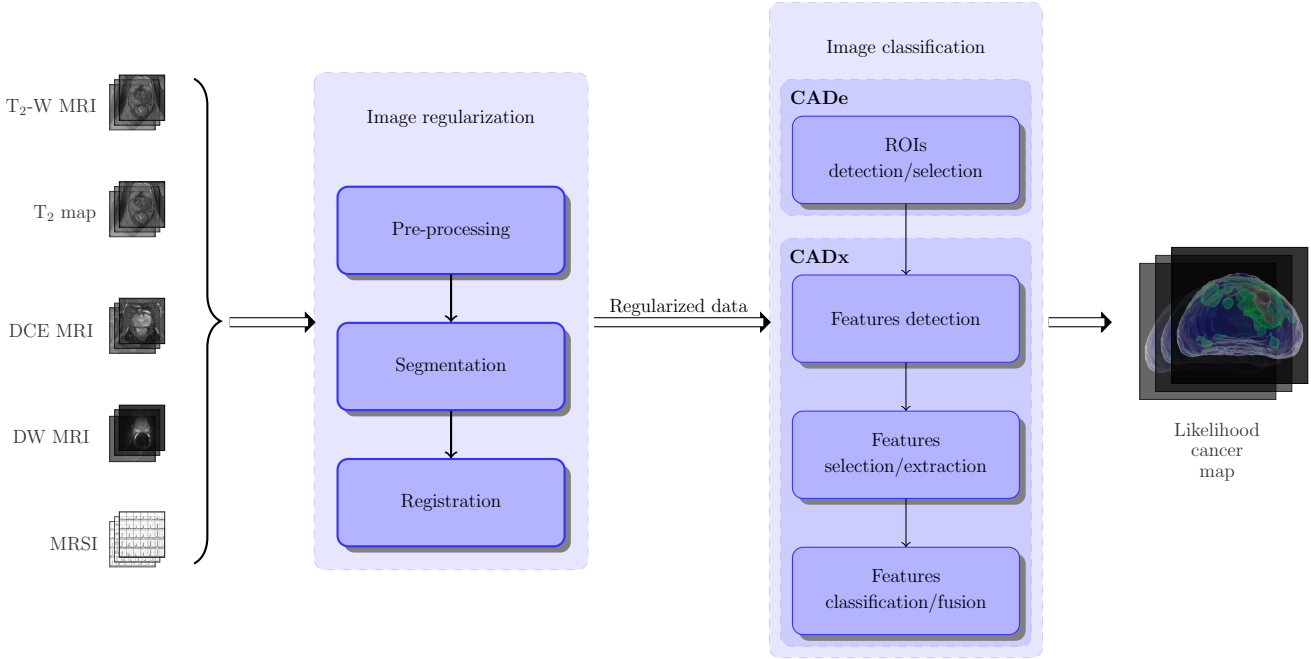
Modality	Significant features	CaP	Healthy tissue	GS correlation
T <sub>2</sub> -W MRI	SI	low-SI	intermediate to high-SI	+
T <sub>2</sub> map	SI	low-SI	intermediate to high-SI	+
DCE MRI	Semi-quantitative features:			
	– wash-in	faster	slower	0
	– wash-out	faster	slower	0
	– integral under the curve	higher	lower	0
	– maximum signal intensity	higher	lower	0
	– time-to-peak enhancement	faster	slower	0
	Quantitative features (Tofts' parameters):			
	– $k_{ep}$	higher	lower	0
	– $K^{trans}$	higher	lower	0
DW MRI	SI	higher-SI	lower-SI	+
ADC map	SI	low-SI	high-SI	+
MRSI	Metabolites:			
	Citrate (2.64 ppm)	lower concentration	higher concentration	+
	Choline (3.21 ppm)	higher concentration	lower concentration	0
	Spermine (3.11 ppm)	lower concentration	higher concentration	+

Notes:

+ = significantly correlated.

0 = no correlation.

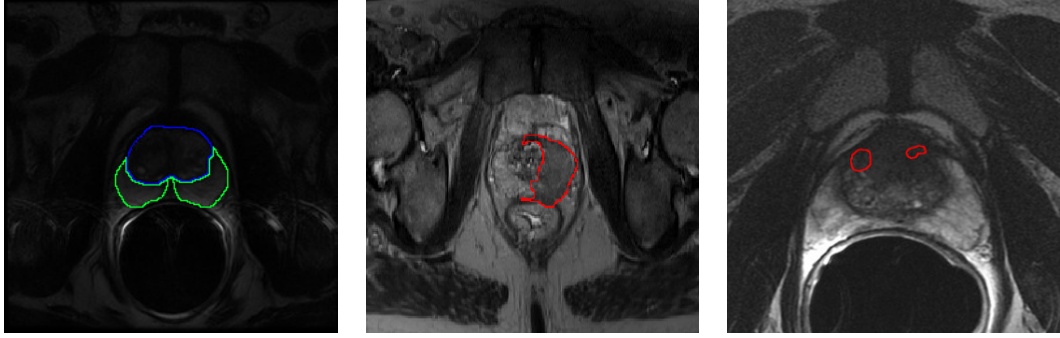




**Figure 2.1:** CAD framework using MRI images. Multiparametric MRI images are provided as inputs. These data arise from heterogeneous sources and need to be regularized. Some studies do not consider this stage as mandatory and do not implement or only partly those processes (see Tab. 3.1). A pre-processing stage is usually applied to standardize the intensity of images, reduce noise and artefacts. Then, in the image set, the prostate organ has to be segmented to focus the next processing stages only on that particular ROI. Moreover, prostate location can vary depending of the modality chosen. Therefore, the images are registered so that all segmented images will be in the same reference frame. Once the image regularisation performed, image classification can be carried out. First, a strategy defining ROIs to focus on is decided. Then, distinctive features are extracted before to be post-processed to select the most salient features. Finally, these salient features will feed a classifier previously trained which will provide a likelihood cancer map associated with either CaP detection or diagnosis.

## 2. MRI PRINCIPLES AND IMAGING TECHNIQUES

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(a) T<sub>2</sub>-W-MRI slice of an healthy prostate acquire with a 1.5 Tesla MRI. The blue contour represents the CG while the PZ corresponds to the green contour.

(b) T<sub>2</sub>-W-MRI slice of a prostate with a CaP highlighted in the PZ using a 3.0 Tesla MRI scanner.

(c) T<sub>2</sub>-W-MRI slice of a prostate with a CaP highlighted in the CG using a 3.0 Tesla MRI scanner.

**Figure 2.2:** Rendering of T<sub>2</sub>-W-MRI prostate image with both 1.5 and 3.0 Tesla MRI scanner.

This modality relies on a sequence based on setting a long repetition time (TR), reducing the T<sub>1</sub> effect in nuclear magnetic resonance (NMR) signal measured, and fixing the echo time (TE) to sufficiently large values in order to enhance the T<sub>2</sub> effect of tissues. Thus, PZ and CG tissues are well perceptible in these images. The former is characterized by an intermediate/high-SI while the latter is depicted by a low-SI (8). An example of a healthy prostate is shown in Fig. 2.2(a).

In PZ, round or ill-defined low-SI masses are synonymous with CaPs (60) as shown in Fig. 2.2(b). Detecting CaP in CG is more challenging. In fact both normal CG tissue and malignant tissue, have a low-SI in T<sub>2</sub>-W MRI reinforcing difficulties to distinguish between them. However, CaPs in CG appear often as homogeneous mass possessing ill-defined edges with lenticular or “water-drop” shapes (34, 66) as depicted in Fig. 2.2(c).

CaP aggressiveness was shown to be inversely correlated with SI. Indeed, CaPs assessed with a GS of 4-5 implied lower SI than the one with a GS of 2-3 (67).

In spite of the availability of these useful and encouraging features, the T<sub>2</sub>-W modality lacks reliability (33, 68). Sensitivity is affected by the difficulties in detecting cancers in CG (68) while specificity rate is highly affected by outliers (34). In fact, various conditions emulate patterns of CaP such as BPH, post-biopsy haemorrhage, atrophy, scars

and post-treatment (8, 34, 63, 69, 70). These issues can be partly addressed using more innovative and advanced modalities.

### 2.2.2 T<sub>2</sub> map

As previously mentioned, T<sub>2</sub>-W MRI modality shows low sensitivity. Moreover, T<sub>2</sub>-W MRI images are a composite of multiple effects (59). However, T<sub>2</sub> values alone have been shown to be more discriminative (71) and highly correlated with citrate concentration, a biological marker in CaP (72, 73).

T<sub>2</sub> values are computed using the characteristics of transverse relaxation which is formalized as:

$$M_{x,y}(t) = M_{x,y}(0) \exp\left(-\frac{t}{T_2}\right), \quad (2.1)$$

where  $M_{x,y}(0)$  is the initial value of  $M_{x,y}(t)$  and  $T_2$  is the relaxation time. By rearranging Eq. 2.1, T<sub>2</sub> map is computed performing a linear fitting on the model in Eq. 2.2 using several TE,  $t = \{TE_1, TE_2, \dots, TE_m\}$ .

$$\ln\left[\frac{M_{x,y}(t)}{M_{x,y}(0)}\right] = -\frac{t}{T_2}. \quad (2.2)$$

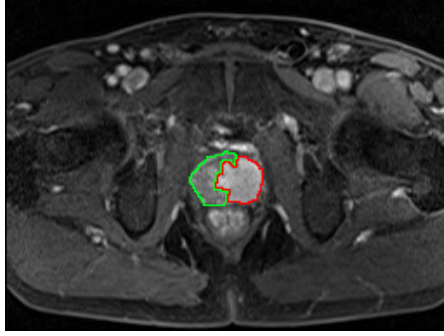
The Fast Spin-Echo (FSE) sequence has been shown to be particularly well suited in order to build a T<sub>2</sub> map and obtain accurate T<sub>2</sub> values (74). Similar to T<sub>2</sub>-W MRI, T<sub>2</sub> values associated with CaP are significantly lower than those of healthy tissues (72, 75).

### 2.2.3 DCE MRI

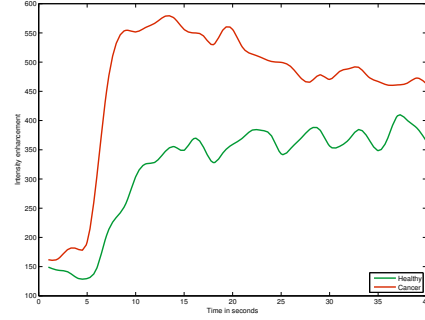
DCE MRI is an imaging technique which exploits the vascularity characteristic of tissues. Contrast media, usually gadolinium-based, is injected intravenously into the patient. The media extravasates from vessels to extravascular-extracellular space (EES) and is released back into the vasculature before being eliminated by the kidneys (76). Furthermore, the diffusion speed of the contrast agent may vary due to several parameters: (i) the permeability of the micro-vessels, (ii) their surface area and (iii) the blood flow (77).

