

© 2014

Robert Toth

ALL RIGHTS RESERVED

EVALUATING TREATMENT RELATED CHANGES FOR PROSTATE CANCER VIA IMAGE ANALYSIS TOOLS AND MAGNETIC RESONANCE IMAGING

BY ROBERT TOTH

A dissertation submitted to the
Graduate School—New Brunswick
Rutgers, The State University of New Jersey
and
The Graduate School of Biomedical Sciences
University of Medicine and Dentistry of New Jersey
in partial fulfillment of the requirements for the
Degree of Doctor of Philosophy
Graduate Program in Biomedical Engineering

Written under the direction of
Anant Madabhushi
and approved by

New Brunswick, New Jersey

January, 2014

ABSTRACT OF THE DISSERTATION

Evaluating Treatment Related Changes for Prostate Cancer via Image Analysis Tools and Magnetic Resonance Imaging

by Robert Toth

Dissertation Director: Anant Madabhushi

The goal of this work is to quantitatively evaluate treatment response (specifically changes in imaging markers and prostate morphology) following treatment for prostate cancer, via the development and application of novel segmentation and registration methods. In this work, we quantitatively evaluate treatment response for three treatment modalities: radical prostatectomy, focal laser ablation (FLA) and external beam radiation treatment (EBRT) imaging data.

Radical prostatectomy specimens are evaluated via accurately quantifying the prostate volume pre- and post-treatment. To this end, a novel Multi-Feature, Landmark Free Active Appearance Model (MFLAAM) algorithm has been developed in order to determine the prostate boundary and therefore associated volume. This is compared to the prostate volume following prostatectomy, which is determined by submersing the removed specimen in water. Quantitative results on over 200 patients show that the MFLAAM yields more accurate segmentations than existing state of the art segmentation systems, and offers highly accurate volume estimations compared to current state of the art clinical volume estimation procedures.

In order to evaluate EBRT and FLA treatments for prostate cancer, the pre-, post-treatment MRI images must be spatially aligned. However, existing registration tools do not take into account specific treatment related changes to the prostate such as radiation-induced shrinkage, and the specific morphological changes which occur within the prostate. In addition, no automatic quantitative tools for specifically evaluating treatment changes exist, which is the main contribution of this work. The prostate consists of distinct internal substructures central gland (CG) and peripheral zone (PZ) which respond to treatment differently. Our model aims to explicitly exploit domain information by taking into account the different effects treatment may have on the shapes of the internal prostatic structures, rather than on the gland as a whole. To model these different substructures, they first must be segmented. In order to automatically segment the CG and PZ, the MFLAAM algorithm was extended to simultaneously segment multiple objects.

Following the automatic segmentation of the CG and PZ, a finite element model (FEM) registration algorithm is introduced to deform the pre-treatment MRI to post-treatment MRI. An FEM uses physical properties of the segmented prostate, CG, and PZ to constrain the registration to only physically-real deformations. This is essential when registering pre- and post-treatment imagery, as the only deformations on the prostate would have occurred from physical forces. In addition, the physical shrinking of the prostate (which occurs due to radiation treatment) is specifically modelled in the FEM. This FEM was quantitatively compared to other linear and non-linear registration techniques, and was the best performing algorithm over 30 patients. Finally, a separate FEM is developed in order to compensate for the changes in the surrounding organs (bladder and rectum filling) between the pre- and post-treatment MRI, which is essential for one to isolate the treatment-related changes in the prostate.

Following an accurate registration of the pre- and post-treatment MRI, changes in the MR parameters, changes in the prostate volume (determined from the MFLAAM segmentation results), and changes in prostate morphology (determined from the FEM) are calculated. We envision that this work will pave the way for predictive models in order to predict patient outcome from early follow-up imaging data.

Preface

This dissertation represents the collective published and unpublished works of the author. It is primarily composed from the content of peer-reviewed journal and conference articles (either published or under review), on which he is the primary author [1, 2, 3, 4] or a coauthor [5, 6].

Acknowledgements

Firstly, I would like to thank my advisor, Dr. Anant Madabhushi, for his help and guidance during the completion of my degree. I would also like to thank each of my committee members for their insight and input throughout this research. My peers in the Laboratory for Computational Imaging and Bioinformatics (LCIB) and Center for Computational Imaging and Personalized Diagnoses (CCIPD) have been instrumental in the completion of this work, as nothing is ever truly done in solidarity. Lastly I would like to acknowledge my family and friends especially my sister Leigha Toth and parents Micheline and Laszlo Toth, whose unwavering support of me throughout this journey made it possible.

This work was made possible by the National Cancer Institute of the National Institutes of Health under award numbers R01CA136535-01, R01CA140772-01, and R21CA167811-01; the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under award number R43EB015199-01; the National Science Foundation under award number IIP-1248316; the QED award from the University City Science Center and Rutgers University. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

Dedication

To my father, who placed tremendous value on education, always encouraged me to unquestioningly pursue my dreams, and who reminded me to never stop learning, I only wish you could have been here to see the completion of this chapter in my life.

Table of Contents

Abstract	ii
Preface	iv
Acknowledgements	v
Dedication	vi
List of Tables	xii
List of Figures	xiii
1. Introduction	1
1.1. Evaluating Radical Prostatectomy	1
1.1.1. Prostate Volume Estimation	1
1.1.2. Prostate Segmentation on MRI	3
1.2. Evaluating External Beam Radiation Treatment (EBRT)	3
1.2.1. Overview of EBRT	3
1.2.2. MRI for EBRT Evaluation	5
1.2.3. Domain Constrained Deformable (DoCD) Model	6
1.3. Evaluating Focal Laser Ablation (FLA) Treatment	7
1.3.1. Overview of FLA	7
1.3.2. MRI for FLA Evaluation	8
1.3.3. Registration of Pre-, Post-FLA Prostate MRI	8
1.4. Organization of this dissertation	9
2. Previous Related Work and Novel Contributions	11
2.1. Previous Work in Prostate Segmentation	11
2.1.1. Shape Based Prostate Segmentation	11

2.1.2.	Limitations with Existing Segmentation Models	12
2.1.3.	Improvements to Statistical Shape Models	13
2.1.4.	Improvements to Statistical Appearance Models	15
2.1.5.	Application to Prostate Segmentation	16
2.2.	Novel Contributions in Prostate Segmentation	16
2.2.1.	Multi-Feature Landmark-Free Active Appearance Model	16
2.2.2.	Segmentation of Prostatic Substructures	18
2.2.3.	Comparison to Closest Related Works	18
2.3.	Previous Work in Prostate Registration	20
2.4.	Novel Contributions in Prostate Registration	21
2.4.1.	Domain Constrained Deformable (DoCD) Model	21
2.4.2.	Comparison to Closest Related Works	22
3.	Segmentation and Registration Methodology	24
3.1.	MFLAAM Segmentation Algorithm	24
3.1.1.	Notation	24
3.1.2.	Theory of MFLAAM	25
	Definitions	26
	Propositions	28
3.1.3.	MFLAAM Training	30
	Calculating Shape	30
	Calculating Projections using PCA	30
3.1.4.	MFLAAM Segmentation	31
	Calculating a Feature Reconstruction using Texture Features	32
	Segmenting a New Image	34
3.1.5.	Feature Extraction and Selection	36
3.2.	Simultaneous PZ/CG Segmentation Methodology	38
3.2.1.	Training Multiple Shape Models	38
3.2.2.	Simultaneous Segmentation	41

3.3.	DoCD EBRT Registration Methodology	42
3.3.1.	Notation	42
3.3.2.	FEM Review	43
3.3.3.	Radiation Induced Shrinkage	43
3.3.4.	FEM Deformation of Prostate MRI	44
3.3.5.	Optimization of EBRT Shrinking Parameters	45
4.	Evaluation of Radical Prostatectomy	47
4.1.	Data Description	47
4.1.1.	Segmentation Accuracy Dataset	47
4.1.2.	Prostatectomy Volume Dataset	48
4.2.	Experimental Design	48
4.2.1.	Segmentation Accuracy Experiments	48
	Measures to Evaluate Segmentation Performance	49
	Experiment $\mathcal{E}_1$: Evaluation of Efficiency	49
	Experiment $\mathcal{E}_2$: Evaluation of Texture Features	49
	Experiment $\mathcal{E}_3$: Comparison of MFLAAM to Existing Prostate Segmentation Algorithms	49
4.2.2.	Prostatectomy Volume Experiments	50
	Prostatectomy Volume Estimation Procedure	50
	Experiment $\mathcal{E}_4$: Comparison of Volume Estimation Methods . . .	51
4.3.	Results and Discussion	52
4.3.1.	Qualitative Results	52
4.3.2.	Experiment $\mathcal{E}_1$: Evaluation of Efficiency	54
4.3.3.	Experiment $\mathcal{E}_2$: Evaluation of Texture Features	55
4.3.4.	Experiment $\mathcal{E}_3$: Comparison of MFLAAM to Existing Prostate Segmentation Algorithms	56
4.3.5.	Experiment $\mathcal{E}_4$: Comparison of Volume Estimation Methods . . .	58
	Distribution of Volumes	58

Volume Estimates with Ellipsoid	58
Volume Estimates with Planimetry	59
Volume Estimates with MFLAAM	59
4.3.6. Discussion of Prostatectomy Volume Estimation	59
4.4. Concluding Remarks	63
5. Evaluation of External Beam Radiation Treatment	65
5.1. Experimental Design	65
5.1.1. PZ/CG Segmentation Experiments	65
Data Description	65
Implementation Details	66
Hierarchical Prostate Segmentation	66
Cross Validation Experiments	66
5.1.2. EBRT Registration Experiments	68
Data Description	68
Quantitative Measures for Evaluating Registration Accuracy . .	69
Comparative Strategies	70
5.2. Results and Discussion	71
5.2.1. PZ/CG Segmentation Results	71
5.2.2. PZ/CG Segmentation Discussion	71
5.2.3. EBRT Registration Results	76
Qualitative Estimation of Location of DoCD Registration Errors	76
Quantitative Evaluation of DoCD versus Comparative Registra- tion Schemes	78
5.2.4. EBRT Registration Discussion	79
Comparison of DoCD to Linear Registration	79
Comparison of DoCD to Traditional FEM	80
5.3. Concluding Remarks	81

6. Evaluation of Focal Laser Ablation Treatment	82
6.1. Focal Laser Ablation Registration Methodology	82
6.1.1. Notation and Overview	82
6.1.2. Linear Alignment $\hat{T}_1$	83
6.1.3. Modelling Changes from Surrounding Tissue $\hat{T}_2$	83
6.1.4. FLA Induced Prostate Deformations T_3	84
6.2. Experimental Design	85
6.2.1. Data Description	85
6.2.2. Testing Accuracy of T_2 via Synthetic Deformations	85
6.2.3. FLA Induced Deformations	85
6.3. Results and Discussion	86
6.4. Concluding Remarks	91
7. Concluding Remarks and Future Directions	92
References	93

List of Tables

2.1. Closest related works to DoCD	21
3.1. MFLAAM Segmentation Notation	24
3.2. Segmentation Features	37
3.3. DoCD Registration Notation	42
4.1. Segmentation Dataset	47
4.2. Segmentation Experiment Models	50
4.3. Segmentation Results	57
4.4. Prostate Volume Distribution	58
4.5. Prostate Volume Regression	61
5.1. Detailed description of the data used to test the MFLAAM.	65
5.2. MFLAAM CG/PZ Segmentation Experiments	68
5.3. EBRT Data Description	68
5.4. Statistical Significance of EBRT Registration Results	78
6.1. Registration steps for FLA experiments	86

List of Figures

1.1. EBRT-induced Prostate MRI Intensity and Shape Changes	6
1.2. 3D Rendering of Prostate, CG, PZ	7
3.1. Theory for MFLAAM Segmentation	26
3.2. Graphical view of MFLAAM feature reconstruction	33
3.3. MFLAAM Reconstruction	34
3.4. MFLAAM Reconstructions for Different Transformations	35
3.5. Multi-levelset MFLAAM training	39
3.6. Comparison of MFLAAM with other coupling methods	40
3.7. Multi-levelset MFLAAM flowchart	41
3.8. FEM registration of EBRT shrinkage	44
3.9. DoCD Methodology Flowchart	45
4.1. Qualitative MFLAAM segmentation results	53
4.2. Qualitative MFLAAM segmentation isosurfaces	53
4.3. MFLAAM Efficiency Results	54
4.4. MFLAAM Accuracy Histogram	55
4.5. MFLAAM-Prostatectomy Volume Correlation	60
5.1. Quantitative CG/PZ Segmentation Results	72
5.2. Qualitative CG/PZ Segmentation Results #1	73
5.3. Qualitative CG/PZ Segmentation Results #2	74
5.4. Qualitative EBRT Registration Results	76
5.5. Location of EBRT Registration Errors	77
5.6. Quantitative DoCD EBRT Registration Results	79
6.1. Focal laser ablation bladder/rectum motion	84
6.2. Synthetically induced bladder/rectum motion results	87

6.3. Change in prostate volume following FLA treatment	88
6.4. FLA induced changes in prostate morphology	89
6.5. Prostate MRI intensity differences following FLA treatment	90

Chapter 1

Introduction

Following a suspicious digital rectal exam, prostate cancer is typically diagnosed via a biopsy. A magnetic resonance image MRI is then used to stage the cancer, help locate the tumor, guide treatment, and to evaluate the treatment. To evaluate the treatment via MRI, one must compare the post-treatment image to the pre-treatment image. However, one must first spatially align (register) the images. Yet challenges exist due to specific treatment related changes to the prostate and its internal substructures, which existing tools currently do not address.