Healthy PZ is mainly made up of glandular tissue, around 70 % (4), which implies a reduced interstitial space restricting exchanges between vessels and EES (78, 79). Normal CG has a more disorganised structure, composed of mainly fibrous tissue (4, 33), which

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(a)  $T_1$ -W-MRI image where the cancer is delimited by the red contour. The green area was still not invaded by the CaP



(b) Enhancement curve computed during the DCE-MRI analysis. The red curve is typical from CaP cancer while the green curve is characteristic of healthy tissue.

**Figure 2.3:** Illustration of typical enhancement signal observed in DCE-MRI analysis collected with a 3.0 Tesla MRI scanner.

facilitates the arrival of the contrast agent in EES (80). To understand the difference between contrast media kinetic in malignant tumours and the two previous behaviours mentioned, one has to focus on the process known as angiogenesis (81). In order to ensure growth, malignant tumours produce and release angiogenic promoter substances (81). These molecules stimulate the creation of new vessels towards the tumour (81). However, the new vessel networks in tumours differ from those present in healthy tissue (76). They are more porous due to the fact that their capillary walls have a large number of “openings” (4, 76). In contrast to healthy cases, this increased vascular permeability results in increased contrast agent exchanges between vessels and EES (82).

By making use of the previous aspects, DCE MRI is based on an acquisition of a set of  $T_1$ -W MRI images over time. The Gadolinium-based contrast agent shortens  $T_1$  relaxation time enhancing contrast in  $T_1$ -W MRI images. The aim is to post-analyse the pharmacokinetic behaviour of the contrast media concentration in prostate tissues (82). The image analysis is carried out in two dimensions: (i) in the spatial domain on a pixel-by-pixel basis and (ii) in the time domain corresponding to the consecutive images acquired with the MRI. Thus, for each spatial location, a signal linked to contrast media concentration is measured as shown in Fig. 2.3(b) (83).

By taking the previous remarks regarding medical aspects and signal theory into

account, CaPs are characterized by a signal having an earlier and faster enhancement and an earlier wash-out (cf., the rate of the contrast agent flowing out of the tissue) (see Fig. 2.3(b)) (82). Three different approaches exist to analyse these signals with the aim of tagging them as corresponding to either normal or malignant tissues. Qualitative analysis is based on assessment of the signal shape (33).

Quantitative approaches consist of inferring pharmacokinetic parameter values (83). Those parameters are part of mathematical-pharmacokinetic models which are directly based on physiological exchanges between vessels and EES. Several pharmacokinetic models were proposed such as the Kety model (84), the Tofts model (85) and mixed models (86, 87). The last family of methods mixed both approaches and are grouped together under the heading of semi-quantitative methods. They rely on shape characterization using mathematical modelling to extract a set of parameters such as wash-in gradient, wash-out, integral under the curve, maximum signal intensity, time-to-peak enhancement and start of enhancement. These parameters will be discussed in a later section (see Fig. ??) (33, 82). It was shown that semi-quantitative and quantitative methods improve localization of CaP when compared with qualitative methods (88). Section ?? provides a full description of quantitative and semi-quantitative approaches.

DCE MRI combined with T<sub>2</sub>-W MRI has shown to enhance sensitivity compared to T<sub>2</sub>-W MRI alone (89, 90, 91, 92). Despite this fact, DCE MRI possesses some drawbacks. Due to its “dynamic” nature, patient motions during the image acquisition lead to spatial misregistration of the image set (82)). Furthermore, it has been suggested that malignant tumours are difficult to distinguish from prostatitis located in PZ and BPH located in CG (33, 82). These pairs of tissues tend to have similar appearances. Later studies have shown that CaPs in CG do not always manifest in homogeneous fashion. Indeed, tumours in this zone can present both hypo-vascularization and hyper-vascularization which illustrates the challenge of CaP detection in CG (80).

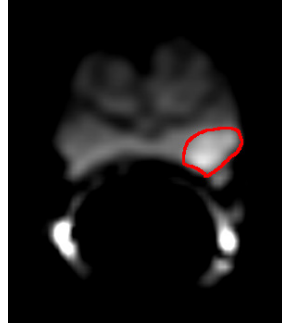
### 2.2.4 DW MRI

As previously mentioned in the introduction, DW MRI is the most recent MRI imaging technique aiming at CaP detection and diagnosis (63). This modality exploits the variations in the motion of water molecules in different tissues (93, 94).

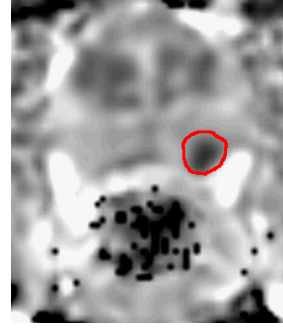
From a physiological point of view, the following facts can be claimed. On the one hand, PZ, as previously mentioned, is mainly glandular and tubular in structure allowing

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(a) DW-MRI image acquired with a 1.5 Tesla MRI scanner. The cancer corresponds to the high SI region highlighted in red.



(b) ADC map computer after acquisition of DW-MRI images with a 1.5 Tesla MRI scanner. The cancer corresponds to the low SI region highlighted in red.

**Figure 2.4:** Illustration of DW-MRI and ADC map. The signal intensity corresponding to cancer are inversely correlated on these two types of imaging techniques.

water molecules to move freely (4, 33). On the other hand, CG is made up of muscular or fibrous tissue causing the motion of the water molecules to be more constrained and heterogeneous than in PZ (33). Then, CaP growth leads to the destruction of normal glandular structure and is associated with an increase in cellular density (33, 94, 95). Furthermore, these factors both have been shown to be inversely correlated with water diffusion (94, 95): higher cellular density implies a restricted water diffusion. Thus, water diffusion in CaP will be more restricted than both healthy PZ and CG (33, 94).

From the NMR principle side, DW MRI sequence produces contrasted images due to variation of water molecules motion. The method is based on the fact that the signal in DW MRI images is inversely correlated to the degree of random motion of water molecules (96). In fact, gradients are used in DW MRI modality to encode spatial location of nuclei temporarily. Simplifying the problem in only one direction, a gradient is applied in that direction, dephasing the spins of water nuclei. Hence, the spin phases vary along the gradient direction depending of the gradient intensity at those locations. Then, a second gradient is applied aiming at cancelling the spin dephasing. Thus, the immobile water molecules will be subject to the same gradient intensity as the initial one while moving water molecules will be subject to a different gradient intensity. Thus, spins

of moving water molecules will stay dephased whereas spins of immobile water molecules will come back in phase. As a consequence, a higher degree of random motion results in a more significant signal loss whereas a lower degree of random motion is synonymous with lower signal loss (96). Under these conditions, the MRI signal is measured as:

$$M_{x,y}(t, b) = M_{x,y}(0) \exp\left(-\frac{t}{T_2}\right) S_{\text{ADC}}(b) , \quad (2.3)$$

$$S_{\text{ADC}}(b) = \exp(-b \times \text{ADC}) , \quad (2.4)$$

where  $S_{\text{ADC}}$  refers to signal drop due to diffusion effect, ADC is the apparent diffusion coefficient and  $b$  is the attenuation coefficient depending only on gradient pulses parameters: (i) gradient intensity and (ii) gradient duration (97).

By using this formulation, image acquisition with a parameter  $b = 0 \text{ s.mm}^{-2}$  corresponds to a  $T_2$ -W MRI acquisition. Then, increasing the attenuation coefficient  $b$  (cf., increase gradient intensity and duration) enhances the contrast in DW MRI images.

To summarize, in DW MRI images, CaPs are characterized by high-SI compared to normal tissues in PZ and CG as shown in Fig. 2.4(a) (34). However, some tissues in CG can look similar to CaP with higher SI (34).

Diagnosis using DW MRI combined with  $T_2$ -W MRI has shown a significant improvement compared with  $T_2$ -W MRI alone and provides highly contrasted images (4, 98, 99). As drawbacks, this modality suffers from poor spatial resolution and specificity due to false positive detection (4). With a view to eliminate these drawbacks, radiologists are extracting quantitative maps from DW MRI. This imaging technique is presented next.

### 2.2.5 ADC Map

The NMR signal measured for DW MRI images is not only affected by diffusion as shown in Eq. (2.3). However, the signal drop (Eq. (2.4)) is formulated such that the only variable is the acquisition parameter  $b$  (97). The ADC is considered as a “pure” diffusion coefficient and can be extracted to build a quantitative map.

From Eq. (2.3), it is clear that performing multiple acquisitions only varying  $b$  will not have any effect on the term  $M_{x,y}(0) \exp\left(-\frac{t}{T_2}\right)$ . Thus, Eq. (2.3) can be rewritten

## 2. MRI PRINCIPLES AND IMAGING TECHNIQUES

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as:

$$S(b) = S_0 \exp(-b \times \text{ADC}) . \quad (2.5)$$

To compute the ADC map, a minimum of two acquisitions are necessary: (i) for  $b_0 = 0 \text{ s.mm}^{-2}$  where the measured signal is equal to  $S_0$ , and (ii)  $b_1 > 0 \text{ s.mm}^{-2}$  (typically  $1000 \text{ s.mm}^{-2}$ ). Then, the ADC map can be computed as:

$$\text{ADC} = -\frac{\ln\left(\frac{S(b_1)}{S_0}\right)}{b_1} . \quad (2.6)$$

More accurate computation of the ADC map can be obtained by performing several acquisitions with different values for the parameter  $b$  and performing a semi-logarithmic linear fitting using the model presented in Eq. (2.5).

Regarding the appearance of the ADC maps, it was previously stated that by increasing the value of  $b$ , the signal of CaP tissue increases significantly. From Eq. (2.6), it can be shown that tissue appearance in the ADC map will be the inverse of DW MRI images. Then, CaP tissue is associated with low-SI whereas healthy tissue appears brighter as depicted in Fig. 2.4(b) (34).

Similar to the gain achieved by DW MRI, diagnosis using ADC map combined with T<sub>2</sub>-W MRI significantly outperforms T<sub>2</sub>-W MRI alone (4, 100). Moreover, it has been shown that ADC is correlated with GS (101, 102, 103).

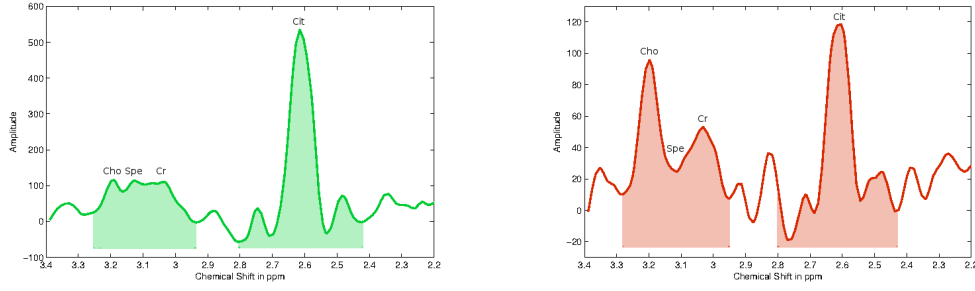
However, some tissues of the CG zone mimic CaP with low-SI (68) and image distortion can arise due to haemorrhage (4). It has also been noted that a high variability of the ADC occurs between different patients making it difficult to define a static threshold to distinguish CaP from non-malignant tumours (4).

### 2.2.6 MRSI

CaP induces metabolic changes in the prostate compared with healthy tissue. Thus, CaP detection can be carried out by tracking changes of metabolite concentration in prostate tissue. MRSI is an NMR-based technique which generates spectra of relative metabolite concentration in a ROI.

In order to track changes of metabolite concentration, it is important to know which metabolites are associated with CaP. To address this question, clinical studies identified





(a) Illustration of an MRSI spectrum of an healthy voxel acquired with a 3.0 Tesla MRI.

(b) Illustration of an MRSI spectrum of a cancerous voxel acquired with a 3.0 Tesla MRI.

**Figure 2.5:** Illustration of an MRSI spectrum both healthy and cancerous voxel with a 3.0 Tesla MRI. The highlighted areas corresponds to the related concentration of the metabolites which is computed by integrating the area under each peak. Acronyms: Choline (Cho), Spermine (Spe), Creatine (Cr) and Citrate (Cit).

three biological markers: (i) citrate, (ii) choline and (iii) polyamines composed mainly of spermine, and in less abundance of spermidine and putrescine (104, 105, 106).

Citrate is involved in the production and secretion of the prostatic fluid, and the glandular prostate cells are associated with a high production of citrate enabled by zinc accumulation by these same cells (105). However, the metabolism allowing the accumulation of citrate requires a large amount of energy (105). In contrast, malignant cells do not have high zinc levels leading to lower citrate levels due to citrate oxydation (105). Furthermore, this change results in a more energy-efficient metabolism enabling malignant cells to grow and spread (105).

An increased concentration of choline is related to CaP (104). Malignant cell development requires epigenetic mechanisms resulting in metabolic changes and relies on two mechanisms: DNA methylation and phospholipid metabolism which both result in choline uptake, explaining its increased level in CaP tissue (104). Spermine is also considered as a biological marker in CaP (106, 107). In CaP, reduction of the ductal volume due to shifts in polyamine homeostasis might lead to a reduced spermine concentration (107).

To determine the concentration of these biological markers, one has to focus on the MRSI modality. In theory, in presence of a homogeneous magnetic field, identical nuclei precesses at the same operating frequency known as the Lamor frequency (108). However, MRSI is based on the fact that identical nuclei will slightly precess at different

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frequencies depending on the chemical environment in which they are immersed (108), a phenomenon known as the chemical shift effect (CSE) (6). Given this property, metabolites can be identified and their concentrations can be determined. In this regard, the Fourier transform is used to obtain the frequency spectrum of the NMR signal (6, 108). In this spectrum, each peak is associated with a particular metabolite and the area under each peak corresponds to the relative concentration of this metabolite (see Fig. 2.5) (6).

Two different quantitative approaches are used to decide or whether not the spectra of a ROI is associated with CaP classified either as relative quantification or absolute quantification (109). In relative quantification, the ratio of choline-polyamines-creatine to citrate is computed. The integral of the signal is computed from choline (cf., 3.21 ppm) to creatine (cf., 3.02 ppm) because the peaks in this region can be merged at clinical magnetic field strengths (see Fig. 2.5) (33, 107). Considering the previous assumption that choline concentration rises and citrate concentration decreases in the presence of CaP, the ratio computed should be higher in malignant tissue than in healthy tissue.

Two different quantitative approaches are used to decide or not the spectra of a ROI is associated with CaP classified either as relative quantification or absolute quantification (109). In relative quantification, the ratio of choline-polyamines-creatine to citrate is computed. The integral of the signal is computed from choline (cf., 3.21 ppm) to creatine (cf., 3.02 ppm) because the peaks in this region can be merged at clinical magnetic field strengths (see Fig. 2.5) (33, 107). Considering the previous assumption that choline concentration rises and citrate concentration decreases in the presence of CaP, the ratio computed should be higher in malignant tissue than in healthy tissue.

In contrast with relative quantification, absolute quantification measures molar concentrations by normalizing relative concentrations using water as reference (109). In this case, “true” concentrations are directly used to differentiate malignant from healthy tissue. However, this method is not commonly used as it requires an additional step of acquiring water signals, inducing time and cost acquisition constraints.

MRSI allows examination with high specificity and sensitivity compared to other MRI modalities (4). Furthermore, it has been shown that combining MRSI with MRI improves detection and diagnosis performance (110, 111, 112). Citrate and spermine concentrations are inversely correlated with the GS allowing us to distinguish low from high grade CaPs (106). However, choline concentration does not provide the same properties (106).

Unfortunately, MRSI also presents several drawbacks. First, MRSI acquisition is time consuming which prevents this modality from being used in daily clinical practise (34). In addition, MRSI suffers from low spatial resolution due to the fact that signal-to-noise (SNR) is linked to the voxel size. However, this issue is addressed by developing new scanners with higher magnetic field strengths such as 7.5 T (106). Finally, a high variability of the relative concentrations between patients was observed (4). The same observation was made depending on the zones studied (cf., PZ, CG, base, mid-gland, apex) (109, 113). Due to this variability, it is difficult to use a fixed thresholds in order to differentiate CaP from healthy tissue.

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## Chapter 3

# Review of CADe and CADx for CaP

As previously mentioned in the introduction (see Sect. 1.4), CADs are developed to advise and backup radiologists in their tasks of CaP detection and diagnosis, but not to provide fully automatic decisions (53). CADs can be divided into two different subgroups either as CADe, with the purpose to highlight probable lesions in MRI images, or CADx, which focuses on differentiating malignant from non-malignant tumours (53). Moreover, an intuitive approach, motivated by developing a framework combining detection-diagnosis, is to mix both CADe and CADx by using the output of the former mentioned as a input of the latter named. Although the outcomes of these two systems should differ, the framework of both CAD systems is similar. A general CAD work-flow is presented in Fig. 2.1.

MRI modalities mentioned in Sect. ?? are used as inputs of CAD for CaP. These images acquired from the different modalities show a large variability between patients: the prostate organ can be located at different positions in images (e.g., patient motion, variation of acquisition plan), and the SI can be corrupted with noise or artefacts during the acquisition process (eg., magnetic field inhomogeneity, use of endorectal coil). To address these issues, the first stage of CAD is to pre-process multiparametric MRI images to reduce noise, remove artefacts and standardize the SI. At most of the later processes will be only focused on the prostate, it is necessary to segment the prostate in each MRI-modality to define it as a ROI. However, data may suffer from misalignment due to patient motions or different acquisition parameters. Therefore, a registration step

### 3. REVIEW OF CADE AND CADX FOR CAP

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is usually performed so that all the previously segmented MRI images will be in the same reference frame. Registration and segmentation can be swapped depending on the strategy chosen.

Some studies do not fully apply the methodology depicted in Fig.. 2.1. Details about those can be found in Tab. 3.1. Some studies proposed methods in which inputs are the MRI raw data inorder to demonstrate the robustness of their approaches to noise or artefacts. In some cases, prostate segmentation is performed manually as well as registration. It is also sometimes assumed that no patient motions occur during the acquisition procedure, removing the need of registering the multiparametric MRI images.

Once the data are regularized, it becomes possible to extract features and classify the data to obtain either the location of possible lesions (CADE) or/and the malignancy nature of these lesions (CADx).

In a CADE framework, *possible lesions will be segmented automatically* and further used as input of CADx. Nevertheless, some works also used a fusion CADE-CADx framework in which a voxel-based features are directly used, allowing to obtain the location of the malignant lesions as results. On the other hand, manual lesions segmentation are not considered to be part of CADE. The output of the CADE is used as input of the CADx.

CADx is composed of the processes allowing to *distinguish malignant from non-malignant tumours*. Here, CaP malignancy is defined using the grade of the GS determined after post biopsy or prostatectomy. As presented in Fig.. 2.1, CADx is usually composed of the three common steps used in classification framework: (i) features detection, (ii) feature extraction/selection and (iii) feature classification.

This chapter is organized using the methodology presented in Fig.. 2.1. Methods embedded in the image regularization framework are presented initially to subsequently focus on the image classification framework, being divided into CADE and CADx. Table 3.1 summarizes the fourty-two different CAD studies reviewed in section. The first set of information reported is linked to the data acquisition such as the number of patients included in the study, the modalities acquired as well as the strength of the field of the scanner used. Subsequently, information about the prostate zones considered in the CAD analysis (PZ or CG) are reported since that detecting CaP in the CG is a more challenging problem and has received particular attention only in the recent publications.

**Table 3.1:** Overview of the different studies reviewed with their main characteristics. Acronyms: number (#) - image regularization (Img. Reg.).