Several prostate cancer treatment options are available including radical prostatectomy, external beam radiation therapy (EBRT), and focal laser ablation (FLA) therapy [7]. The overarching objective of the work presented in this dissertation is to evaluate treatment efficacy via development of sophisticated segmentation and registration algorithms on prostate MRI. Our work represents the first use of these tools for evaluating prostate cancer treatment following the aforementioned treatments.

1.1 Evaluating Radical Prostatectomy

1.1.1 Prostate Volume Estimation

In the context of radical prostatectomy, determining prostate volume allows one to assess pathological stage of prostate cancer, can offer insights into prognosis, and help predict treatment response [8, 9]. Prostate volume has been shown to be a strong predictor of treatment outcome for patients with prostate cancer [10, 11], especially when combined with a baseline prostate-specific antigen (PSA) level [12]. Prostate volume has also been shown to be useful in determining PSA density [13]. The most

common method for estimating the prostate volume involves modeling the prostate as a simple geometric shape based on manually estimated measurements of the anterior-posterior, transverse, and cranio-caudal lengths of the prostate.

The most common models for approximating the prostate shape are the ellipsoid model [13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] and the prolate spheroid model [13, 15, 18]. It is important to note that the ellipsoidal model has been a clinical standard for comparisons from at least 1991 [16] to the present day [21, 23]. Some researchers have reported that in several cases the ellipsoid model underestimated the prostate volume [15, 17, 20, 24]. Eri et al. [15] and Tewari et al. [20] both found that the ellipsoid model underestimated the prostate volume by about 10%. Matthews et al. [17] found that the ellipsoid model from transrectal ultrasound (TRUS) imagery underestimated the volume for large prostates (>50 mL), but overestimated the volume for small prostates (<30 mL). Myschetzky et al. overcame this underestimation by proposing a new formula in which the ellipsoid volume estimation is multiplied by a factor of 1.34 [24]. Additionally, methods involving manual intervention are typically subject to inter- and intra-observer variability [25, 26] and these volume estimations are not highly reproducible.

While most prostate volume estimations are done using TRUS imagery, a strong correlation ($R^2 = 0.925$) has been shown between the volume estimations obtained using TRUS and from MR imagery [14]. In addition, the ellipsoidal model was found to yield accurate volume estimations for T2-w MR imagery of the prostate, even when an endorectal coil was used [21]. In [22] it was found that the ellipsoidal volume estimations were more accurate than a planimetry-based approach (aggregating a series of measurements from each slice) when using a surface coil; in contrast to [21] where planimetry estimates were found to yield more accurate volume estimations compared to the ellipsoidal model estimates when using an endorectal coil. In [14], a planimetry based volume estimation was performed by measuring the areas from manual 2D segmentations of the prostate on each slice.

1.1.2 Prostate Segmentation on MRI

Segmentation is the process of locating an object’s boundaries in an image. With the recent advancements of prostate MRI, several prostate segmentation schemes have been developed [27, 28, 29, 30, 31, 32, 33, 34, 35, 36]. Segmentation of the prostate is useful for a number of tasks, including calculating the prostate volume pre- and post-treatment [5, 11, 14, 37], for creating patient specific anatomical models [18], and for planning radical prostatectomies. Additionally, identifying the prostate capsule is clinically significant for determining whether extra-capsular spread of cancer has occurred, which is used as a determining factor when planning the extent of the excision.

Manual segmentation of the prostate, however, is not only laborious, but is also subject to a high degree of inter-, and intra-observer variability [38, 39]. Our prostate volume estimation method is related to the technique used by Hoffelt et al. [14], where the gland areas obtained by manual segmentation of the capsule were aggregated across multiple 2D sections. However, while Hoffelt et al. [14] obtained the prostate areas manually, we aim to perform the capsule segmentations automatically, via the use of a shape-based model. Our segmentation algorithm yields a 3D model of the prostate, the volume of which is compared to the volume of prostatectomy specimens.

1.2 Evaluating External Beam Radiation Treatment (EBRT)

1.2.1 Overview of EBRT

A second treatment option for prostate cancer is EBRT. EBRT involves irradiating the affected anatomical region with ionizing radiation, in an effort to destroy cancer cells. During treatment, the radiation disrupts the natural mitotic process in cells [40]. When apoptosis naturally occurs, the tumor cells have not had a chance to divide as rapidly, and therefore get eliminated naturally. Since tumor cells divide at a faster rate than benign cells [41], the radiation implicitly affects tumor cells more than benign cells, and can be effective at reducing the tumor volume. There is also significantly gland shrinkage following the radiation treatment period due to the elimination of tumor cells, as well as atrophy which can also occur to benign prostatic tissue [42].

Despite being a useful treatment option, EBRT may not be effective at completely eradicating prostate cancer, as there may be either residual disease or local recurrence following EBRT [43]. A study by Westphalen et al. [43] identified locally recurrent prostate cancer (via biopsy) in 58% of men deemed suspicious post-EBRT. To determine whether EBRT was effective, Prostate Specific Antigen (PSA) concentrations (in ng/ml) are tracked post-treatment. PSA values are currently used to evaluate treatment efficacy [44], in which a rise in PSA levels post-treatment is deemed to constitute biochemical failure. Approximately one fourth of EBRT patients undergo biochemical failure [45]. It was reported that approximately 23% of EBRT patients (381 out of 1650) had biomechanical failure with a 5-year incidence rate of prostate cancer metastases of 29% [45].

PSA velocity, defined as the change in PSA concentration (units of ng/ml/year), has been found to be statistically significantly predictive of metastatic disease post-EBRT [46]. Thus tracking PSA values is the current clinical standard in evaluating EBRT efficacy. A meta-analysis found that a higher than normal radiation dose during EBRT helped prevent biochemical failure in prostate cancer patients compared to the traditional dose [44]. However, while higher EBRT doses were found to significantly reduce biochemical failure, no changes in mortality rates were noticed over 2555 patients from 6 randomized trials [44]. Therefore, a more accurate method for evaluating treatment efficacy may be required.

PSA cannot typically be used to evaluate early treatment response. Determining early treatment response in the cases of residual or recurrent disease is necessary to allow for an early image guided intervention which will allow for complete disease response. PSA is usually measured at intervals of 3 to 6 months [45]. For favorable risk patients, the median PSA doubling time (PSA-DT), a useful prognostic tool, is 18 months, and 8 months for unfavorable risk patients [45]. In addition, a PSA-DT of less than 10 months is considered rapid [46]. Consequently there appears to exist a need for a way of assessing very early treatment changes to be able to modulate therapy if necessary via an image guided intervention.

1.2.2 MRI for EBRT Evaluation

MRI has shown to be useful in the detection of recurrent disease post-treatment and can potentially be used to discern and quantify treatment efficacy [47, 48, 49, 50, 51, 52, 53]. Over a cohort of 32 patients, the sensitivity of detecting locally recurrent prostate cancer post-EBRT was 71% with T2-weighted MRI, 96% for dynamic contrast enhanced (DCE) MRI, and 100% for a combination of T2-weighted and DCE [49].

Quantifying voxel-level changes within the tumor region on MRI can potentially be used to quantify early treatment related changes [54]. Foltz et al. [54] studied the association between changes in T2-w and apparent diffusion coefficient (ADC) MRI parameters following EBRT. The tumor was manually identified on pre-EBRT MRI, and mapped onto the post-treatment MRI. The changes in MRI parameter values 6 weeks following treatment were statistically significantly correlated with PSA velocity values (ng/ml/year), suggesting that early changes in voxel-by-voxel MRI imaging markers could be used to predict biochemical treatment response [54].

To determine voxel level changes in imaging markers, one must first register, or spatially align, the pre- and post-treatment imagery. Registration will allow one to (1) accurately localize the tumor region to study, so as not to confuse changes in tumor appearance with radiation necrosis of benign tissue, (2) determine precise voxel-by-voxel changes in imaging markers, and (3) determine EBRT induced morphologic changes to the prostate. Yet registration of EBRT MRI is not a trivial task, due to changes in MRI intensity values, atrophic shrinkage resulting from radiation, and local morphologic changes occurring within the gland [42] (Figure 1.1). While registration was performed manually in [54], this is time-consuming, may be prone to errors and inter-observer variability, and may be infeasible for large-scale studies. This work aims to create a domain constrained deformable (DoCD) biomechanical model to study early treatment related changes. The EBRT induced shrinkage effects and changes to the internal structures of the prostate are used create a domain-specific biomechanical model. DoCD is then used to register pre-, post-treatment MRI for (1) determining voxel-by-voxel changes, and (2) quantify changes in gland morphology following radiation.

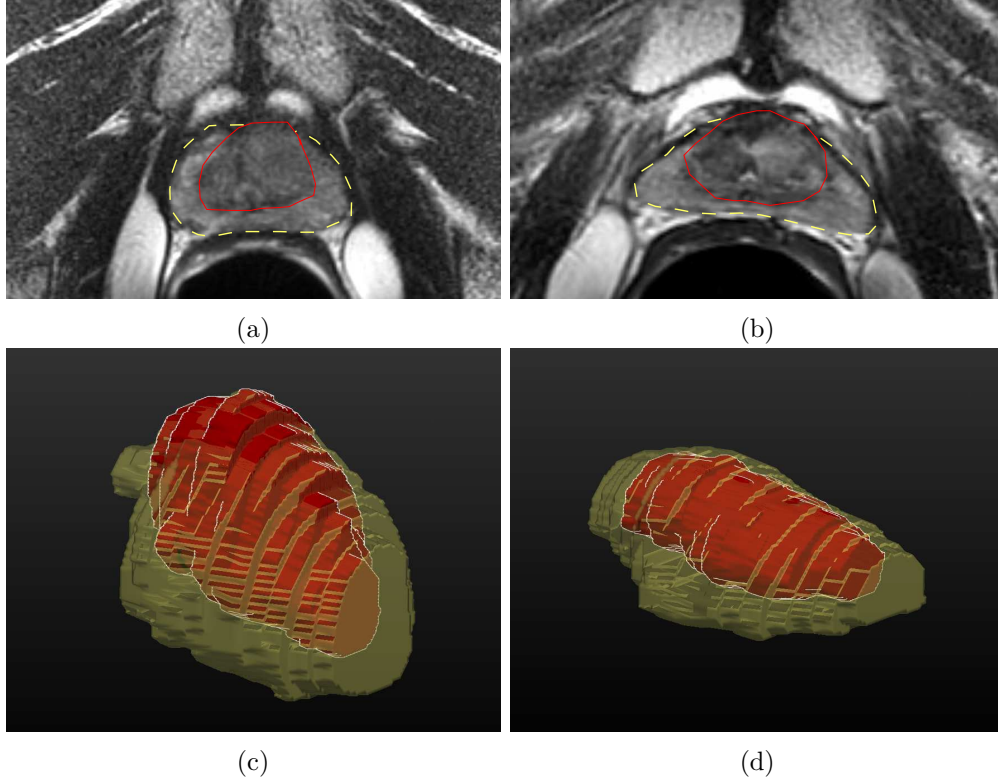


Figure 1.1: Prostate MRI intensity changes as a result of EBRT, where the PZ boundary is shown with a dotted yellow outline, and the CG boundary with a solid red outline in (a) and (b). (a) and (c) show the pre-EBRT MRI and (b) and (d) show the post-EBRT MRI. In (c) and (d) 3D renderings of the CG (red) and PZ (yellow) are shown. It can be seen that there are not only significant changes in volume to the prostate as a whole following EBRT, but also changes to the shapes of the PZ and CG, which DoCD aims to model.

1.2.3 Domain Constrained Deformable (DoCD) Model

The prostate gland consists of internal structures including the peripheral zone (PZ), central zone (CZ), and transition zone (TZ), where the latter 2 structures are jointly referred to as the central gland (CG) [55] (see Figure 1.2).

In the context of EBRT evaluation, the different zones can have different tissue compositions [56], suggesting that they may respond to EBRT differently. Following EBRT, there can be a significant loss in visible zonal anatomy on MRI [57]. Our model aims to explicitly exploit domain information by taking into account the different effects EBRT may have on the shapes of the internal prostatic structures, rather than on the gland as a whole. A domain constrained deformable (DoCD) biomechanical model

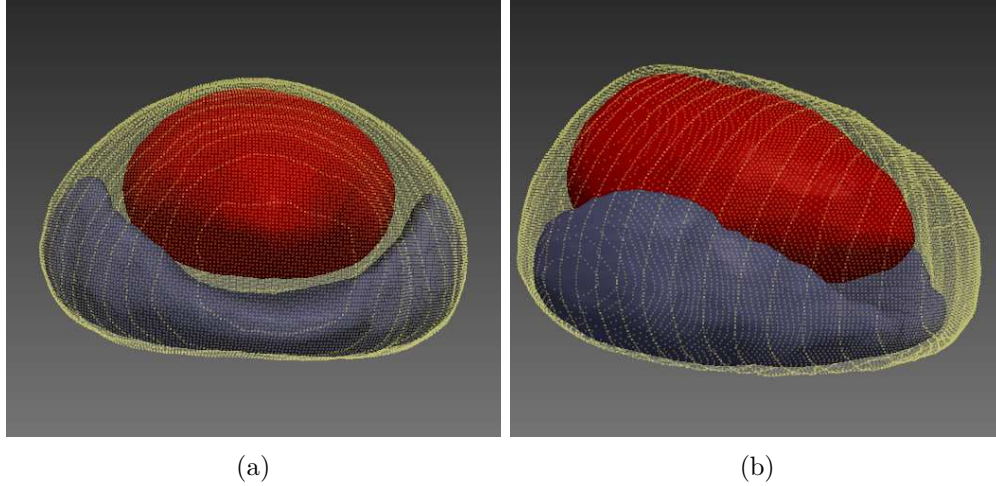


Figure 1.2: Two different 3D views of the prostate (yellow) with the central gland (CG) (red) and peripheral zone (PZ) (purple) segmented.

aims to take advantage of these different zones for automatically registering pre- and post-treatment MRI. Our DoCD model is driven by physical properties of the organ, specifically Young’s modulus and Poisson’s ratio. Young’s modulus defines the hardness of the tissue, and defines the degree to which a force applied to the prostate will deform the tissue. Poisson’s ratio determines the compressibility of the tissue, and can act as a volume-preserving property. DoCD is used to automatically register the pre-, post-treatment imagery, following which a voxel-level evaluation of the EBRT efficacy can be performed.