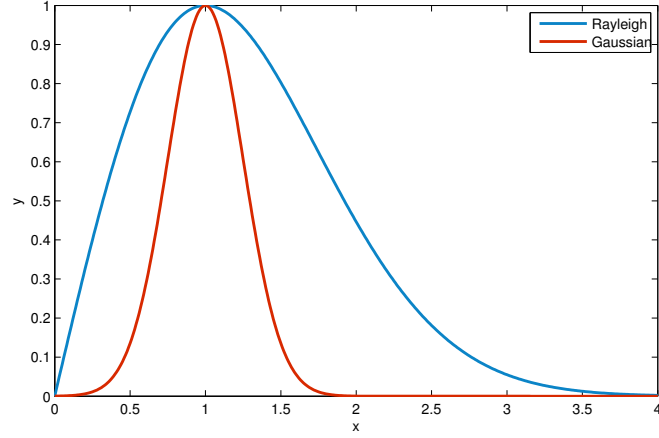
Index	Study	# patients	MRI-modality				Strength of field		Studied zones		CAD stages		
			T <sub>2</sub> -W MRI	DCE MRI	DW MRI	MRSI	1.5 T	3.0 T	PZ	CG	Img. Reg.	CADe	CADx
[1]	(114)	25	✓	✓	✗	✗	✓	✗	✓	✗	✓!	✗	✓
[2]	(115)	25	✓	✓	✗	✗	✓	✗	✓	✗	✓!	✗	✓
[3]	(116)	53	✓	✗	✓	✗	✓	✗	✓	✓	✗	✗	✓
[4]	(117)	10	✓	✓	✓	✗	✓	✗	✓	✗	✗	✓	✓
[5]	(118)	21	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✓	✓
[6]	(119)	15	✓	✗	✓	✗	✓	✗	✓	✗	✗	✗	✓
[7]	(120)	10	✓	✓	✓	✗	✓	✗	✓	✗	✓	✓	✓
[8]	(121)	24	✗	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[9]	(122)	25	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✗	✓
[10]	(123)	188	✓	✓	✓	✗	✗	✓	✓	✗	✓!	✓	✓
[11]	(124)	288	✓	✓	✓	✗	✗	✓	✓	✓	✓!	✓	✓
[12]	(125)	11	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✓	✓
[13]	(126)	54	✓	✓	✓	✗	✗	✓	✓	✓	✓!	✗	✓
[14]	(127)	27	✓	✗	✗	✗	✓	✗	✓	✗	✓!	✓	✓
[15]	(128)	55	✓	✗	✗	✗	✓	✗	✓	✗	✓!	✗	✓
[16]	(129)	18	✗	✗	✗	✓	✗	✓	✓	✓	✗	✓	✓
[17]	(130)	10	✗	✓	✗	✗	✓	✗	✓	✗	✓!	✓	✓
[18]	(2)	23	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✗	✓
[19]	(3)	30	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✗	✓
[20]	(131)	20	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✓	✓
[21]	(132)	20	✓	✓	✓	✗	✓	✗	✓	✗	✓!	✓	✓
[22]	(133)	22	✗	✗	✗	✓	✗	✓	✓	✓	✓!	✓	✓
[23]	(103)	48	✓	✓	✓	✗	✗	✓	✓	✓	✗	✗	✓
[24]	(134)	100	✗	✓	✗	✗	✓	✗	✓	✓	✗	✗	✓
[25]	(135)	42	✗	✓	✗	✗	✗	✓	✓	✓	✗	✓	✓
[26]	(136)	14	✗	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[27]	(137)	18	✗	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[28]	(138)	18	✗	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[29]	(139)	15	✓	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[30]	(140)	19	✓	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[31]	(141)	36	✓	✗	✗	✓	✓	✗	✓	✓	✗	✓	✓
[32]	(142)	29	✓	✗	✗	✓	✓	✗	✓	✓	✓!	✓	✓
[33]	(143)	16	✓	✗	✗	✓	✓	✗	✓	✓	✗	✓	✓
[34]	(144)	6	✓	✓	✗	✗	✗	✓	✓	✓	✓!	✓	✓
[35]	(145)	6	✓	✓	✗	✗	✗	✓	✓	✓	✓	✓	✓
[36]	(146)	12	✓	✓	✓	✗	✗	✓	✓	✓	✓!	✓	✓
[37]	(147)	22	✓	✗	✗	✗	✗	✓	✓	✓	✓	✓	✓
[38]	(148)	29	✓	✓	✗	✗	✓	✗	✓	✗	✓!	✗	✓
[39]	(149)	29	✗	✓	✗	✗	✓	✗	✓	✗	✓!	✗	✓
[40]	(150)	29	✓	✓	✗	✗	✓	✗	✓	✗	✓!	✗	✓
[41]	(151)	NA	✓	✓	✓	✗	✗	✓	✓	✗	✓!	✓	✓

Notes:

✗: not used or not implemented.

✓!: partially implemented.

✓: used or implemented.



**Figure 3.1:** Illustration of a Gaussian distribution ( $\mu = 1, \sigma = 0.25$ ) and a Rayleigh distribution ( $\sigma = 2$ ). It can be seen that the Rayleigh distribution is suffering of a bias term when compared with the Gaussian distribution.

## 3.1 Image regularization framework

This section provides a review of the methods used in CADs for CaP in order to regularize input images. We start with pre-processing methods presented in Sect. 3.1.1, focusing mainly on the reduction of noise level and artefacts as well as standardization of SI. Sections 3.1.2 and ?? will be dedicated to segmentation methods, so that later methods only operate on the segmented prostate, and registration to align segmented images from different MRI-modalities in the same reference frame.

### 3.1.1 Pre-processing

Three different groups of pre-processing methods are commonly applied to images as initial stage in CAD for CaP. These methods are explained for both MRI and MRSI modalities, while a summary of the applied methods in CAD is presented in Table. 3.2.

**Noise filtering:** The NMR signal measured and recorded in the k-space during an MRI acquisition is affected by noise. This noise obeys a complex Gaussian white noise mainly due to thermal noises in the patient area (152). Furthermore, MRI images visualized by radiologists are in fact the magnitude images resulting from the complex Fourier transform of the k-space data. The complex Fourier transform, being a linear and orthogonal transform, does not affect the Gaussian noise characteristics (152). However, the function involved in the magnitude computation is a non-linear transform (i.e., the square root of the sum of squares of real and the imaginary parts), implying that the noise distribution is no longer Gaussian; it indeed follows a Rician distribution making the denoising task harder. Briefly, a Rician distribution can be characterized as follows:



in low-SI region (low SNR), it can be approximated with a Rayleigh distribution while in high-SI region (high SNR), it is similar to a Gaussian distribution (see Fig. 3.1) (153). Reviews of all denoising methods can be found in (154, 155).

Median filtering is the simplest approach used to address the denoising issue in MRI images (131, 132). In both studies, Ozer *et al.* used a square kernel of size  $5 \times 5$  pixels with the image resolutions ranging from  $320 \times 256$  (cf., T<sub>2</sub>-W MRI) to  $256 \times 128$  (cf., T<sub>2</sub> map, DCE and DW MRI) and a field of view (FOV) ranging from 14 cm (cf, T<sub>2</sub>-W and DW MRI) to 20 cm (cf, T<sub>2</sub> map and DCE MRI). However, from a theoretical point of view, this simple filtering method is not well formalized to address the noise distribution in MRI images.

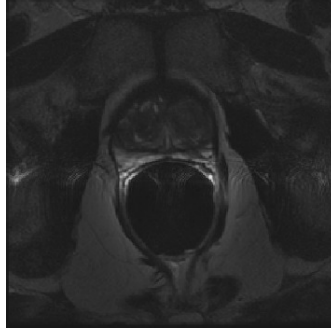
More complex approaches were proposed to overcome this problem. A common method used to denoise MRI images is based on wavelet-based filtering. This filtering exploits the sparsity property of the wavelet decomposition. The projection of a noisy signal from the spatial-domain to the wavelet-domain implies that only few wavelet coefficients contribute to the “signal-free noise” while all wavelet coefficients contribute to the noise (156). Therefore, denoising is performed by thresholding/attenuating the insignificant wavelet coefficients to enforce the sparsity in the wavelet-domain. Investigations focus on the strategies to perform the most adequate coefficient shrinkage method (e.g., using thresholding, singularity property or Bayesian framework) (157).

Ampeliotis *et al.* in (114, 115) performed wavelet shrinkage to denoise magnitude MRI images (cf., T<sub>2</sub>-W-MRI and DCE-MRI) using thresholding techniques (158). However, since the wavelet transform is an orthogonal transform, the Rician distribution of the noise is preserved in the wavelet-domain. Hence, for low SNR, the wavelet and scaling coefficients still suffer from a bias due to this specific noise distribution (152).

Lopes *et al.* in (127) used the filtering technique proposed by (159) to denoise T<sub>2</sub>-W-MRI which was based on joint detection and estimation theory (159). In this approach, the wavelet coefficients “free-of-noise” are estimated from the noisy wavelet coefficients using a maximum *a posteriori* (MAP) estimate. Furthermore, the estimator designed takes spatial context into account by including both local and global information in the prior probabilities. The different probabilities needed by the MAP are empirically estimated by using mask images representing the locations of the significant wavelet coefficients. These mask images are computed by thresholding the detail images obtained from the wavelet decomposition. To remove the bias from the wavelet and scaling coefficients, the squared magnitude MRI image used instead of the magnitude MRI image as proposed by (152). This involves changing the Rician distribution to a scaled non-central Chi-square distribution. It implies that the wavelet coefficients are also unbiased estimators and the scaling coefficients are unbiased estimators but up to a constant  $C$  as defined in Eq. (3.1) which needs to be subtracted from each scaling coefficient,

$$C = 2^{(J+1)}\hat{\sigma}^2, \quad (3.1)$$

where  $J$  is the number of levels of the wavelet decomposition and  $\hat{\sigma}$  is an estimate of the noise standard deviation.



**Figure 3.2:** Example of artefacts with high SI due to perturbation from the endorectal coil which create inhomogeneity.

**Bias correction:** Besides being corrupted by noise, MRI images are also affected by the inhomogeneity of the MRI field commonly referred to as bias field (160). This bias field results in a smooth variation of the SI through the image. When an endorectal coil is used, an artefact resulting of an hyper-intense signal can be observed around the coil on the images (see Fig. 3.2).

As a consequence, the SI of identical tissues varies depending on their spatial location in the image making further processes such as segmentation or registration harder (161, 162). A review of bias correction methods can be found in (162).

The model of image formation is usually formalized such that:

$$s(\mathbf{x}) = o(\mathbf{x})b(\mathbf{x}) + \eta(\mathbf{x}) , \quad (3.2)$$

where  $s(\mathbf{x})$  is the corrupted SI at the pixel for the image coordinates  $\mathbf{x} = \{x, y\}$ ,  $o(\mathbf{x})$  is the “noise-free signal” ,  $b(\mathbf{x})$  is the bias field function and  $\eta(\mathbf{x})$  is an additive white Gaussian noise.

Hence, the task of bias correction involves estimating the bias function  $b(\mathbf{x})$  in order to infer the “signal-free bias”  $o(\mathbf{x})$ .

Viswanath *et al.* (145) performed bias correction on T<sub>2</sub>-W-MRI using a parametric Legendre polynomial model proposed in (160) and available in the Insight Segmentation and Registration Toolkit (ITK) library<sup>1</sup>.

Styner *et al.* (160) chose to model the bias field by using a linear combination of Legendre polynomials as:

$$\hat{b}(\mathbf{x}, \mathbf{p}) = \sum_{i=0}^{m-1} p_i f_i(\mathbf{x}) = \sum_{i=0}^l \sum_{j=0}^{l-i} p_{ij} P_i(x) P_j(y) , \quad (3.3)$$

where  $\hat{b}$  is the bias estimation with the image coordinates  $\mathbf{x} = \{x, y\}$  and the  $m$  coefficients of the linear combination  $\mathbf{p} = p_{11}, \dots, p_{ij}$  ;  $m$  can be defined as  $m = (l + 1) \frac{(l+2)}{2}$

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<sup>1</sup>The ITK library is available at: <http://www.itk.org/>

where  $l$  is the degree of Legendre polynomials chosen and  $P_i(\cdot)$  denotes a Legendre polynomial of degree  $i$ .