1.3 Evaluating Focal Laser Ablation (FLA) Treatment

1.3.1 Overview of FLA

Over 90% of low risk prostate cancer is currently treated with radical treatment such as prostatectomy or EBRT [58], which can cause significant quality of life issues and side effects such as incontinence, impotence, and damage to surrounding organs [59, 60, 61]. One alternative to radical treatment is active surveillance, which intends to simply wait to see if the tumor progresses before treatment is performed, in order to minimize the quality of life issues associated with radical treatment. However, this fails to address the underlying disease, and many patients wish to proactively attack the prostate cancer.

Focal treatments aim to destroy cancer cells with a high degree of precision, in order to avoid the quality of life issues associated with radical treatments while not sacrificing treatment efficacy. One type of focal treatment, FLA, has recently emerged as an extremely promising cancer treatment since it includes the best aspects of radical treatment (the ability to eradicate cancer cells), and its precision allows one to minimize the risk of side effects [58, 59, 60, 61, 62, 63]. FLA causes thermal destruction of tissue by a laser [58]. Radiation from a laser is absorbed by the tissue, causing homogeneous necrosis [59]. Due to the lack of excess vascularity in the prostate (which could cause unwanted excess conduction of heat), prostate cancer is well-suited for FLA treatment [63]. FLA for prostate cancer has the additional advantages of ease of use, and lower cost than some radical treatments [58].

1.3.2 MRI for FLA Evaluation

MRI is frequently used to both guide the treatment, and evaluate its efficacy [59, 61, 62, 63]. Prior to FLA, MRI is used to locate the tumor [59, 63], and to guide the laser during treatment [59]. Following FLA, MRI can be used to determine the effect of ablation [62], calculate the size of the ablated lesion [62], detect cancerous tissue [59, 61], and detect complications with surrounding organs such as the rectum or neurovascular bundle [61]. Raz et al. stated that a contrast-enhanced MRI directly following treatment can be used to confirm the treatment success, or to immediately repeat the FLA treatment [61]. Only seven days following treatment, hypoperfused lesions (lesions with decreased blood flow) were evident on MRI [60]. Eggener et al. recommended that following FLA, periodic MRI should be performed in order to characterize treatment effects [60].

1.3.3 Registration of Pre-, Post-FLA Prostate MRI

To the best of our knowledge, no system exists to quantitatively evaluate the post-FLA treatment effects on the prostate via MRI. In order to determine the effects of FLA following treatment, the ablated zone must first be calculated on the post-FLA MRI. However, a direct spatial mapping is not possible due to:

1. Different patient position within the MRI machine.
2. Changes in the prostate due to motion and filling of nearby tissue and organs such as the bladder and rectum.
3. Morphological changes in the prostate due to the ablation.

As such, a registration algorithm is employed to address these changes. Issue 1 can be addressed by a linear (rigid or affine) alignment of the pre-, post-FLA MRI. Issue 2 can be addressed by a non-linear (deformable) model specifically designed to simulate the changes to the prostate due to nearby tissues. Issue 3 can be addressed by a non-linear alignment of the pre-, post-FLA prostate, CG, and PZ. In fact, as stated previously, an exploration of #3 (the morphological changes due to FLA) is one of the state goals of this work. It is important to note that the motion of the nearby organs must be done separately since we wish to explicitly determine the deformations induced solely by the FLA.

This work aims to compare pre- and post-treatment MRI in order to quantify (a) functional and (b) morphological changes to the prostate due to the FLA. In this work, we will generate a FEM to determine how the motion and filling of the bladder and rectum affect the prostate. This simulated motion will be inverted, so that the only remaining changes in the prostate are due to the FLA. A second FEM will then be used to model the morphological changes in the prostate due to the FLA. This will allow us to (1) determine the changes to the MRI parameters specifically at the ablated zone, and (2) determine the morphological changes induced by FLA to the prostate and its internal structures.

1.4 Organization of this dissertation

The organization of this dissertation is as follows. In Chapter 2, existing literature concerning each of the different goals in this dissertation is reviewed, and the specific novel contributions of this dissertation are presented. In Chapter 3, the segmentation and registration methodology to be used for treatment evaluation is presented with associated

definitions, theory, algorithms. In Chapter 4, the evaluation of radical prostatectomy treatment via the use of a sophisticated segmentation methodology is described. In Chapter 5, the evaluation of external beam radiation treatment (EBRT) via the use of a deformable, biomechanical model (DoCD) is described. In Chapter 6, the evaluation of focal laser ablation (FLA) via DoCD is described. Finally, in Chapter 7, we present our concluding remarks and suggest directions for future work.

Chapter 2

Previous Related Work and Novel Contributions

2.1 Previous Work in Prostate Segmentation

Segmentation is the process of locating the an object’s boundaries in an image. In this work, we developed a segmentation algorithm to be used for volume estimation, and for generating a model of the prostate and its internal substructures for registration. In this section, we provide a brief review of recent attempts to improve segmentation algorithms in the context of prostate imagery.

2.1.1 Shape Based Prostate Segmentation

In medical imagery, shape model based segmentation has been used in a number of applications including volume estimation [5, 37], surgical intervention [64], and detecting disease within an organ for targeted therapy [65]. Active Shape Model (ASM) [66] and Active Appearance Model (AAM) [67] frameworks are two shape based methods commonly used for object segmentation, from which our segmentation scheme is derived.

The premise of both ASM’s and AAM’s is that a low dimensional representation can accurately describe the shape and intensity appearance of an object. Traditionally, ASM’s define a set of landmarks (specified by their Cartesian coordinates) on the boundary of an object, and Principal Component Analysis (PCA) is performed on the coordinates of the landmarks to yield a statistical shape model (SSM) of the object of interest [66]. Following the generation of the SSM, the intensities surrounding each border landmark are modeled as Gaussian distributions. To segment a new image, boundary locations are automatically ascertained [66], to which the SSM is fit.

However, no information from inside or outside the object of interest is taken into account when using ASM's. In addition, the shape and appearance have interdependencies, which ASM's do not consider. To overcome these limitations, the AAM framework was developed [67]. With AAM's, PCA is first performed on the set of image intensities inside the object of interest to generate a low dimensional appearance projection of each training image. A set of low dimensional "linked projections" are then calculated by concatenating the Cartesian coordinates, representing the shape, with the appearance projections, and performing PCA a second time [68]. A linked projection defines both the shape and appearance of an object. To segment a new image, the linked projections are varied, and the original, high dimensional shape and appearance are reconstructed. This process of varying the linked projections is repeated until the reconstructed intensities best match the original intensities [67].

2.1.2 Limitations with Existing Segmentation Models

Despite their widespread use, several ASM limitations in the context of prostate segmentation are listed below.

1. ASM's exclude information regarding the object's appearance everywhere except the object boundary.
2. ASM's assume independence of the shape and appearance models.
3. The traditional ASM appearance model assumes a Gaussian distribution for the underlying intensities, an assumption that may not always be valid [69].

In addition, there are several limitations common to both ASM's and AAM's. Some of these are listed below.

1. Performing PCA on a set of landmarks may not always accurately capture shape variations in the organ.
2. A large number of anatomical landmarks may be required (usually manually selected) to accurately capture shape variations.

3. Landmark-based models require accurate alignment of an equal number of corresponding landmarks on all training images [66]. To accurately capture the underlying image intensity statistics, each landmark should represent the same anatomical location in each training image [70, 71]. Generating accurate correspondences quickly becomes infeasible on account of the large number of landmarks, and an automated method for landmark detection and alignment can be prone to errors [72].
4. Landmarks require triangulation, and the triangulation algorithm could have a significant computational overhead, and may be prone to errors [73].
5. Both ASM's and AAM's traditionally use image intensities [66, 67]. Texture features such as edge gradients have been previously shown to yield more accurate segmentation results [74].

Our segmentation scheme is called the multi-feature landmark-free AAM model (MFLAAM) and extends the traditional AAM framework in two ways.

Firstly, the MFLAAM uses a levelset to capture the shape information [75]. A levelset is defined as a set of positive values at every pixel outside the object of interest, and negative values inside, and 0 at the surface of the object.

Secondly, while the traditional AAM was developed using image intensities, our MFLAAM allows for incorporation of multiple textures (such as grayscale intensities), providing the model with additional discriminability. Instead of using a low-dimensional projection to link the landmark coordinates with image intensities, the MFLAAM links the levelset (representing the shape) with a series of texture features.

2.1.3 Improvements to Statistical Shape Models

As stated previously, traditional ASM's and AAM's use PCA on a collection of landmarks to define the shape of an object, which performs a linear embedding of the landmarks into a low dimensional space. Yet a simple linear model may not necessarily be sufficient to accurately capture variations in the object's shape, and to overcome

this limitation a bilinear model could be used to create a SSM [76]. Owing to the previously mentioned problems with the use of landmarks to define SSM's, some researchers have investigated levelset based representations of object shape, initially proposed by Leventon et al. [75].

Leventon et al. [75] first proposed performing PCA on a series of signed distance maps (levelsets) to capture shape variations, to overcome the issues with landmark based SSMs. A levelset is defined as a set of positive values at every pixel outside the object of interest, and a set of negative values at every pixel inside the object of interest. Therefore, a value of 0 would represent the surface of the object. The simplest way to compute a levelset is at each pixel in the image, calculate the Euclidean distance to the closest border pixel, and negate that value if the pixel values within the object of interest. To define multiple levelsets, the signed distance to the border of *each* object is computed.

This approach involves first performing PCA on a set of minimum signed distances from each pixel to the object's surface, to yield a set of shape projections. The original levelsets can be reconstructed from these shape projections. It was noted in [75] that reconstructing the levelset from the shape projections will not necessarily result in a signed distance levelset, yet the reconstructed levelsets will be smooth and accurate enough for shape modeling.

This work was later incorporated into the ASM framework by Tsai et al. in 2004 [77] in which the levelset representations of multiple objects were concatenated prior to performing PCA. This allowed for the creation of a set of "linked" projections. In this context, a linked projection is a low dimensional embedding which defines the linear relationship between levelsets of multiple objects. Tsai et al. [77] used this low dimensional linked projection to segment multiple objects simultaneously. However, despite the merits of using levelset-based SSM's, traditional landmark based SSM's are still more common [71]. Levelsets were considered as a shape model in the context of AAM's in [78], in which an AAM was trained to segment out the lateral ventricles on 20 3D MRI volumes.

In addition, coupling the individual SSMs allows one to take advantage of the inherent dependency between the spatial location of multiple adjoining organs. The technique used by Tsai et al. [77] was in 2D, and the SSMs included not just shape, but also pose information. Akhondi-Asl et al. [79] developed a coupled SSM in 3D, which only accounted for shape variations (but not pose) by first aligning the training shapes. Akhondi-Asl et al. [79] then explored whether coupling the SSMs actually improved segmentation accuracy over simply constructing individual SSMs. It was found that in most cases, shape coupling improves results only when the levelsets were first aligned prior to training.

2.1.4 Improvements to Statistical Appearance Models

Traditional AAM's define the appearance of an object based on the intensities within that object [67]. Yet complementing image intensities with texture features may yield more accurate segmentations [37]. Seghers et al. [80] convolved the intensities of lung CT images with 25 different kernels, and the average Mahalanobis distance over all 25 texture features was shown to yield accurate localization of the border. Van Ginneken et al. [81] calculated a Taylor series approximation of image intensities and the optimal texture features were then selected and used in an ASM framework.

M. de Bruijne [69] and B. van Ginneken [81] showed that a non-linear k-nearest-neighbor (kNN) based appearance model yields improved segmentation accuracy in terms of both image intensities [69] and texture features [81] instead of invoking the normal distribution for modeling the object boundary in traditional ASM's. These methods demonstrated the utility of using non-Gaussian descriptions of appearance, as well as the usefulness of texture features, over simple intensity based appearance models.

In [82], Larsen et al. extended the traditional AAM framework to use wavelet features instead of intensities for 2D images. The image intensities were converted into Haar wavelet projections, mainly as a means to reduce computational cost. The wavelet projections were then utilized to reconstruct the original image intensities. Ghose et al. [83] employed intelligent wavelet coefficient selection by discarding several wavelet

coefficients, to yield an even more efficient, although still highly accurate, implementation of a wavelet based AAM. In addition, Hu et al. [78] used different MR imaging modalities (specifically T1-weighting, T2-weighting, and proton density) as three features used to drive an AAM. Finally, Baka et al. [84] showed an AAM derivation which used multiple texture features to segment 19 2D cardiac MR images.

2.1.5 Application to Prostate Segmentation

Several segmentation schemes for MR imagery of the prostate have been recently presented, including Klein et al. [85], Martin et al. [86], Pasquier et al. [87], and Makni et al. [88]. Klein et al. [85] performed a registration between an MR image of the prostate and an atlas of training data to achieve a segmentation of the prostate. Martin et al. [86] also used an atlas of training images, but constrained the segmentation model through the use of a statistical shape model. Pasquier et al. [87] used an Active Shape Model [66] method for extracting a statistical shape model of the prostate, which then looked for strong gradients to identify the prostate edge. Finally, Makni et al. [88] used a statistical shape model of the prostate, and clustered the intensities within a manually placed region of interest into 3 clusters: surrounding tissues and fat, central prostate zone, and the peripheral prostate zone. Any pixels within the latter 2 zones were determined to be in the prostate.

2.2 Novel Contributions in Prostate Segmentation

2.2.1 Multi-Feature Landmark-Free Active Appearance Model

In this work we present the multi-feature, landmark-free AAM (MFLAAM), a framework for (1) incorporating multiple texture features into an AAM, (2) defining the shape using a levelset, and (3) linking multiple levelsets to the textures to simultaneously segment multiple objects.

PCA is used to link multiple objects by first concatenating the objects, and performing PCA on this concatenated space [67, 77]. This is achieved either by (1) Concatenating High-Dimensional Features (CHF), in which one aggregates all the original high

dimensional data, similar to Tsai et al. [77], or (2) Concatenating Low-Dimensional Projections (CLP), in which one first performs PCA to reduce the dimensionality of the shape and appearance, and those projections are concatenated, similar to traditional AAM's [67]. Overall, this work differs from Tsai et al. [77] in that (1) PCA is used to link a multiple levelsets with multiple texture features instead of just multiple levelsets, and (2) PCA is performed using the CLP method instead of the CHF method.

With each application of PCA, the data is embedded in a lower dimensional space, thereby decreasing the data variance. While the CHF approach involves a single application of PCA, and the CLP approach involves two successive applications of PCA, one would assume that CHF would be the appropriate strategy since it involves lower loss in variance. However, CHF results in a space with extremely high dimensionality, and performing PCA on this high dimensional space can be computationally infeasible. CLP is a computationally tractable method, one employed by the traditional AAM [67], and hence the one we adopt for the MFLAAM. The benefits of performing PCA twice include (1) the ability to process each feature in parallel, and (2) the reduced memory requirements of the Eigen-analysis and covariance matrix calculation. In addition, we show that there is only a marginal loss of variance from performing PCA twice.

To segment a new image, the texture features are first extracted, and the goal is to calculate the associated shape, and therefore the resulting segmentation. Given a set of linked projections, one can reconstruct an approximation of the original high dimensional data. The MFLAAM is rotated, translated, and scaled, and the texture features are reconstructed. The location of the best reconstructions is found, and the shape is reconstructed at this location. The hypothesis is that an accurate texture reconstruction will correspond to a proper shape reconstruction, and thus a correct segmentation. This segmentation is then used to automatically compute the volume *in vivo* prior to radical prostatectomy, and compared to the volume of the excised specimens.

2.2.2 Segmentation of Prostatic Substructures

In addition to using the MFLAAM to evaluate radical prostatectomy volume changes, it is also used to guide the registration for EBRT and FLA evaluation. As stated previously, DoCD aims to take into account specific changes to the prostate substructures CG and PZ, and the MFLAAM is therefore extended to segment those substructures.

In [54], outlines of the prostate, tumor, CG, and PZ were manually identified on both the pre- and post-treatment MRI in order to guide the registration. Subsequent to delineating the structures, the regions so identified were manually brought into alignment between the pre-, post-treatment MRI [54]. This work aims to automatically segment these structures using the MFLAAM for use in guiding the registration.

In order to segment these boundaries automatically, the MFLAAM was extended to simultaneously segment multiple objects. As stated previously, to estimate the prostate volume, the MFLAAM was trained with a levelset of the prostate. In order to extend this method to segment multiple objects, we take an approach similar to that of Tsai et al. [77], in which concatenating the levelsets of multiple objects is performed prior to performing PCA, essentially “coupling” the levelsets. Hence a single set of low dimensional values (a “projection”) is used to represent the shape of multiple objects. This allows for simultaneous segmentation of multiple objects. Our approach employs the concept of coupling multiple shapes’ levelsets (i.e. the prostate capsule, CG, and PZ) with multiple textures with the MFLAAM framework.

2.2.3 Comparison to Closest Related Works

While [78] used a levelset in an AAM framework, there are several important differences with the work presented in this work. (1) The low dimensional projections for the levelsets were constrained to between ± 2 standard deviations from the mean shape. While this may be a reasonable assumption for most scenarios, it is entirely possible that a new image might be better segmented where the extent of shape variation falls outside this range. (2) No alignment was performed for the training images in [78]. This is not typically an issue with brain MRI, but critical to address with prostate

MRI data, where deformation and the presence or absence of the endorectal coil can cause differences in relative orientations of the gland from patient to patient. (3) No alignment of the AAM model to a new image was performed. Since there is a large region in which the object can appear in a new image, we find that this affine alignment is a crucial step in the MFLAAM algorithm. Without any rotation, translation, or scaling, one assumes that the training levelsets include sufficient pose information, which is not guaranteed. (4) Intensity differences were used to drive the segmentation in [78], whereas we employed normalized cross correlation on account of non-standard intensity values between patient studies in the present work.

We note that texture features have been previously used in conjunction within an AAM framework [78, 82, 83, 84]. In [82] and [83] the AAM's were developed in conjunction with wavelets, while in [78] and [84] the AAM's were generalized to work in conjunction with any type of texture features. While [78] and [84] attempted to maximize the similarity between the reconstructions and original features using the L_2 norm, the MFLAAM maximizes normalized cross correlation, a useful similarity measure to help overcome intensity non-standardness and extreme intensity values. Another fundamental difference between the MFLAAM and related works [78, 82, 83, 84] is that it employs an explicit feature selection scheme specifically tailored to identifying those attributes that will yield the most accurate shape reconstruction (and therefore most accurate segmentation). Additionally, unlike [84] which only utilized pose information to drive the AAM, the MFLAAM utilizes a full range of affine transformations to determine the optimal segmentation.

Our model uses multiple coupled level sets to model the 3D shapes, thereby helping to alleviate many of the issues facing traditional landmark-based AAMs. The MFLAAM offers the advantage of (1) not having to deal with the landmark identification problem, and (2) not having to triangulate a series of landmarks to generate a 3D model. In addition, we take a similar approach that proposed by Leventon et al. [75] and Akhondi-Asl et al. [79], in that multiple levelsets are coupled to allow for simultaneous segmentation of multiple objects.

In addition, the MFLAAM can also use existing segmentations of one or more organs

to generate more accurate segmentations of the adjacent organs (for example using the prostate segmentation to simultaneously segment the bladder and rectum [89]). This is accomplished by generating the coupled projections using both intensities and levelsets, whereas prior AAM models are only able to consider intensity information [67].

This approach also allows the MFLAAM to be used hierarchically, in which one object can first be segmented, and then used to drive the segmentations of other embedded objects. For example, in the case of prostate MRI, the central gland (CG) and peripheral zone (PZ) are substructures of the prostate itself (see Figure 1.2). Using an existing prostate segmentation to segment the CG and PZ reduces the search space, which can help hone in on the embedded substructures within the gland. In addition, the coupled model allows for structural linking of the adjoining sub-structures, thereby permitting incorporation of anatomic constraints.

2.3 Previous Work in Prostate Registration

There are several examples of biomechanical models being used to (1) register prostate MRI and CT imagery [90, 91, 92, 93, 94, 95], and to (2) register brain MRI following radiation treatment [96, 97, 98] (Table 2.1). Biomechanical models have been used to model morphologic and volumetric changes as a result of tumor growth and shrinkage on brain MRI. Karacali et al. [98] attempted to study brain tissue atrophy which was simulated by prescribing volume changes to the region of atrophy. In addition, Kyriacou et al. [97] modeled the effects of tumor shrinkage on surrounding tissue using a biomechanical model.

Existing prostate biomechanical models have focused on how external loads on the surface of the prostate deform the gland [90, 91, 92, 93, 94, 95], which is extremely useful when modeling how organs move relative to each other [91, 94], or how a probe deforms the prostate [93]. Chi et al. [91] modeled the motion of the bladder, prostate, and rectum on CT imagery, and explored different material properties for benign prostate tissue, prostate tumors, and benign prostatic hyperplasia using a FEM model. Boubaker et al. [94] used a FEM to model how the bladder, rectum, and prostate moved on CT

Table 2.1: DoCD (last row) and closest related work. Most existing works either model shrinkage in brain imagery, use 2D models, or model external surface forces on the prostate, unlike DoCD which models EBRT-induced changes to substructures within the prostate.

Image Type	Brief Description
2D Brain MRI	FEM strains model tumor shrinkage [97]
3D Brain MRI	Tissue atrophy modeled by reducing volume of pixels [98]
2D Brain MRI	Tumor growth modeled using a FEM [96]
3D Prostate CT	Prostate, bladder, rectum modeled with FEM [91, 94]
3D Prostate MRI	Endorectal coil deformation modeled with FEM [93]
3D Prostate MRI	External forces with FEM align prostate surfaces [90]
<i>3D Prostate MRI</i>	<i>DoCD: Internal shrinkage models EBRT deformations.</i>

imagery, and compared the results to a cadaver. Crouch et al. [92] used a FEM to register the prostate surfaces on CT imagery. Hensel et al. [93] used a FEM to register a prostate MRI with an endorectal coil to an MRI without. Brock et al. [90] used an FEM to register a prostate MRI acquired prior to treatment to an MRI acquired during treatment by automatically aligning nodes on the prostate surface.

2.4 Novel Contributions in Prostate Registration

2.4.1 Domain Constrained Deformable (DoCD) Model

We use the MFLAAM to yield simultaneous segmentation of prostatic substructures, and bring them into spatial alignment via the use of a biomechanical model. In this work we employ a finite element model (FEM) as the choice of biomechanical model. The FEM is a biomechanical model which uses physical properties such as elasticity and compressibility to deform one or more objects, in our case the CG and PZ.

Brock et al. [90] used a Young’s modulus of 21 kPa for the prostate, and Chi et al. [91] claimed that normal prostate tissue has a Young’s modulus of 40-80 kPa, benign hypertrophic prostate tissue has a value of 30-50 kPa, and cancerous prostate tissue has a value of 80-120 kPa. Based off these findings, we employed a Young’s modulus of 30 kPa.

A Poisson’s ratio of 0.50 indicates that compressing in one direction results in

stretching in the perpendicular direction. A value of 0.0 indicates that compressing in one direction yields no changes in the perpendicular direction, and as such reduces the volume. Chi et al. [91] noted that an accurate Poisson’s ratio is critical for an accurate registration. Brock et al. [90] modeled the prostate with a Poisson’s ratio of 0.40 and Crouch et al. [92] used a value of 0.49.

The methods in [90, 92] use a high Poisson’s ratio because the prostate capsule is essentially modeled as a volume-preserving entity, such that compressing one part of the prostate yields an expansion elsewhere. While this is likely a correct assumption for modeling how various external forces affect the prostate capsule, such as the pressure from an endorectal coil [93] or the bladder [91], this may not be a valid assumption for EBRT induced deformations. In this work, we wish to model the EBRT induced shrinkage effects on the PZ and CG of the prostate, and therefore use a Poisson’s ratio of 0.0, which allows changes in the volume.

For DoCD, strains are induced at the boundaries of these prostatic substructures, as well as on the prostate surface itself. A 3D FEM is then used to deform the entire prostate as a result of these strains. Similar to [96], an optimization scheme is used to determine the model parameters which best deform the pre-treatment MRI to post-treatment MRI.

2.4.2 Comparison to Closest Related Works

Existing biomechanical models of the prostate have focused on external forces, and models for registering radiation treatment have mainly focused on 2D brain MRI. By contrast, DoCD uses a 3D FEM to register pre-, post-treatment MRI due to the FEM’s ability to explicitly incorporate prior domain knowledge about the treatment induced effects on the prostate. The approach we take is similar to that of [98] in which brain atrophy was modeled by shrinking the volume of certain pixels in the image. However, while domain-specific information was used in [98], no physical tissue information was incorporated, as we aim to do via the use of a FEM. In this case, the effects of shrinkage are modeled by supplying known loads at locations *within* the prostate (rather than only at the surface, as in traditional prostate FEM schemes [90]).

In addition, in this work, we will also generate a FEM to determine how the motion and filling of the bladder and rectum affect the prostate. This simulated motion will be inverted, so that the only remaining changes in the prostate are due to the FLA. This will allow us to (1) determine the changes to the MRI parameters specifically at the treatment location, and (2) determine the morphological changes induced by treatment to the prostate and its internal structures.

In summary, DoCD makes the following novel contributions:

1. DoCD uses an FEM generated from the PZ and CG substructures of the prostate, rather than the capsule as a whole (as in [90, 92, 93, 94]), in order to more precisely model the treatment induced changes to the internal prostate morphology.
2. DoCD applies strains *within* the prostate towards the centroid of the PZ and CG, in order to model the unique shrinking effects of treatment, unlike only applying loads on the surface of the prostate as in [90, 92, 93, 94].
3. DoCD employs physical properties specifically chosen to allow changes in volume of the prostate and substructures in order to model the shrinkage, unlike [91, 93] which models the prostate as volume-preserving.
4. DoCD specifically models, and removes, the deformations on the prostate from surrounding organs to isolate the treatment-induced morphology changes.

Chapter 3

Segmentation and Registration Methodology

3.1 MFLAAM Segmentation Algorithm

This content is primarily derived from [1], on which Robert Toth is the first author.