This family of functions allows us to model the bias as a smooth inhomogeneity function across the image. To estimate the set of parameters  $\mathbf{p}$ , a cost function is defined which relies on the following assumptions: (i) an image is composed of  $k$  regions with  $\mu_k$  being the mean SI and a variance  $\sigma_k^2$  of each particular class, and (ii) each noisy pixel belongs to one of the  $k$  regions with its SI value close to the class mean  $\mu_k$ . Hence, the cost function is defined as:

$$C(\mathbf{p}) = \sum_{\mathbf{x}} \prod_k \rho_k(s(\mathbf{x}) - \hat{b}(\mathbf{x}, \mathbf{p}) - \mu_k) , \quad (3.4)$$

$$\rho_k(x) = \frac{x^2}{x^2 + 3\sigma_k^2} , \quad (3.5)$$

where  $\rho_k(\cdot)$  is a M-estimator allowing estimations to be less sensitive to outliers than usual square distance (163).

Finally, estimation of the parameters  $\mathbf{p}$  results in finding the minimum of the cost function  $C(\mathbf{p})$ . This optimization was performed using the non-linear (1 + 1) Evolution Strategy (ES) optimizer (164).

In a later publication, (147) make use of the well known N3 algorithm<sup>1</sup> to correct T<sub>2</sub>-W-MRI developed by (165). To estimate the bias function, (165) proposed to estimate the probability density functions (PDFs) of the signal and bias.

Recalling Eq. (3.2) and taking advantage of logarithm property, it implies that this model becomes additive such that:

$$\begin{aligned} \log s(\mathbf{x}) &= \log b(\mathbf{x}) + \log \left( o(\mathbf{x}) + \frac{\eta(\mathbf{x})}{b(\mathbf{x})} \right) , \\ &\approx \log b(\mathbf{x}) + \log \hat{o}(\mathbf{x}) , \end{aligned} \quad (3.6)$$

where  $\hat{o}(\mathbf{x})$  is the signal only degraded by noise. (165) shows that Eq. (3.6) can be related to PDFs such that:

$$S(s) = B(s) * O(s) , \quad (3.7)$$

where  $S$ ,  $B$  and  $O$  are respectively the probability densities of  $s$ ,  $b$  and  $o$ .

Restoring the corrupted signal  $s$  is carried out by finding the multiplicative field  $b$  which maximizes the frequency content of the distribution  $O$ . Sled *et al.* (165) argue that a search through all possible fields  $b$  and selection of the one which maximizes the high frequency content of  $O$  could be carried out but results in an exhaustive search. However, they show that the bias field distribution can be assimilated to a near Gaussian distribution. Using this fact as *a priori*, it is then possible to infer the distribution  $O$

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<sup>1</sup>The N3 algorithm implementation is available at: <http://www.bic.mni.mcgill.ca/software/N3/>

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using Wiener deconvolution given  $B$  and  $S$  and later estimate the corresponding smooth field  $b$ .

Lv *et al.* (128) corrected the inhomogeneity in T<sub>2</sub>-W-MRI images by using the method proposed in (166). In this method, the MRI images are corrected iteratively by successively detecting the image foreground via generalized scale ( $g$ -scale) and estimating a bias field function based on a second-order polynomial model. First the background of the MRI image is eliminated by thresholding. The threshold value is commonly equal to the mean SI of the considered image. Then, in the seeded region growing algorithm is applied considering every thresholded pixel as a potential seed. However, pixels already assigned to a region will not be considered any more as seed. As in seeded region growing algorithm (167), two criteria are taken into account to expand the region. First, the region will grow using a connected-neighbourhood, initially defined by the user. Then, the homogeneity of SI is based on a fuzzy membership function taking into account the absolute difference of the SIs of two pixels. Depending on the membership value (cf., a threshold has to be defined), the pixel considered is merged or not to the region. Once this segmentation is performed, the largest region  $R$  is used as a mask to select pixels of the original image and the mean SI,  $\mu_R$ , is computed. The background variation  $b(\mathbf{x})$  is estimated as:

$$b(\mathbf{x}) = \frac{s(\mathbf{x})}{\mu_R}, \quad \forall \mathbf{x} \in R, \quad (3.8)$$

where  $s(\mathbf{x})$  is the original MRI image.

Finally, a second order polynomial  $\hat{b}_\Theta(\mathbf{x})$  is fitted in a least-squares sense (Eq. (3.9)),

$$\hat{\Theta} = \arg \min_{\Theta} |b(\mathbf{x}) - \hat{b}_\Theta(\mathbf{x})|^2, \quad \forall \mathbf{x} \in R. \quad (3.9)$$

Finally, the whole original MRI image is corrected by dividing it by the estimated bias field function  $\hat{b}_\Theta(\mathbf{x})$ . This process is repeated until the number of pixels in the largest region  $R$  does not change significantly between two iterations.

**SI normalization/standardization:** As discussed in the later section, segmentation or classification tasks are usually performed by first learning from a training set of patients. Hence, one can emphasize the desire to perform MRI examinations with a high repeatability or in other words, one would ensure to obtain similar MRI images (cf., similar SIs) for patients of the same group (cf., healthy patients *vs.* patients with CaP), for a similar sequence.

However, it is a known fact that variability between patients occurs during the MRI examinations even using the same scanner, protocol or sequence parameters (168). Hence, the aim of normalization or standardization of the MRI data is to remove the variability between patients and enforce the repeatability of the MRI examinations. Approaches used to standardize MRI images can be either categorized as statistical-based standardization or organ SI-based standardization.

### 3.1 Image regularization framework

Artan *et al.* (117, 118) as well as Ozer *et al.* (131, 132) standardized T<sub>2</sub>-W, DCE and DW MRI images by computing the *standard score* (also called *z-score*) of the pixels of the PZ as:

$$I_s(\mathbf{x}) = \frac{I_r(\mathbf{x}) - \mu_{pz}}{\sigma_{pz}}, \quad \forall \mathbf{x} \in \text{PZ}, \quad (3.10)$$

where  $I_s(\mathbf{x})$  is the standardized SI with the image coordinates  $\mathbf{x} = \{x, y\}$ ,  $I_r(\mathbf{x})$  is the raw SI,  $\mu_{pz}$  is the mean-SI of the PZ and  $\sigma_{pz}$  is the SI standard deviation in the PZ. This transformation enforces the image PDF to have a zero mean and a unit standard deviation.

In a similar way, Liu *et al.* (126) normalized T<sub>2</sub>-W-MRI by making use of the median and interquartile range for all the pixels.

Lv *et al.* (128) scaled the SI of T<sub>2</sub>-W-MRI images using the method proposed in (1) based on PDF matching. This approach is based on the assumption that MRI images from the same sequence should share the same PDF appearance. Hence, one can approach this issue by transforming and matching the PDFs using some statistical landmarks such as median and different quantiles. Using a training set, these statistical landmarks are extracted for  $N$  training images as for instance for the minimum, the 25<sup>th</sup> quantile, the median, the 75<sup>th</sup> quantile and the maximum:

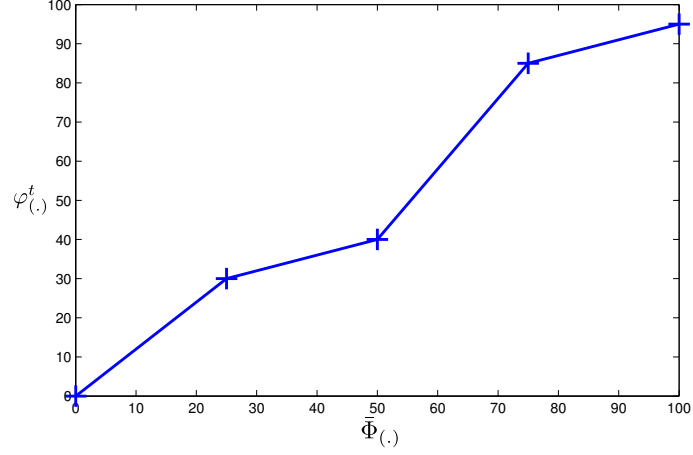
$$\begin{aligned} \Phi_0 &= \{\phi_0^1, \phi_0^2, \dots, \phi_0^N\}, \\ \Phi_{25} &= \{\phi_{25}^1, \phi_{25}^2, \dots, \phi_{25}^N\}, \\ \Phi_{50} &= \{\phi_{50}^1, \phi_{50}^2, \dots, \phi_{50}^N\}, \\ \Phi_{75} &= \{\phi_{75}^1, \phi_{75}^2, \dots, \phi_{75}^N\}, \\ \Phi_{100} &= \{\phi_{100}^1, \phi_{100}^2, \dots, \phi_{100}^N\}, \end{aligned} \quad (3.11)$$

where  $\phi_n^{i^{\text{th}}}$  is the  $n^{\text{th}}$  quantile of the  $i^{\text{th}}$  training image.

Then, the mean of each quantile  $\{\bar{\Phi}_0, \bar{\Phi}_{25}, \bar{\Phi}_{50}, \bar{\Phi}_{75}, \bar{\Phi}_{100}\}$  is also calculated. Once this training stage is performed, a linear transformation by parts  $\mathcal{T}(\cdot)$  can be computed (Eq. (3.12)) for each test image  $t$  by mapping each statistical landmark  $\varphi_{(\text{cdot})}^t$  of this image with the pre-learned statistical landmarks  $\bar{\Phi}_{(\cdot)}$ . This linear mapping is also depicted in Fig. 3.3.

$$\mathcal{T}(s(\mathbf{x})) = \begin{cases} \lceil \bar{\Phi}_0 + (s(\mathbf{x}) - \varphi_0^t) \left( \frac{\bar{\Phi}_{25} - \bar{\Phi}_0}{\varphi_{25}^t - \varphi_0^t} \right) \rceil, & \text{if } \varphi_0^t \leq s(\mathbf{x}) < \varphi_{25}^t, \\ \lceil \bar{\Phi}_{25} + (s(\mathbf{x}) - \varphi_{25}^t) \left( \frac{\bar{\Phi}_{50} - \bar{\Phi}_{25}}{\varphi_{50}^t - \varphi_{25}^t} \right) \rceil, & \text{if } \varphi_{25}^t \leq s(\mathbf{x}) < \varphi_{50}^t, \\ \lceil \bar{\Phi}_{50} + (s(\mathbf{x}) - \varphi_{50}^t) \left( \frac{\bar{\Phi}_{75} - \bar{\Phi}_{50}}{\varphi_{75}^t - \varphi_{50}^t} \right) \rceil, & \text{if } \varphi_{50}^t \leq s(\mathbf{x}) < \varphi_{75}^t, \\ \lceil \bar{\Phi}_{75} + (s(\mathbf{x}) - \varphi_{75}^t) \left( \frac{\bar{\Phi}_{100} - \bar{\Phi}_{75}}{\varphi_{100}^t - \varphi_{75}^t} \right) \rceil, & \text{if } \varphi_{75}^t \leq s(\mathbf{x}) \leq \varphi_{100}^t, \end{cases} \quad (3.12)$$

Viswanath *et al.* (145, 146, 147) use a variant of this previous approach presented in (169) aiming to standardize the T<sub>2</sub>-W-MRI images. Instead of computing the PDF of an entire image, a pre-segmentation of the foreground is carried out via  $g$ -scale which



**Figure 3.3:** Example of linear mapping by parts as proposed by (1).

was discussed in the bias correction section. Once the foreground is detected, the largest region is extracted and the same process than previously mentioned (see Eq. (3.12)) takes place in order to align PDFs of the foreground of the MRI images.

The methods described above were statistical-based methods. However, the standardization problem can be tackled by normalizing the MRI images using the SI of some known organs present in these images. Niaf *et al.* (2, 3) normalized T<sub>2</sub>-W-MRI images by dividing the original SI of the images by the mean SI of the bladder (see Fig. 3.4(a)). Likewise, (2) standardized the T<sub>1</sub>-W-MRI images using the arterial input function (AIF). They computed the AIF by taking the mean of the SI in the most enhanced part of the common femoral arteries (see Fig. 3.4(b)) as proposed in (170).

Presented in Sect. 2.2.6, MRSI is a modality related to a one dimensional signal. Hence, specific pre-processing steps for this type of signals have been applied instead of standard signal processing methods.

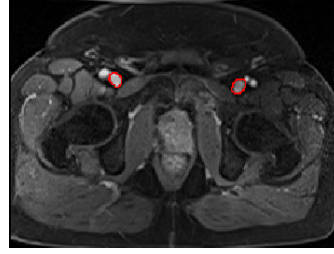
**Phase correction:** MRSI data acquired suffer from zero-order and first-order phase misalignments as shown in Fig. 3.5 (171, 172). Parfait *et al.* (133) used a method proposed in (171) where the phase of MRSI signal is corrected based on entropy minimization in the frequency domain. The corrected MRSI signal  $o(\xi)$  can be expressed as:

$$\begin{aligned}
 \Re(o(\xi)) &= \Re(s(\xi)) \cos(\Phi(\xi)) - \Im(\xi) \sin(\Phi(\xi)) , \\
 \Im(o(\xi)) &= \Im(s(\xi)) \cos(\Phi(\xi)) + \Re(\xi) \sin(\Phi(\xi)) , \\
 \Phi(\xi) &= \phi_0 + \phi_1 \frac{\xi}{N} ,
 \end{aligned} \tag{3.13}$$

where  $\Re(\cdot)$  and  $\Im(\cdot)$  are the real and imaginary part of the complex signal respectively,

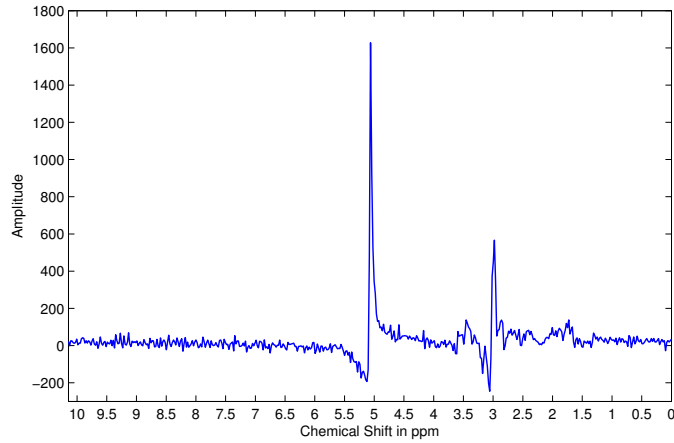


(a) Illustration and location of the bladder on a  $T_2$ -W-MRI image acquired with a 3.0 Tesla MRI scanner

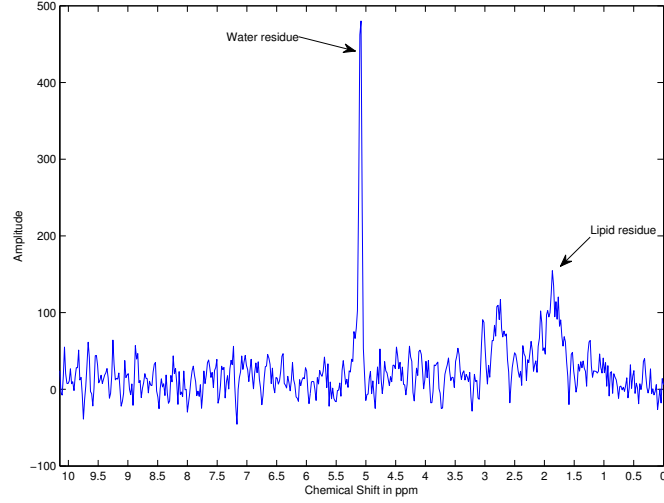


(b) Illustration and location of the femoral arteries on a  $T_1$ -W-MRI image acquired with a 3.0 Tesla MRI scanner

**Figure 3.4:** Illustration of the two organs used by (2, 3) to normalize  $T_2$ -W and  $T_1$ -W MRI images.



**Figure 3.5:** Illustration of phase misalignment in an MRSI spectra acquire with a 3.0 Tesla MRSI scanner. Note the distortion of the signal specially visible for the water and citrate peaks.



**Figure 3.6:** Illustration of the residues of water and fat even after their suppression during the acquisition protocol. The acquisition was carried out with a 3.0 Tesla MRI.

$s(\xi)$  is the corrupted MRSI signal,  $\phi_0$  and  $\phi_1$  are the zero-order and first-order phase correction terms respectively and  $N$  is the total number of samples of the MRSI signal.

Chen *et al.* (171) tackled this problem using an optimization framework where  $\phi_0$  and  $\phi_1$  had to be inferred. Hence, the simplex Nelder-Mead optimization method was used to minimize the following cost function based on the *Shannon entropy* formulation:

$$\hat{\Phi} = \arg \min_{\Phi} \left[ - \sum \Re(s'(\xi)) \ln \Re(s'(\xi)) + \lambda \|\Re(s(\xi))\|_2 \right], \quad (3.14)$$

where  $s'(\xi)$  is the first derivative of the corrupted signal  $s(\xi)$  and  $\lambda$  is a regularization parameter. Once the best parameter  $\Phi$  is obtained, the MRSI signal is corrected using Eq. (3.13).

**Water and lipid residuals filtering:** The water and lipid metabolites occur in much higher concentrations than the metabolites of interests (cf., choline, creatine and citrate) (172, 173). Fortunately, specific MRSI sequences were developed in order to suppress water and lipid metabolites using pre-saturation techniques (173). However, these techniques do not perfectly remove water and lipids peaks and some residuals are still present in the MRSI spectra as shown in Fig. 3.6. Therefore, different post-processing methods have been proposed to enhance the quality of the MRSI spectra by removing these residuals. For instance, Kelm *et al.* (121) used the well known HSVD algorithm proposed by (174) which models the MRSI signal by a sum of exponentially damped sinusoids in the time



domain (see Eq. (3.15)).

$$s(t) = \sum_{k=1}^K a_k \exp(i\phi_k) \exp(-d_k + i2\pi f_k)t + \eta(t) , \quad (3.15)$$

where  $a_k$  is the amplitude proportional to the metabolite concentration with a resonance frequency  $f_k$ ,  $d_k$  represents the damping factor of the exponential,  $\phi_k$  is the first-order phase and  $\eta(t)$  is a complex white noise.

Pijnappel *et al.* (174) showed that the “noise-free signal” can be found using the singular value decomposition (SVD) decomposition. First the noisy signal is reorganized inside a Hankel matrix  $H$ . It can be shown that if the signal considered would be a “noise-free signal”, the rank of  $H$  would be equal to rank  $K$ . However, due to the presence of noise,  $H$  is in fact a full rank matrix. Thus, to recover the “noise-free signal”, the rank of  $H$  can be truncated to  $K$  using its SVD decomposition. Hence, knowing the cut off frequencies of water (cf., 4.7 ppm) and lipid (cf., 2.2 ppm) metabolites, their corresponding peaks can be reconstructed and subtracted from the original signal (175).

**Baseline correction:** Sometimes, the problem discussed in the above section regarding the lipid molecules is not addressed simultaneously with water residuals suppression. Lipids and macromolecules are known to affect the baseline of the MRSI spectra. They could cause errors during further fitting processes aiming to quantify the metabolites, especially regarding the citrate metabolite.

Parfait *et al.* (133) made the comparison of two different methods to detect the baseline and correct the MRSI spectra which are based on (176, 177). Lieber *et al.* (176) addressed the problem of baseline detection in the frequency domain by fitting a low degree polynomial whereas Parfait *et al.* (133) modified this algorithm by convolving a Gaussian kernel to smooth the MRSI signal instead of fitting a polynomial function.

**Check the tex file to see the commented area pre-processing.tex**

Unlike in (176), Devos *et al.* (177) proposed to correct the baseline in the time domain by multiplying the MRSI signal by a decreasing exponential function as:

$$c(t) = \exp(-\beta t) , \quad (3.16)$$

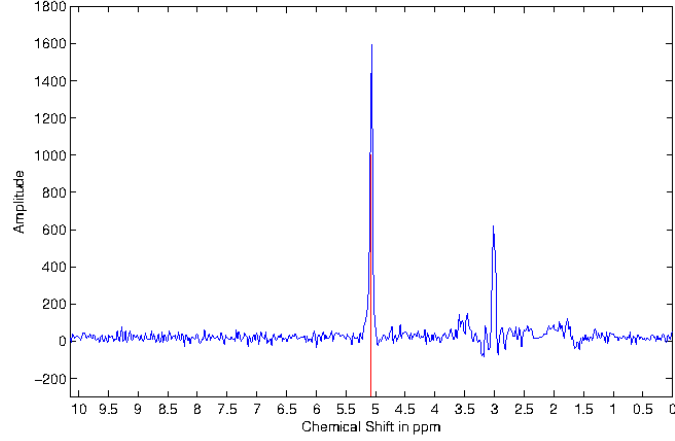
Having a typical value for  $\beta$  of 0.15. However, Parfait *et al.* (133) concluded that the method proposed in (176) outperformed the one in (177).

In the contemporary work of Tiwari *et al.* (141), the authors detected the baseline using a local non-linear fitting method avoiding regions with significant peaks which were detected using a experimentally parametrised signal-to-noise ratio (i.e. a value larger than 5 dB).

**Frequency alignment:** Due to variations of the experimental conditions, a frequency shift can be observed in the MRSI spectra (171, 172) as shown in Fig. 3.7.

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**Figure 3.7:** Illustration of frequency misalignment in an MRSI spectra acquired with a 3.0 Tesla MRSI scanner. The water peak is known to be aligned at 4.65 ppm. However, it can be seen that the peak on this spectra is aligned at around 5.1 ppm.

Tiwari *et al.* (141) corrected the frequency shift by first detecting known metabolite peaks such as choline, creatine and citrate. The frequency shift is corrected by minimizing the frequency error between the experimental and theoretical values of each of these peaks.