3.1.1 Notation

An image scene is defined as $I = (C, f)$. $C \in \mathbb{R}^P$ represents a set of P pixels, and each $c_k \in C, k \in \{1, \dots, P\}$ is defined by its Cartesian coordinates (x, y, z) . $f(k)$ represents the intensity at pixel k . $F_{i,j} \in \mathbb{R}^P$ represents feature j of image i , where $F_{i,j} = \{f_{i,j}(k) \mid k \in \{1, \dots, P\}\}$ and $f_{i,j}(k)$ represents the value of feature j at pixel k of image i . $f_{i,1}(k)$ represents the levelset value at pixel k and $f_{i,2}(k)$ through $f_{i,M}(k)$ represent the $(M - 1)$ texture features at pixel k .

For a segmented image I_i , $C^{(In)} \subset C$ represents an unordered set of pixels inside the object. Each $c \in C^{(In)}$ is therefore a pixel inside the object. A summary of the notation used throughout the section is illustrated in Table 3.3 [1].

Table 3.1: Notation and symbols used.

Symbol	Description	Formula/Domain
N	Number of images.	$N \in \mathbb{N}^1$
i	Image index.	$0 < i \leq N$
M	Number of features.	$M \in \mathbb{N}^1$
j	Feature index.	$0 < j \leq M$
P	Number of pixels.	$P \in \mathbb{N}^1$
Continued on next page		

Table 3.1 – continued from previous page

Symbol	Description	Formula/Domain
k	Pixel index.	$0 < k \leq P$
$\hat{P}_j$	Feature projection dimensionality.	$\hat{p}_j \leq P$.
$\hat{k}$	Feature projection index	$0 < \hat{k} \leq \hat{P}_j$
$\tilde{P}$	Linked projection dimensionality.	$\tilde{P} \leq \left(\sum_j \hat{P}_j\right)$
$\tilde{k}$	Linked projection index.	$0 < \tilde{k} \leq \tilde{P}$
$\hat{\psi}_j^{(\hat{k})}$	$\hat{k}^{th}$ feature projection eigenvector.	$\hat{\psi}_j^{(\hat{k})} \in \mathbb{R}^P$.
$f_{i,j}(k)$	Feature value at pixel k .	$f_{i,j}(k) \in \mathbb{R}^1$
$\tilde{\psi}^{(\tilde{k})}$	$\tilde{k}^{th}$ linked projection eigenvector.	$\tilde{\psi}^{(\tilde{k})} \in \mathbb{R}(\sum_j P_j)$.
$\hat{f}_{i,j}(\hat{k})$	Feature projection value at index $\hat{k}$.	$\hat{f}_{i,j}(\hat{k}) \in \mathbb{R}^1$
$\hat{\lambda}_j^{(\hat{k})}$	$\hat{k}^{th}$ feature projection eigenvalue.	$\hat{\lambda}_j^{(\hat{k})} \in \mathbb{R}^1$
$\tilde{f}_i(\tilde{k})$	Linked projection value at index $\tilde{k}$.	$\tilde{f}_i(\tilde{k}) \in \mathbb{R}^1$
$\tilde{\lambda}_j^{(\tilde{k})}$	$\tilde{k}^{th}$ linked projection eigenvalue.	$\tilde{\lambda}_j^{(\tilde{k})} \in \mathbb{R}^1$
$F_{i,j}$	Feature image.	$F_{i,j} \in \mathbb{R}^P$
$\check{F}_{i,j}$	Concatenation of feature projections.	$\check{F}_{i,j} \in \mathbb{R}(\sum_j P_j)$.
$\hat{F}_{i,j}$	Feature projection.	$\hat{F}_{i,j} \in \mathbb{R}^{\hat{P}_j}$
$\dot{F}_{i,j}$	Feature reconstruction.	$\dot{F}_{i,j} \in \mathbb{R}^P$
$\tilde{F}_i$	Linked projection.	$\tilde{F}_i \in \mathbb{R}^{\tilde{P}}$
C	Collection of P pixels.	$C \in \mathbb{R}^P$
$C^{(In)}$	Pixels inside an object.	$C^{(In)} \subset C$

3.1.2 Theory of MFLAAM

The MFLAAM training involves Concatenating Low-dimensional Projections (CLP) prior to performing PCA. An alternative to the CLP scheme is the Combining High-dimensional Features (CHF) scheme [77]. In the CHF scheme, the original features are simply concatenated and embedded into a low dimensional linked projection. This section explores the additional loss of variance from using CLP versus CHF.

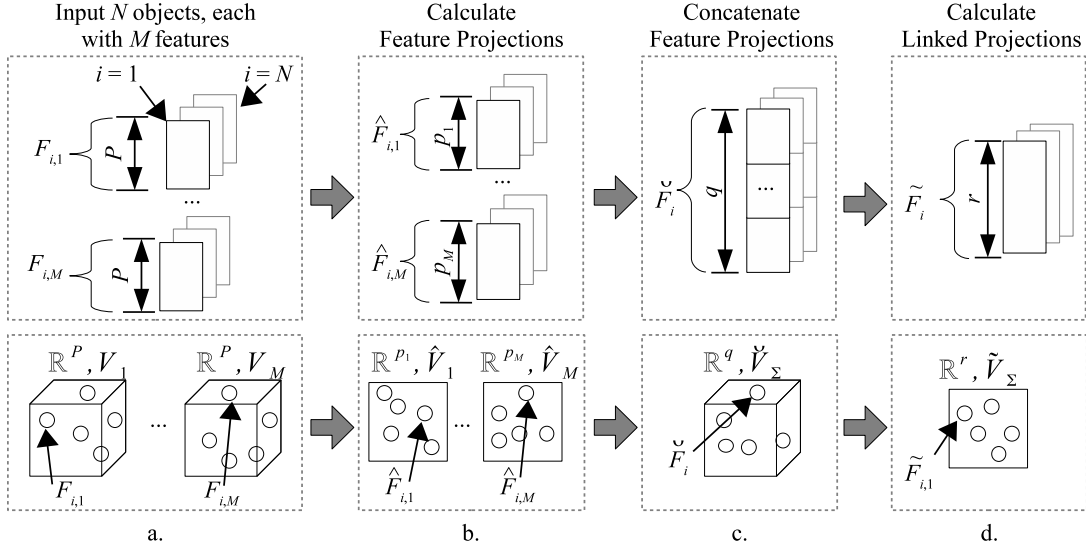


Figure 3.1: The CLP process (computing a set of linked projections from features). (a). M features from N objects are input. (b). Compute a series of feature projections $\hat{F}_{i,j}$. (c). Concatenate feature projections as $\check{F}_i$. (d). Calculate a set of linked projections $\tilde{F}_i$ from the concatenated projections. At every step, a certain percentage (α) of the data's variance is required to be retained in the projections. The top row represents the steps performed on each object, while the bottom row represents the variance retained in each step.

Definitions

An object $C \in \mathbb{R}^P$ contains P elements. For each element $k \in \{1, \dots, P\}$, there is an associated scalar value $f(k)$. Each C_i is associated with a set of M features, $F_{i,j} \in \mathbb{R}^P, j \in \{1, \dots, M\}$.

The variance $V(S)$ of a set $S = \{C_1, \dots, C_N\}$ is defined as the accumulated variance of each element,

$$\begin{aligned}
 V(S) &= \sum_{k=1}^P \left(\frac{1}{N-1} \sum_{i=1}^N (f_i(k) - \bar{f}(k))^2 \right) \\
 &= \frac{1}{N-1} \sum_{i=1}^N \sum_{k=1}^P (f_i(k) - \bar{f}(k))^2
 \end{aligned} \tag{3.1}$$

where $\bar{f}(k) = \frac{1}{N} \sum_{i=1}^N f_i(k)$ represents the mean of element k across all N objects.

Definition 1. Given a set S_j of feature j across N images, $S_j = \{F_{1,j}, \dots, F_{N,j}\}$, the

corresponding feature variance V_j is given as $V_j = V(S_j)$, $\forall j \in \{1, \dots, M\}$.

The total feature variance V_Σ is defined as the feature variance accumulated over all M features, $V_\Sigma = \sum_{j=1}^M V_j$.

A low dimensional embedding of feature $F_{i,j}$ is called a feature projection and denoted by $\hat{F}_{i,j}$ (Figure 3.1b). A feature projection $\hat{F}_{i,j} \in \mathbb{R}^{p_j}$, where $p_j \ll P$ is defined by its scalar values $\hat{f}_{i,j}(\hat{k})$, $\hat{k} \in \{1, \dots, p_j\}$. Each feature projection $\hat{F}_{i,j}$, $\forall j \in \{1, \dots, M\}$, is required to retain at least $(\alpha \cdot V_j)$ variance, where α is a pre-determined value such that $0 < \alpha \leq 1$. Note $\hat{F}_{i,j}$ is computed independently for each j .

Definition 2. Given a set $\hat{S}_j$ of N feature projections $\hat{S}_j = \{\hat{F}_{1,j}, \dots, \hat{F}_{N,j}\}$, the projection variance $\hat{V}_j$ is defined as $\hat{V}_j = V(\hat{S}_j)$, $\forall j \in \{1, \dots, M\}$.

By definition, $\hat{V}_j \geq \alpha \cdot V_j$, which is rewritten as $\hat{V}_j = \hat{\alpha}_j \cdot V_j$, where $\alpha \leq \hat{\alpha}_j \leq 1$. The total feature projection variance $\hat{V}_\Sigma$ is defined as the accumulated projection variances, $\hat{V}_\Sigma = \sum_{j=1}^M \hat{V}_j$.

Definition 3. Given M feature projections $\{\hat{F}_{i,1}, \dots, \hat{F}_{i,M}\}$, associated with object C_i , $\forall i \in \{1, \dots, N\}$, the corresponding concatenated projection $\check{F}_i$ is defined as,

$$\check{F}_i = \{\hat{f}_{i,1}(1), \dots, \hat{f}_{i,1}(p_1), \dots, \hat{f}_{i,M}(1), \dots, \hat{f}_{i,M}(p_M)\}. \quad (3.2)$$

The dimensionality of $\check{F}_i$ is given by $q = \sum_{j=1}^M p_j$, so $\check{F}_i \in \mathbb{R}^q$ (Figure 3.1c).

Definition 4. Given a set $\check{S}$ of N concatenated projections $\check{S} = \{\check{F}_1, \dots, \check{F}_N\}$, the total concatenated variance $\check{V}_\Sigma$ is defined as $\check{V}_\Sigma = V(\check{S})$.

After concatenation, a second low dimensional embedding is performed (Figure 3.1d). A linked projection $\check{F}_i \in \mathbb{R}^q$, which is required to retain at least $(\alpha \cdot \check{V}_\Sigma)$ variance, is denoted as $\tilde{F}_i \in \mathbb{R}^r$ where $r \leq q$.

Definition 5. Given N linked projections $\{\tilde{F}_1, \dots, \tilde{F}_N\}$, the total linked variance $\tilde{V}_\Sigma$ is defined as $\tilde{V}_\Sigma = V(\{\tilde{F}_1, \dots, \tilde{F}_N\})$.

By definition, $\tilde{V}_\Sigma \geq \alpha \cdot \check{V}_\Sigma$, which can be rewritten as $\tilde{V}_\Sigma = \tilde{\alpha} \cdot \check{V}_\Sigma$, where $\alpha \leq \tilde{\alpha} \leq 1$.

Propositions

Propositions 1 and 2 below show that the CLP method (using $\check{F}$ to calculate $\tilde{F}$) will allow for retention of most of the original variance V_Σ .

Proposition 1. *Given N concatenated projections $\{\check{F}_1, \dots, \check{F}_N\}$, with a total concatenated variance of $\check{V}_\Sigma$, and total feature projection variance of $\hat{V}_\Sigma$, $\check{V}_\Sigma = \hat{V}_\Sigma$.*

Proof.

$$\begin{aligned}
 \check{V}_\Sigma &= V\left(\{\check{F}_1, \dots, \check{F}_N\}\right) \\
 &= \frac{1}{N-1} \sum_{i=1}^N \sum_{j=1}^M \sum_{\hat{k}=1}^{p_j} \left(\hat{f}_{i,j}(\hat{k}) - \bar{f}_j(\hat{k}) \right)^2 \\
 &= \sum_{j=1}^M \left(\frac{1}{N-1} \sum_{i=1}^N \sum_{\hat{k}=1}^{p_j} \left(\hat{f}_{i,j}(\hat{k}) - \bar{f}_j(\hat{k}) \right)^2 \right) \\
 &= \sum_{j=1}^M \left(\hat{V}_j \right) \\
 &= \hat{V}_\Sigma
 \end{aligned}$$

□

$\tilde{V}_\Sigma$ can now be rewritten as,

$$\tilde{V}_\Sigma = \tilde{\alpha} \cdot \check{V}_\Sigma = \tilde{\alpha} \cdot \hat{V}_\Sigma = \tilde{\alpha} \cdot \sum_{j=1}^M \hat{V}_j = \tilde{\alpha} \cdot \sum_{j=1}^M \hat{\alpha}_j \cdot V_j. \quad (3.3)$$

Proposition 2. *Given a total linked variance of $\tilde{V}_\Sigma$ and total feature variance of V_Σ , $\tilde{V}_\Sigma \geq \alpha^2 \cdot V_\Sigma$.*

Proof. By definition, α is the lower bound of $\tilde{\alpha}$ and $\hat{\alpha}_j$. Substituting α into Equation (3.3) yields the lower bound of $\tilde{V}_\Sigma$:

$$\begin{aligned}
\tilde{V}_\Sigma &= \tilde{\alpha} \cdot \sum_{j=1}^M \hat{\alpha}_j \cdot V_j \\
\tilde{V}_\Sigma &\geq \alpha \cdot \sum_{j=1}^M \alpha \cdot V_j \\
\tilde{V}_\Sigma &\geq \alpha^2 \cdot \sum_{j=1}^M V_j \\
\tilde{V}_\Sigma &\geq \alpha^2 \cdot V_\Sigma
\end{aligned}$$

□

As stated previously, the CHF method [77] could have been used to compute $\tilde{F}_i$. A concatenated feature $\mathbf{F}_i \in \mathbb{R}^{(P \cdot M)}$ can be defined as,

$$\mathbf{F}_i = \{f_{i,1}(1), \dots, f_{i,1}(P), \dots, f_{i,M}(1), \dots, f_{i,M}(P)\}. \quad (3.4)$$

It can be shown that $V(\{\mathbf{F}_1, \dots, \mathbf{F}_N\}) = V_\Sigma$ in a manner similar to Proposition (1). However, there are several reasons our MFLAAM uses $\check{F}_i$ (the CLP method) instead of $\mathbf{F}_i$ (the CHF method) for calculating $\tilde{F}_i$:

1. **Minimal Loss of Data Variance.** Using $\mathbf{F}_i$ retains at least $\alpha \cdot V_\Sigma$ variance while using $\check{F}_i$ retains at least $\alpha^2 \cdot V_\Sigma$ variance. Since $\lim_{\alpha \rightarrow 1} (\alpha \cdot V_\Sigma - \alpha^2 \cdot V_\Sigma) = 0$, the additional loss of variance is minimal if $\alpha \approx 1$.
2. **Computational Efficiency.** The CHF method involves projecting a set of $P \cdot M$ objects to a lower dimensional space. By comparison, the CLP method only requires projecting a set of P dimensional objects. In addition, calculating $\hat{F}_{i,j}$ can be performed in parallel for each j using the CLP method, which isn't possible using the CHF method.