**Normalization:** Due to variations of the experimental conditions, the MRSI signal may also vary between patients. Parfait *et al.* (133) as in (177) compared two methods to normalize MRSI signal. In each method, the original MRSI spectra is divided by a normalization factor, similar to the intensity normalization described earlier. The first approach to obtain the normalization factor is based on an estimation of the water concentration. It is required to have an additional MRSI sequence where the water metabolites are unsuppressed. Using this sequence, an estimation of the water concentration can be performed using the previously reported HSVD algorithm. The second approach to normalization is based on using the  $L_2$  norm of the MRSI spectra  $\|s(\xi)\|_2$ . It should be noted that both (133) and (177) concluded that the  $L_2$  normalization was more efficient in their framework.

#### 3.1.2 Segmentation

The segmentation task consists of delineating the prostate boundaries in the MRI and is of particular importance for focusing the posterior processing on the organ of interest (178). In this section, only the segmentation methods used in CAD for CaP are presented and summarized in Table. 3.3. These methods are mostly intensity based. An exhaustive review of prostate segmentation methods in MRI can be found in (178).

### 3.1 Image regularization framework

**Table 3.2:** Overview of the pre-processing methods used in CAD systems.

Pre-processing operations	References
<i>MRI pre-processing:</i>	
Noise filtering:	
Median filtering	[20-21]
Wavelet-based filtering	[1-2,14]
Bias correction:	
Parametric methods	[15-35]
Non-parametric methods	[36]
Standardization:	
Statistical-based normalization:	[3-4,15,20-21,35,37]
Organ SI-based normalization	[18-19]
<i>MRSI pre-processing:</i>	
Phase correction	[22]
Water and lipid residuals filtering	[8]
Baseline correction	[22,31]
Frequency alignment	[31]
Normalization	[22]

**Table 3.3:** Overview of the segmentation methods used in CAD systems.

Segmentation methods	References
<i>MRI-based segmentation:</i>	
Manual segmentation	[4-5,16,18-21,24,38-40]
Region-based segmentation	[11]
Hybrid segmentation	[10,34-36,41]
<i>MRSI-based segmentation:</i>	
Clustering	[28]

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**Manual segmentation:** To highlight the importance of prostate segmentation task in CAD systems, it is interesting to note the large number of studies which manually segment the prostate organs (2, 3, 117, 118, 129, 131, 132, 134, 148, 149). In all the cases, the boundaries of the prostate gland are manually defined in order to limit further processing to only this area. This approach ensures the right delineation of the organ nevertheless this procedure is highly time consuming and should be performed by a radiologist.

**Region-based segmentation:** Litjens *et al.* in (124) used a multi-atlas-based segmentation using multi-modal images (e.g.,  $T_2$ -W-MRI and ADC map) to segment the prostate with an additional pattern recognition method to differentiate CG and PZ as proposed in (179). This method consists in three different steps: (i) the registration between each atlas and the multi-modal images, (ii) the atlas selection and finally (iii) the classification of the prostate segmented voxels in either CG or PZ. The registration between each atlas and the MRI images is performed using two successive registrations; the first registration is a rigid registration to roughly aligned the atlases and the MRI images and the second is an elastic registration using B-spline transformation. The objective function to perform the registration is defined as the weighted sum of the metric of both  $T_2$ -W-MRI and ADC map. The metric is based on mutual information (MI) (please refer to the next section for more details in regard to registration). Two strategies of atlas selection were performed by using either a majority voting approach or the simultaneous truth and performance level estimation (STAPLE) approach (180).

Subsequently, CG and PZ segmentation within the prostate region is achieved by classifying each voxel using a linear discriminant analysis (LDA) classifier. Three types of features were considered: (i) anatomy, (ii) intensity and (iii) texture. Regarding the anatomy, relative position and relative distance from the pixel to the border of the prostate were used. The intensity features consist in the intensity of the voxel in the ADC coefficient and the  $T_2$  map. The texture features were composed of five different features: homogeneity, correlation (181), entropy, texture strength (182) and local binary pattern (LBP) (183). Finally, some morphological operations were applied to remove artefact and the contour between the zones were smooth using the thin plate spline (TPS) (184).

Litjens *et al.* in (185) used an almost identical algorithm proposed by PROMISE12 challenge (186). Their segmentation method is also based on multi-atlas multi-modal images, but the SIMPLE method (187) is used instead to combine labels after the registration of the different atlas to obtain the final segmentation.

**Model-based segmentation:** Viswanath *et al.* in (144, 145) used a multi-attribute non-initializing texture reconstruction based active shape model (MANTRA) method as proposed in (188). MANTRA is closely related to the active shape model (ASM) from (189). This algorithm consists of two stages: (i) a training stage where a shape and appearance model is generated and (ii) the actual segmentation performed based on the learned model. For the training stage, a set of landmarks is defined and the shape model is generated as in the original ASM method (189). Then, to model the appearance, a set

of  $K$  texture images  $\{I_1, I_2, \dots, I_k\}$  based on first and second order statistical texture features are computed. For a given landmark  $l$  with its given neighbourhood  $\mathcal{N}(l)$ , its feature matrix extracted can be expressed as:

$$f_l = \{I_1(\mathcal{N}(l)), I_2(\mathcal{N}(l)), \dots, I_k(\mathcal{N}(l))\}, \quad (3.17)$$

where  $I_k(\mathcal{N}(l))$  represents a feature vector obtained by sampling the  $k^{\text{th}}$  texture map using the neighbourhood  $\mathcal{N}(l)$ . By generating multiple landmarks in the same fashion as ASM, principal components analysis (PCA) (190) is applied to learn the appearance variations.

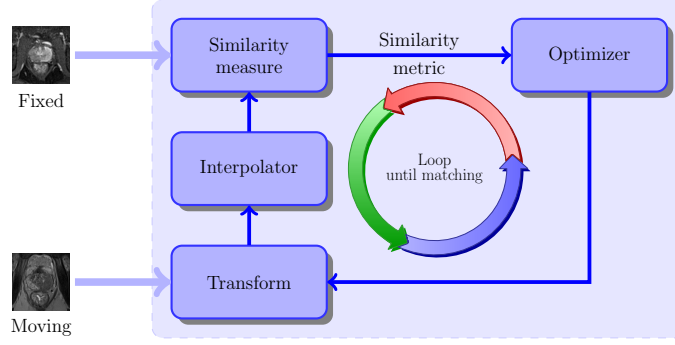
For the segmentation stage, the mean shape learned previously is initialised in the test image. The same associated texture images as in the training stage are computed. For each landmark  $l$ , a neighbourhood of patches are used to sample the texture images and a reconstruction is obtained using the appearance model previously trained. The new landmark location will be defined as the position where the MI is maximal between the reconstructed and original values. This scheme is performed in a multi-resolution manner as in (189).

Subsequently, Viswanath *et al.* in (147), used the weighted ensemble of regional image textures for active shape model segmentation (WERITAS) method also proposed by (191). WERITAS and MANTRA methods, both are based on the ASM formulation. However, they differ in the last stage, where in WERITAS instead of using MI to adapt the positions of new landmarks, a Mahalanobis distance metric is used. In the training stage, the Mahalanobis distance is computed between landmarks and neighbour patches for each of the features. Subsequently, a new metric is proposed as a linear weighted combination of those Mahalanobis distances which maximises the correlation with the Euclidean distance between the patches and the true landmarks. In the segmentation step, this metric is then computed between the initialised landmarks and neighbouring patches in order to update landmark positions, in a similar fashion to other active contour model (ACM) models. [Check the commented senetence in the tex file.](#)

Litjens *et al.* (123) and Vos *et al.* (151) used an approach proposed in (192) in which the bladder, prostate and rectum are segmented. The segmentation task is performed as an optimization problem taking three parameters into account linked to organs such as: (i) the shape (an ellipse), (ii) the location and (iii) the respective angles between them. Furthermore, Litjens *et al.* (123) used only ADC map to encode the appearance whereas Vos *et al.* (151) used both ADC and  $T_2$  maps. Then, during the optimization using a quasi-Newton optimizer, an objective function is minimized. This function is defined as the sum of the deviations from the above model learnt. This rough segmentation is then used inside a Bayesian framework to refine the segmentation.

Only the work of Tiwari *et al.* in (138) propose a segmentation based on MRSI. Authors localized the voxels corresponding to the prostate organ using a hierarchical spectral clustering. First, each MRSI spectrum is projected into a lower dimension space using graph embedding (193). To proceed, a similarity matrix  $W$  is computed

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**Figure 3.8:** Typical framework involved to solve the registration problem.

using a Gaussian similarity measure from Euclidean distance (194)) such that:

$$W(\mathbf{x}, \mathbf{y}) = \begin{cases} \exp\left(-\frac{\|s(\mathbf{x}) - s(\mathbf{y})\|_2^2}{\sigma^2}\right) & , \text{ if } \|\mathbf{x} - \mathbf{y}\|_2 < \epsilon \\ 0 & , \text{ if } \|\mathbf{x} - \mathbf{y}\|_2 > \epsilon \end{cases} \quad (3.18)$$

where  $s(\mathbf{x})$  and  $s(\mathbf{y})$  are the MRSI spectra for the voxels  $\mathbf{x}$  and  $\mathbf{y}$  respectively,  $\sigma$  is the standard deviation of the Gaussian similarity measure and  $\epsilon$  is the parameter to defined an  $\epsilon$ -neighbourhood.

The MRSI spectra projection into the lower dimension space is approached as a generalized eigenvector problem. Subsequently, a replicate k-means clustering method is run defining two clusters. The data corresponding to larger cluster is assumed to belong to the non-prostate voxels and these voxels will be eliminated from the processing. The full procedure is repeated until the total number of voxels left is inferior to a given threshold set experimentally.

#### 3.1.3 Registration

The role of image registration is vital in CAD systems using multi-parametric MRI images. As it will be discussed in Sect. ??, for the sake of an optimal classification, the features detected in each modality will be grouped depending of their spatial locations. Hence, one has to ensure the perfect alignment of the multi-modal MRI images ahead of performing any classification.

Image registration is the procedure consisting of aligning an unregistered image (also called moving image) into a template image (also called fixed image) via a geometric transformation. This problem is usually addressed as presented in Fig. 3.8. An iterative procedure takes place to infer the geometric transformation (parametric or non-parametric) via an optimizer, which maximizes the similarity between the two images. In the following, a review of the different components of a typical registration framework: transformation model, similarity metric, optimizer and interpolation are presented, followed by a summary of registratio approaches applied in CAD for CaP

systems. Exhaustive reviews covering all registration methods in computer science and medical fields can be found in (195) and (196).

**Geometric transformation models:** As previously mentioned, the registration problem is to align two images or volumes by finding the geometric transformation. Regarding the transformation, from all CAD systems reviewed, only parametric methods have been implemented. Three different groups of parametric transformation models have been used, rigid, affine, and elastic, each of them are characterized by the degree of freedom that they offer.