3.1.3 MFLAAM Training

The MFLAAM is trained with N images $\{I_i, \dots, I_N\}$. First, the shape $F_{i,1}$ and the texture features $F_{i,j}, j > 1$ are computed, followed by the calculation of the feature projections $\hat{F}_{i,j}$ and linked projections $\tilde{F}_i$.

Calculating Shape

The shape $F_{i,1} = \{f_{i,1}(1), \dots, f_{i,1}(P)\}$ for I_i is represented by the signed distances to the object's surface [75], and is calculated as,

$$f_{i,1}(k) = \begin{cases} -\min_{c \in C^{(In)}} \|c_k - c\|_2 & \text{if } c_k \in C_i^{(In)} \\ +\min_{c \in C^{(In)}} \|c_k - c\|_2 & \text{if } c_k \notin C_i^{(In)}. \end{cases} \quad (3.5)$$

Calculating Projections using PCA

Performing PCA on $\{F_{1,j}, \dots, F_{N,j}\}$ results in P ordered eigenvectors $\hat{\psi}_j^{(1)}, \dots, \hat{\psi}_j^{(P)}$ and associated eigenvalues $\hat{\lambda}_j^{(1)}, \dots, \hat{\lambda}_j^{(P)}$, where $\hat{\lambda}_j^{(1)} > \dots > \hat{\lambda}_j^{(P)}$.

Each eigenvector $\hat{\psi}_j^{(\hat{k})}, \forall \hat{k} \in \{1, \dots, \hat{P}_j\}$ is defined by its P elements

$$\psi_j^{(\hat{k})} = \left\{ \psi_j^{(\hat{k})}(1), \dots, \psi_j^{(\hat{k})}(P) \right\}. \quad (3.6)$$

$\hat{P}_j$ is chosen to be as small as possible such that

$$\sum_{\hat{k}=1}^{\hat{P}_j} \hat{\lambda}_j^{(\hat{k})} \geq \alpha \cdot \sum_{k=1}^P \hat{\lambda}_j^{(k)}, \quad (3.7)$$

and α is predetermined and $0 < \alpha \leq 1$. The feature projection $\hat{F}_{i,j} = \left\{ \hat{f}_{i,j}(1), \dots, \hat{f}_{i,j}(p_j) \right\}$ for image i and feature j is calculated as,

$$\hat{f}_{i,j}(\hat{k}) = \sum_{k=1}^P (f_{i,j}(k) - \bar{f}_j(k)) \cdot \psi_j^{(\hat{k})}(k), \quad (3.8)$$

where $\bar{f}_j(k) = \frac{1}{N} \sum_{i=0}^N f_{i,j}(k)$. The feature projections are concatenated as,

$$\check{F}_i = \left\{ \hat{f}_{i,1}(1), \dots, \hat{f}_{i,1}(\hat{P}_1), \dots, \hat{f}_{i,M}(1), \dots, \hat{f}_{i,M}(\hat{P}_M) \right\}. \quad (3.9)$$

Performing PCA on $\{\check{F}_1, \dots, \check{F}_N\}$ results in $q = \sum_{j=0}^M \hat{P}_j$ ordered eigenvectors $\tilde{\psi}^{(1)}, \dots, \tilde{\psi}^{(q)}$ and associated scalar eigenvalues $\tilde{\lambda}^{(1)}, \dots, \tilde{\lambda}^{(q)}$, where $\tilde{\lambda}^{(1)} > \dots > \tilde{\lambda}^{(q)}$.

Each eigenvector $\tilde{\psi}^{(\tilde{k})}, \forall \tilde{k} \in \{1, \dots, \tilde{P}\}$ is defined by its q elements

$$\tilde{\psi}^{(\tilde{k})} = \left\{ \tilde{\psi}^{(\tilde{k})}(1), \dots, \tilde{\psi}^{(\tilde{k})}(q) \right\}, \quad (3.10)$$

which can be rewritten as,

$$\begin{aligned} \tilde{\psi}^{(\tilde{k})} = & \left\{ \tilde{\psi}_1^{(\tilde{k})}(1), \dots, \tilde{\psi}_1^{(\tilde{k})}(\hat{P}_1), \dots \right. \\ & \left. \tilde{\psi}_M^{(\tilde{k})}(1), \dots, \tilde{\psi}_M^{(\tilde{k})}(\hat{P}_M) \right\}. \end{aligned} \quad (3.11)$$

$\tilde{P}$ is chosen to be as small as possible such that,

$$\sum_{\tilde{k}=1}^{\tilde{P}} \tilde{\lambda}^{(\tilde{k})} \geq \alpha \cdot \sum_{k=1}^q \tilde{\lambda}^{(k)}. \quad (3.12)$$

The linked projections $\tilde{F}_i = \left\{ \tilde{f}_i(1), \dots, \tilde{f}_i(r) \right\}$ are calculated as,

$$\tilde{f}_i(\tilde{k}) = \sum_{j=1}^M \sum_{\hat{k}=1}^{\hat{P}_j} \hat{f}_{i,j}(\hat{k}) \cdot \tilde{\psi}_j^{(\tilde{k})}(\hat{k}). \quad (3.13)$$

Since the feature projections retain a certain percentage (α) of the variance, and the linked projections also retain α of the variance, the total variance retained in the final model is α^2 of the original variance. This was shown analytically above.

3.1.4 MFLAAM Segmentation

A new, unsegmented image is denoted as I_θ , where $F_{\theta,j}$, for $j > 1$ represents the texture features of the new image, and $F_{\theta,1}$ represents the unknown shape of the new image. The goal is to determine the final segmentation $C_\theta^{(In)}$ given the texture features. The texture features are used to estimate $\tilde{F}_\theta$, which can then be used to reconstruct an estimate of $F_{\theta,1}$ (denoted as $\hat{F}_{\theta,1} \in \mathbb{R}^P$) and yield a final segmentation $C_\theta^{(In)}$.

Calculating a Feature Reconstruction using Texture Features

The first step is to calculate a set of linked projections $\tilde{F}_\theta$ using the texture features. Given linked projections $\tilde{F}_\theta$, the feature projections $\hat{F}_{\theta,j}$, for $\forall j \in \{1, \dots, M\}$ are estimated as $\hat{F}_{\theta,j,\tilde{F}} = \left\{ \hat{f}_{\theta,j,\tilde{F}}(1), \dots, \hat{f}_{\theta,j,\tilde{F}}(p_j) \right\}$,

$$\hat{f}_{\theta,j,\tilde{F}}(\hat{k}) = \sum_{\tilde{k}=1}^r \tilde{\psi}_j^{(\tilde{k})}(\hat{k}) \cdot \tilde{f}_\theta(\tilde{k}). \quad (3.14)$$

The linked projections $\tilde{F}_\theta = \left\{ \tilde{f}_\theta(1), \dots, \tilde{f}_\theta(r) \right\}$ which minimize the sum of squared differences between $\hat{F}_{\theta,j,\tilde{F}}$ and $\hat{F}_{\theta,j}$ are calculated,

$$\tilde{F}_\theta = \arg \min_{\tilde{F}} \sum_{j=2}^M \sum_{k=1}^{p_j} \left(\hat{f}_{\theta,j,\tilde{F}}(\hat{k}) - \hat{f}_{\theta,j}(\hat{k}) \right)^2. \quad (3.15)$$

Equation (3.13) cannot be used to estimate $\tilde{F}_\theta$ directly since we only have the texture features ($j \geq 2$) and not the shape ($j = 1$).

The next step is to use $\tilde{F}_\theta$ to reconstruct a full P dimensional feature. Given a set of estimated feature projections $\hat{F}_{\theta,j,\tilde{F}}$, the reconstructed features $\dot{F}_{\theta,j}$ are calculated as, $\dot{F}_{\theta,j} = \left\{ \dot{f}_{\theta,j}(1), \dots, \dot{f}_{\theta,j}(P) \right\}, j \in \{1, \dots, M\}$,

$$\dot{f}_{\theta,j}(k) = \bar{f}_j + \sum_{\hat{k}=1}^{\hat{P}_j} \hat{\psi}_j^{(\hat{k})}(k) \cdot \hat{f}_{\theta,j,\tilde{F}}(\hat{k}). \quad (3.16)$$

The entire process of reconstructing feature j from the texture features is illustrated in Algorithm 1.

Algorithm 1 ReconstructNewFeature

Input: texture features $F_{\theta,2}$ through $F_{\theta,M}$, feature index $j \in \{1, \dots, M\}$

Output: Reconstruction $\dot{F}_{\theta,j} \in \mathbb{R}^P$

- 1: Calculate $\hat{F}_{\theta,j}$, for $\forall j \geq 2$ using Equation (3.8);
 - 2: Calculate $\tilde{F}_\theta$ using Equation (3.15);
 - 3: Calculate $\hat{F}_{\theta,j,\tilde{F}}$ using Equation (3.14);
 - 4: Calculate $\dot{F}_{\theta,j}$ using Equation (3.16);
 - 5: **return** $\dot{F}_{\theta,j}$
-

Step 1 in Algorithm 1 calculates the texture feature projections $\hat{F}_{\theta,j}$. Step 2 uses the feature projections $\hat{F}_{\theta,j}$ to estimate the linked projections $\tilde{F}_{\theta}$. Step 3 calculates a feature projection estimate $\hat{F}_{\theta,j,\tilde{F}}$ for feature j using the linked projections $\tilde{F}_{\theta}$. Step 4 calculates the feature reconstruction $\dot{F}_{\theta,j}$ using the feature projection estimate $\hat{F}_{\theta,j,\tilde{F}}$. Figure 3.2 shows a graphical overview of the process for reconstructing all features (levelset and texture) from a collection of input features. An example of a reconstruction overlaid with the original image is shown in Figure 3.3 [1].

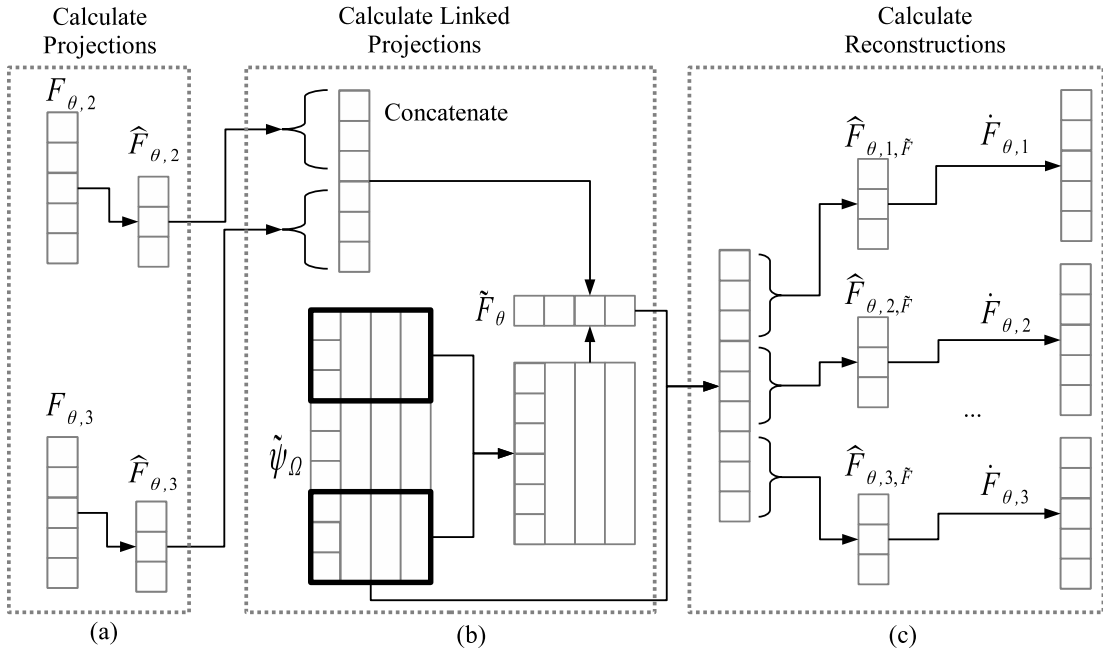


Figure 3.2: (a) The projections from the input intensities and levelsets are calculated using Equation (3.8). (b) Only the rows from the coupled matrix corresponding to the given inputs are extracted. The projections are used to estimate a set of linked projections $\tilde{F}_{\theta}$ using Equation (3.15). The linked projections $\tilde{F}_{\theta}$ are used to reconstruct the entire set of projections $\hat{F}_{\theta,j,\tilde{F}}$ using Equation (3.14). Finally, a set of reconstructions $\dot{F}_{\theta,j}$ using Equation (3.16) are calculated using Equation (3.16).