The first type of transformation is usually referred to as rigid transformation. These transformations are only composed of rotation and translation transforms. Hence, for a 2D space where  $\mathbf{x} = (x, y) \in \mathbb{R}^2$ , a rigid transformation  $\mathcal{T}_R$  is formalized as as:

$$\begin{aligned}\mathcal{T}_R(\mathbf{x}) &= \begin{bmatrix} R & \mathbf{t} \\ \mathbf{0}^T & 1 \end{bmatrix} \mathbf{x}, \\ &= \begin{bmatrix} \cos \theta & -\sin \theta & t_x \\ \sin \theta & \cos \theta & t_y \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ 1 \end{bmatrix},\end{aligned}\tag{3.19}$$

where  $\theta$  is the rotation angle and  $\{t_x, t_y\}$  represents the translation along  $\{x, y\}$  respectively.

In the case of 3D registration using volume, an additional component  $z$  has to be taken into account such that  $\mathbf{x} = (x, y, z)$ . Thus, the rotation matrix  $\mathbf{R}$  becomes of size  $3 \times 3$  whereas the translation vector  $\mathbf{t}$  consists of a vector of three elements. Hence, the geometric transformation  $\mathcal{T}_R(\cdot)$  is embedded into a matrix of size  $4 \times 4$ .

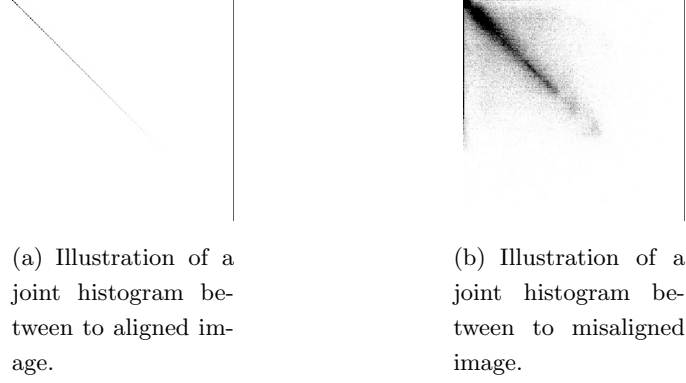
Affine transformations provide additional degrees of freedom managing rotations and translation as with the rigid transformations but also shearing and scaling. Hence, for a 2D space where  $\mathbf{x} = (x, y) \in \mathbb{R}^2$ , an affine transformation  $\mathcal{T}_A$  is formalized as:

$$\begin{aligned}\mathcal{T}_A(\mathbf{x}) &= \begin{bmatrix} A & \mathbf{t} \\ \mathbf{0}^T & 1 \end{bmatrix} \mathbf{x}, \\ &= \begin{bmatrix} a_{11} & a_{12} & t_x \\ a_{21} & a_{22} & t_y \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ 1 \end{bmatrix}.\end{aligned}\tag{3.20}$$

Hence the four parameters  $\{a_{11}, a_{12}, a_{21}, a_{22}\}$  of the affine matrix and  $\{t_x, t_y\}$  of the translation encode an affine transformation.

Regarding volume registration, the previously mentioned remark can be applied as well. Thus the geometric transformation  $\mathcal{T}_A(\cdot)$  is of size  $4 \times 4$  with nine parameters involved.

Finally, the last group of transformations is known as elastic transformations and offer the advantage to handle local distortions. In the reviewed CAD systems, the radial



**Figure 3.9:** Difference observed in joint histogram between aligned and misaligned images. The joint measure will be more concentrated of the histogram in the case that the images are aligned and more randomly distributed in the case that both images are more misaligned.

basis functions are used to formalize the local distortions such as:

$$\mathcal{T}_E(\mathbf{x}) = \frac{a_{11}x - a_{12}y + t_x + \sum_i c_i g(\|\mathbf{x} - p_i\|)}{a_{21}x + a_{22}y + t_y + \sum_i c_i g(\|\mathbf{x} - p_i\|)}, \quad (3.21)$$

where  $\mathbf{x}$  are the control points in both images and  $g(\dots)$  is the actual radial basis function.

Two radial basis functions are used: (i) the TPS and (ii) the B-splines. Apart from the formalism, these two approaches have a main difference: with B-splines, the control points are usually uniformly and densely placed on a grid where as with TPS, the control points correspond to detected or selected key points. By using TPS, Mitra *et al.* (197) obtained more accurate and time efficient results than with the B-splines strategy (198).

It is reasonable to point out that usually only rigid or affine registrations are used to register multi-parametric images from a same protocol. Elastic registration methods are more commonly used to register multi-protocol images (e.g., histopathology with MRI images) (188, 191).

**Similarity measure:** The most naive similarity measure used in reviewed registration framework is the mean squared error (MSE) of the SI of MRI images. For a pair of images  $I$  and  $J$ , the MSE is formalized as:

$$\text{MSE} = \frac{1}{N} \sum_x \sum_y (I(x, y) - J(x, y))^2, \quad (3.22)$$

where  $N$  is the total number of pixels. This metric is not well suited when multi-parametric images are involved due to the tissue appearance variations between the different modalities.



In that regard, MI was introduced as a registration measure in the late 1990's by (199). The MI measure finds its foundation in the assumption that a homogeneous region in the first modality image should also appear as a homogeneous region in the second modality even if their SIs are not identical. Thus, those regions share information and the registration task can be achieved by maximizing this common information. Hence, MI of two images  $A$  and  $B$  is defined as:

$$MI(A; B) = S(A) + S(B) - S(A, B) , \quad (3.23)$$

where  $S(A)$  and  $S(B)$  are the marginal entropies and  $S(A, B)$  is the joint entropy. Then, maximizing the MI is equivalent to minimizing the joint entropy. The joint entropy measure is related with the degree of uncertainty or dispersion of the data in the joint histogram of the images  $A$  and  $B$ . As shown in Fig. ??, the data in the joint histogram will be concentrated in the case of aligned images while will be more randomly distributed in the case of misaligned images. Regarding the computation of the entropies, an estimation of the PDFs have to be carried out. Histogram or Parzen window methods are a common way to estimate these PDFs.

A generalized form of MI, combined mutual information (CMI), was proposed by (200). CMI encompasses interdependent information such as texture and gradient into the metric. Hence, for both of images  $A$  and  $B$ , the image ensembles  $\epsilon_n^A$  and  $\epsilon_m^B$  are generated and composed of  $n$  and  $m$  images based on the texture and gradient. Then, the CMI can be formulated such as:

$$CMI(\epsilon_n^A; \epsilon_m^B) = S(\epsilon_n^A) + S(\epsilon_m^B) - S(\epsilon_n^A, \epsilon_m^B) . \quad (3.24)$$

**Check the commented text, It is not well written and I did not include them**

**Optimization methods:** Registration is usually regarded as an optimization problem where the parameters of the geometric transformation model have to be inferred by minimizing the similarity measure. Iterative estimation methods are commonly used being the L-BFGS-B quasi-Newton method (201) and gradient descent (202) the most common ones. During our review, we noticed that authors do not usually linger over optimizer choice.

**Interpolation:** The registration procedure involves transforming an image, and pixels mapped to non-integer points must be approximated using interpolation methods. As for the optimization methods, we notice that little attention has been paid on the choice of those interpolations methods. However, commonly used methods are bilinear, nearest-neighbour, bi-cubic, spline and inverse-distance weighting method (203).

**Registration methods used in CAD systems:** Studies presenting CAD pipeline incorporating an automatic registration procedure are summarized in Tab. 3.4.

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**Table 3.4:** Classification of the different registration methods used in the CAD systems reviewed. Acronyms: gradient descent (GD), Nelder-Mead (NM).

Study index	Modality registered	Type	Geometric transform			Similarity measure			Optimizer		
			Rigid	Affine	Elastic	MSE	MI	CMI	GD	L-BFGS-B	NM simplex
[1-2]	T <sub>2</sub> -W - DCE	2D	—	✓	—	✓	—	—	—	—	—
[7]	T <sub>2</sub> -W - DW	2D	—	✓	✓	—	—	—	—	—	—
[7]	T <sub>2</sub> -W - DCE	2D	—	✓	✓	—	✓	—	✓	—	—
[34-35]	T <sub>2</sub> -W - DCE	2D	—	✓	—	—	✓	—	—	—	—
[36]	T <sub>2</sub> -W - DCE - DW	3D	—	✓	—	—	—	✓	✓	—	—
[38]	T <sub>2</sub> -W - DCE	3D	—	✓	—	—	✓	—	—	—	—
[40]	T <sub>2</sub> -W - DCE	3D	—	✓	✓	—	✓	—	—	✓	—

Notes:

—: not used or not mentioned.

✓: used or implemented.

Ampeliotis *et al.* in (114, 115) did not use the framework as presented in Fig. 3.8 to register 2D T<sub>2</sub>-W and DCE images. By using image symmetries and the MSE metric, they find the parameters of an affine transformation but without using a common objective function. They were finding independently and sequentially the scale factor, the rotation and finally the translation.

Giannini *et al.* (120) used also a in-house registration method for 2D T<sub>2</sub>-W and DW images using an affine model. The bladder is first segmented in both modalities in order to obtain its contours and to focus the registration.

Giannini *et al.* (120) and also Vos *et al.* (150) used the same framework which is based on finding an affine transformation to register the T<sub>2</sub>-W and DCE images using MI (204). Then, an elastic registration using B-spline takes place using the affine parameters to initialize the geometric model with the same similarity measure. However, the approaches differ regarding the choice of the optimizer since a gradient descent is used in (120) and the same optimization problem is tackled via quasi-Newton method in (150). Moreover, Giannini *et al.* (120) performed a 2D registration whereas Vos *et al.* (150) registered 3D volumes.

Viswanath *et al.* in (144, 145) as well as Vos *et al.* (148) performed an affine registration using the MI as similarity measure to correct the misalignment between T<sub>2</sub>-W and DCE images. The choice of the optimizer was not specified. Viswanath *et al.* (144, 145) focused on 2D registration while Vos *et al.* (148) performed 3D registration.

Finally, Viswanath *et al.* in (146) performed a 3D registration with the three modal-

ities, T<sub>2</sub>-W and DCE and DW MRI, by using an affine transformation model combined with the CMI similarity measure as presented in (200). Moreover, in this latter work, the authors employed gradient descent (200) employed gradient descent approach to solve this problem but suggested Nelder-Mead simplex and quasi-Newton method as other solutions.

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## Declaration

I herewith declare that I have produced this paper without the prohibited assistance of third parties and without making use of aids other than those specified; notions taken over directly or indirectly from other sources have been identified as such. This paper has not previously been presented in identical or similar form to any other German or foreign examination board.

The thesis work was conducted from XXX to YYY under the supervision of PI at ZZZ.

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