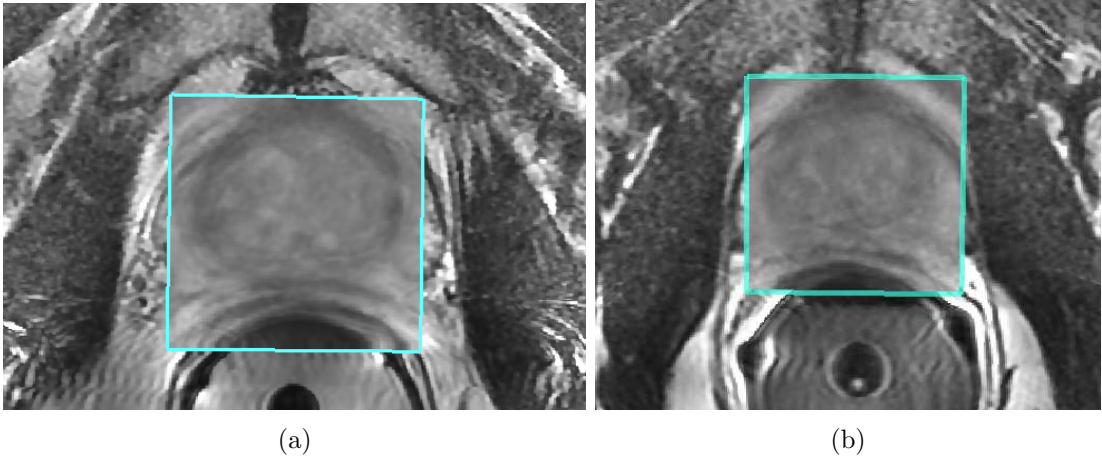


Figure 3.3: (a) and (b) represent $F_{\theta,j}^{(T)}$ and $\hat{F}_{\theta,j}^{(T)}$ for two different patient studies. In both (a) and (b), the original feature image $F_{\theta,j}^{(T)}$ is shown as the background image. The reconstruction $\hat{F}_{\theta,j}^{(T)}$ resulting from the MFLAAM is shown inside the blue box.

Segmenting a New Image

To segment I_θ , a template matching algorithm is employed. The location with the best texture feature reconstructions (based on normalized cross correlation (NCC)) are found. $F_{\theta,1}$ is then reconstructed, and a segmentation $C_\theta^{(In)}$ is calculated.

If $F_{\theta,j}^{(T)}$ represents applying an affine transformation T to feature $F_{\theta,j}$, then $\hat{F}_{\theta,j}^{(T)}$ is defined as

$$\hat{F}_{\theta,j}^{(T)} = \text{ReconstructNewFeature} \left(F_{\theta,2}^{(T)}, \dots, F_{\theta,M}^{(T)} \right). \quad (3.17)$$

After each texture feature is transformed ($F_{\theta,j}^{(T)}$), there is an associated reconstructed texture feature ($\hat{F}_{\theta,j}^{(T)}$). NCC was used to determine how well each feature was reconstructed, denoted as $\text{NCC} \left(\hat{F}_{\theta,j}^{(T)}, F_{\theta,j}^{(T)} \right)$. A value of 1.0 would represent a transformation that yielded a perfect reconstruction, while lower values represent transformed texture features which the MFLAAM could not reconstruct from the training data. NCC was chosen as the similarity measure instead of the L_2 norm because of its ability to overcome intensity non-standardness and its robustness to extreme intensity values. For example, a few extremely bright or extremely dark pixels would contribute to driving the metric if the L_2 norm was used, while the NCC would not suffer from this limitation

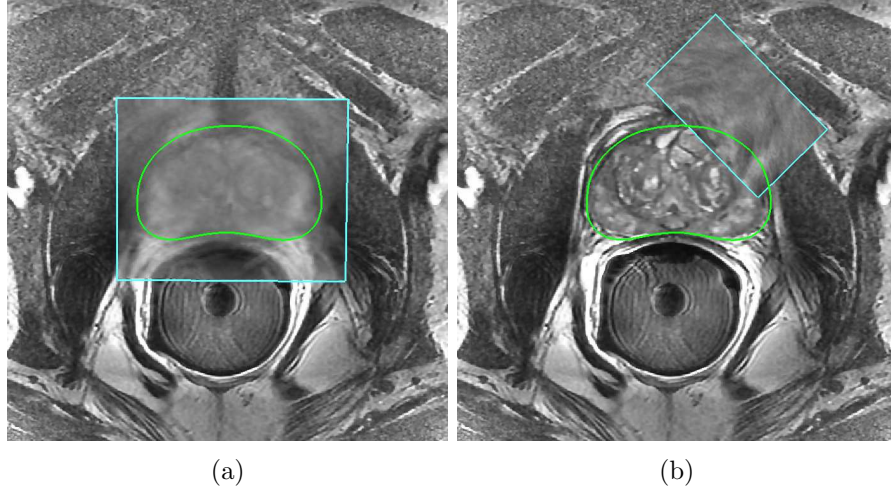


Figure 3.4: (a) and (b) each show the same image as the background. In both (a) and (b), the ground truth prostate segmentation is shown in green. However, during the segmentation process, different transformations T yield different reconstructions. The reconstructions for two different transformations $\dot{F}_{\theta,j}^{(T)}$ are shown in blue squares in (a) and (b). When T is well aligned with the object of interest, the reconstruction results in a high NCC value (0.65 in (a)), yet when T causes the feature to be far from the object of interest, the MFLAAM is unable to reconstruct the texture feature, which results in a low NCC value (0.42 in (b)).

due to the fact that it is inherently normalized. The hypothesis is that a high NCC value would occur if the feature is transformed such that the object of interest is in perfect alignment with the trained MFLAAM (Figure 3.4). However, since each texture feature is reconstructed independently, each texture feature would have a distinct NCC value. Therefore, the average NCC over all texture features is maximized to determine the best transformation T ,

$$T = \arg \max_T \frac{1}{M-1} \sum_{j=2}^M \text{NCC} \left(\dot{F}_{\theta,j}^{(T)}, F_{\theta,j}^{(T)} \right) \quad (3.18)$$

where $\text{NCC} \left(\dot{F}_{\theta,j}^{(T)}, F_{\theta,j}^{(T)} \right)$ represents the normalized cross correlation [99] between $\dot{F}_{\theta,j}^{(T)}$ and $F_{\theta,j}^{(T)}$.

Equation 3.18 must be optimized to determine the set of affine parameters for which the NCC is maximized. This is a crucial step, since the working hypothesis is that the NCC will be maximized if and only if the MFLAAM is properly aligned with the new image, and hence the reconstruction will properly capture the desired segmentation. A

global optimization is first performed, followed by a local optimization to properly hone in on the maximum NCC. To perform the global optimization, an initialization-biased particle swarm optimizer [100] is used, in which 100 random affine parameters (100 particles) are each allowed to converge independently on the maximum NCC, and the particle with the maximum NCC overall is chosen. Then, a local Powell optimization [101] is performed, in which each of the 12 affine parameters is optimized independently. This process of optimizing each parameter independently is repeated until convergence, thus driving the transformations to the maximum NCC value [1].

The optimal transformation T , can now be used to calculate the reconstructed levelset $\dot{F}_{\theta,1}^{(T)} = \left\{ \dot{f}_{\theta,1}^{(T)}(1), \dots, \dot{f}_{\theta,1}^{(T)}(P) \right\}$ using Equation (3.16). The final segmentation $C_{\theta}^{(In)}$ is now calculated as all pixels in which the reconstructed levelset is negative,

$$C_{\theta}^{(In)} = \left\{ c_k \mid T^{-1} \left(\dot{f}_{\theta,1}^{(T)}(k) \right) < 0 \right\}, \quad (3.19)$$

since the levelset is represented by a signed distance function.

The images were first affinely aligned to a single study to serve as part of the training. The MFLAAM was implemented in a multi-resolution fashion, with 4 resolutions from $50 \times 50 \times 40$ pixels up to the full resolution of $256 \times 256 \times 40$ pixels. For all experiments, $\alpha = 0.95$ was used, similar to [67].

3.1.5 Feature Extraction and Selection

For our experiments, we employed several texture features. These included first order grey level features (median and variance of neighborhoods surrounding a given pixel) as well as Kirsch [102] and Sobel [103] texture features. Table 3.2 contains a complete list of the texture features used for the MFLAAM [1].

The texture features are utilized to estimate the linked projection $\tilde{F}_{\theta}$ using Equation (3.15). $\tilde{F}_{\theta}$ is then employed to reconstruct our final segmentation $\dot{F}_{\theta,1}$. Knowing the true shape $F_{\theta,1}$ would have allowed us to use Equation (3.13) to estimate $\tilde{F}_{\theta}$. However, $F_{\theta,1}$ is unknown, and as such Equation (3.15) was used. We work under the assumption the difference between using Equations (3.13) and (3.15) would be insignificant if the feature

Table 3.2: Texture features employed with the MFLAAM.

j	Name	Operation
2	Kirsh (0°)	Convolution
3	Kirsh (90°)	Convolution
4	Kirsh (180°)	Convolution
5	Kirsh (270°)	Convolution
6	Sobel (0°)	Convolution
7	Sobel (90°)	Convolution
8	Gaussian	Convolution (Standard Deviation of 0.5)
9	Gaussian	Convolution (Standard Deviation of 2.5)
10	Gaussian	Convolution (Standard Deviation of 4.5)
11	Variance	Neighborhood of $(3 \text{ mm})^3$
12	Variance	Neighborhood of $(8 \text{ mm})^3$
13	Variance	Neighborhood of $(15 \text{ mm})^3$
14	Median	Neighborhood of $(3 \text{ mm})^3$
15	Median	Neighborhood of $(8 \text{ mm})^3$
16	Median	Neighborhood of $(15 \text{ mm})^3$

projections of the texture features and shape are highly correlated. This correlation R can be quantified, and employed for identifying the most discriminating features [1].

The correlation R between a given texture feature projection $\hat{f}_{i,j}(\hat{k}_j)$ and shape feature projection $\hat{f}_{i,j}(\hat{k}_1)$ is defined as,

$$R(\hat{k}_1, \hat{k}_j) = \frac{\sum_{i=1}^N \hat{f}_{i,1}(\hat{k}_1) \cdot \hat{f}_{i,j}(\hat{k}_j)}{(N-1) \cdot \sqrt{\hat{V}_1 \cdot \hat{V}_j}}, \quad (3.20)$$

where $\hat{V}_j$ indicates the variance of $F_{i,j}$ and is described analytically in the Appendix. We were able to compute a score ϕ_j defining the correlation between the shape and texture feature as,

$$\phi_j = \frac{1}{p_1 \cdot p_j} \cdot \sum_{\hat{k}_1=1}^{p_1} \sum_{\hat{k}_j=1}^{p_j} R(\hat{k}_1, \hat{k}_j). \quad (3.21)$$

The M features with the highest scores are then identified and incorporated into the MFLAAM [1].

3.2 Simultaneous PZ/CG Segmentation Methodology

This content is primarily derived from [2], on which Robert Toth is the first author.

3.2.1 Training Multiple Shape Models

The previous section discussed the use of texture features with a levelset in an AAM context (denoted as MFLAAM). The ability to simultaneously segment multiple shapes is implemented by extending the MFLAAM to include multiple levelsets.

All training images are first aligned, as described in [79]. A single training image is chosen as the template, and an affine alignment is applied to align all the segmentations to the template. The next step is to generate a levelset from each training object, such that negative levelset values represent pixels inside the object, and positive levelset values represent pixels outside the object, using Equation 3.5.

In the MFLAAM used to segment prostate volumes for evaluating prostatectomy, the first feature $F_{i,1}$ for training image i represented a levelset, and the remaining $M - 1$ features represented textures used to drive the segmentation process. In order to segment multiple objects simultaneously, the first L features $F_{i,1}, \dots, F_{i,L}$ represent levelsets, and the remaining $M - L$ features represent texture features.

Following the extraction of multiple levelsets, the entire MFLAAM training process as described in the previous chapter remains unchanged. The only difference is that instead of performing PCA on 1 levelset and $M - 1$ texture features, PCA is performed on L levelsets and $M - L$ texture features.

A graphical display of the coupling process is shown in Figure 3.5. The boxes in the left column represent the high dimensional texture features and levelsets. The boxes in the middle column represent the projections of each intensity and levelset. Finally, the boxes in the right column represent the coupled matrix, where each column represents a single eigenvector.

A comparison between the multi-shape MFLAAM with a traditional AAM and the coupled levelsets proposed by Tsai et al. [77] is shown in Figure 3.6. Traditional AAMs

couple intensities with landmarks, and traditional coupled levelsets involve concatenating a set of levelsets, which can be computationally infeasible. The MFLAAM, by comparison, allows for coupling of the projections of multiple levelsets with the intensity projections, essentially allowing simultaneous segmentations in an AAM framework. This helps avoid the computational cost of concatenating high dimensional levelsets [2].

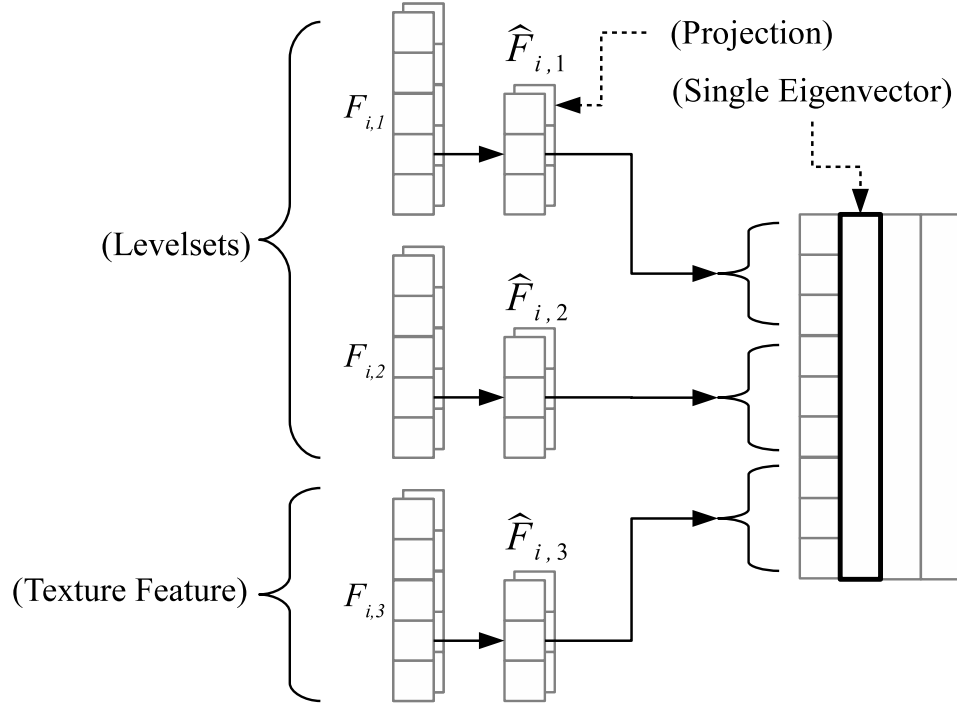


Figure 3.5: Coupling intensities with multiple levelsets for the MFLAAM training. First, PCA is used to project each texture $F_{i,3}$ and levelset $F_{i,1}$, $F_{i,2}$ down into a lower dimensional space, denoted as $\hat{F}_{i,j}$. Then, a second PCA is performed, creating a coupled matrix, where each row corresponds to a specific projection value, and each column represents a single eigenvector.

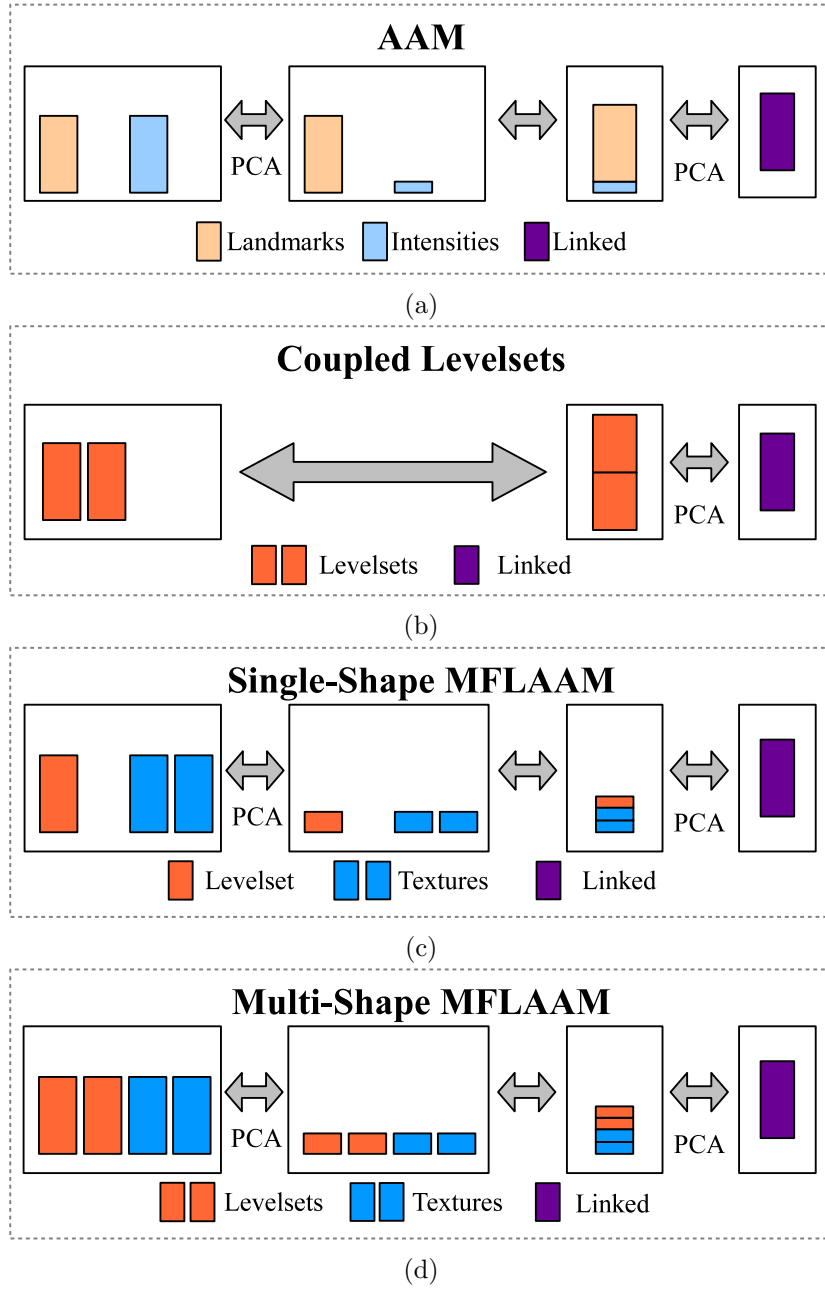


Figure 3.6: (a) Traditional AAMs [67] perform PCA on a set of intensities, and link the intensity projections with the shape by performing a second PCA. (b) Traditional coupled levelsets [77] concatenate the high dimensional levelsets, and perform PCA on the result. (c),(d) The MFLAAM projects each levelset and texture to a low dimensional space prior to coupling for either one (c) or multiple (d) shapes.

3.2.2 Simultaneous Segmentation

In the single-shape (prostate-only) MFLAAM, Equation 3.17 used features 2 through M (the texture features) to drive the reconstruction of any feature. For the multi-shape MFLAAM, Equation 3.17 is also used, but instead of using only the textures, the MFLAAM can additionally use a presegmented levelset to drive the reconstruction. Figure 3.2 shows the process of reconstructing any feature (including multiple levelsets) from any inputs (textures or levelsets).

Equation 3.18 is used to determine the location of the best reconstruction, and Equation 3.19 is used to reconstruct multiple shapes simultaneously (see Figure 3.2(c)). Given the optimal transformation, the high dimensional levelsets of all objects are reconstructed and thresholded, yielding a set of segmentations for all objects in the image. This allows one to use the given prostate segmentation, as well as the texture features, to drive the simultaneous reconstruction and segmentation of the CG and PZ. Figure 3.7 shows the entire segmentation process on a new image.

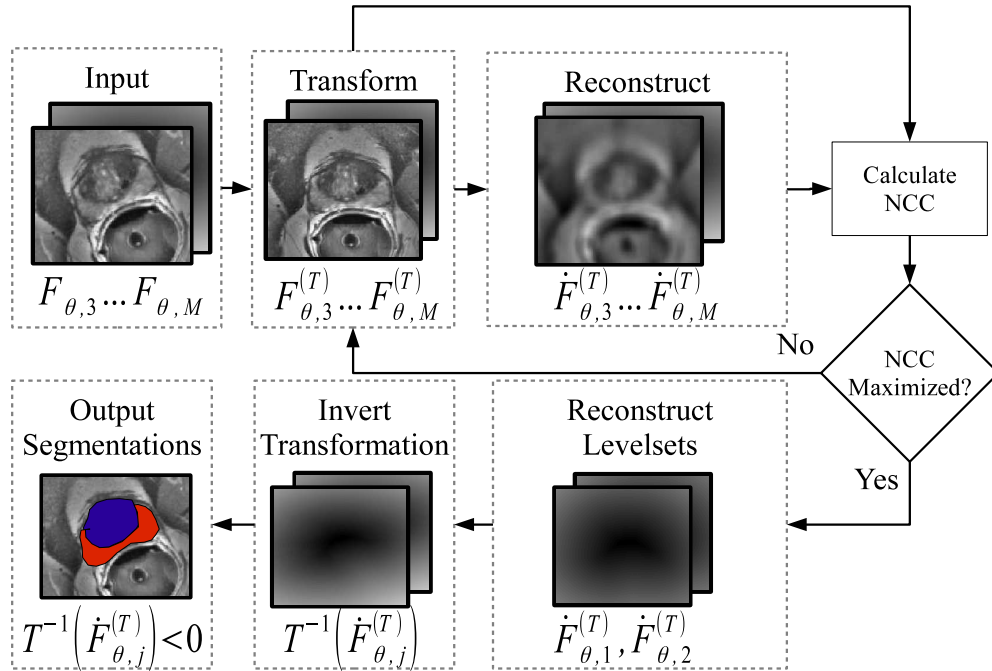


Figure 3.7: The MFLAAM uses input levelsets $F_{\theta,3}, \dots, F_{\theta,L}$ and texture features $F_{\theta,L+1}, \dots, F_{\theta,M}$. The inputs are transformed $F_{\theta,j}^{(T)}, j \geq 3$ and reconstructed $\dot{F}_{\theta,j}^{(T)}, j \geq 3$. When the NCC between the reconstructions and transformed inputs is maximized, the MFLAAM reconstructs all levelsets $T^{-1}(\dot{F}_{\theta,j}^{(T)}), j = 1, 2$, which are then thresholded.

3.3 DoCD EBRT Registration Methodology

3.3.1 Notation

A 3D MRI image scene $I = (C, f)$ is defined by a collection of voxels $c = (x_c, y_c, z_c)$, $\forall c \in C$, and MRI intensity information for each voxel, $f(c) \in \mathbb{R}$, $\forall c \in C$. Each voxel c is manually labeled as either the PZ, CG, or background (the prostate is simply CG + PZ), such that $L(c) = \{CG, PZ, background\}$. The pre-EBRT MRI is denoted as I_{Pre} and the post-EBRT MRI is denoted as I_{Post} . A region R upon which to induce shrinking is defined by a collection of voxels, such that $R \subset C$. A collection of N nodes $\mathcal{N}_I$ representing the meshed discretization of I is defined as a collection of voxels $\mathcal{N}_I \subset C$. A full list of notation used throughout this section is presented in Table 3.3.

Table 3.3: Notation and symbols used.

Symbol	Description
C	Collection of voxels.
c	Single voxel $c \in C$, $c = (x_c, y_c, z_c)$.
$f(c)$	Intensity at voxel c .
I_{Pre}	Pre-EBRT MRI.
I_{Post}	Post-EBRT MRI.
$L(c)$	Label of voxel c (CG, PZ, background).
R	Region consisting of a collection voxels ($R \subset C$).
$\bar{c}_R$	Center of mass of region R ($\bar{c}_R \in C$).
Δ_R	Magnitude to shrink region R .
$\mathcal{N}$	Collection of voxels representing FEM nodes ($\mathcal{N} \subset C$).
N	Number of nodes in FEM.
K	$3N \times 3N$ matrix representing FEM material properties.
F	$3N \times 1$ vector representing FEM forces.
U	$3N \times 1$ vector representing FEM displacements.
S_c	Nodes representing corners of an element in the FEM.
$T(c)$	Transformation applied to voxel c .

3.3.2 FEM Review

An FEM contains elements (e.g. hexahedrons) connected at nodes. Given N nodes $\mathcal{N}$ in a 3D FEM, a $3N \times 3N$ sparse, symmetric “stiffness” matrix K defines how each node interacts with every other node. A $3N \times 1$ vector V represents the coordinates of the nodes, a $3N \times 1$ vector F represents a series of external forces applied to each node, and a $3N \times 1$ vector U represents the final displacements of each node (the final result of the FEM calculation). Mathematically, this is stated as solving for U in the following equation,

$$K \cdot U = F. \quad (3.22)$$

However, solving $(U = K^{-1} \cdot F)$ directly is computationally infeasible; iterative algorithms such as the biconjugate gradient stabilized method algorithm [104] estimate U by solving,

$$U = \arg \min_U \| F - K \cdot U \|_2, \quad (3.23)$$

which we employ in DoCD.

3.3.3 Radiation Induced Shrinkage

The collection of nodes associated with region R , upon which to apply a shrinking strain, is defined as $\mathcal{N}_R = \mathcal{N}_I \cap R$. To shrink region R with magnitude $\Delta_R \in \mathbb{R}$, we define a radial displacement $\mathbf{u}_c \in \mathbb{R}^3$ at each node $c \in \mathcal{N}_R$ relative to its centroid as,

$$\mathbf{u}_c = \Delta_R \cdot \frac{c - \bar{c}_R}{\|c - \bar{c}_R\|_2}, \text{ where } \bar{c}_R = \frac{1}{|R|} \sum_{c \in R} (x_c, y_c, z_c), \text{ for } \forall c \in \mathcal{N}_R. \quad (3.24)$$

Essentially, Equation 3.24 represents inducing a strain (fixed displacement $\mathbf{u}$) of a given magnitude Δ towards the center of a region R .

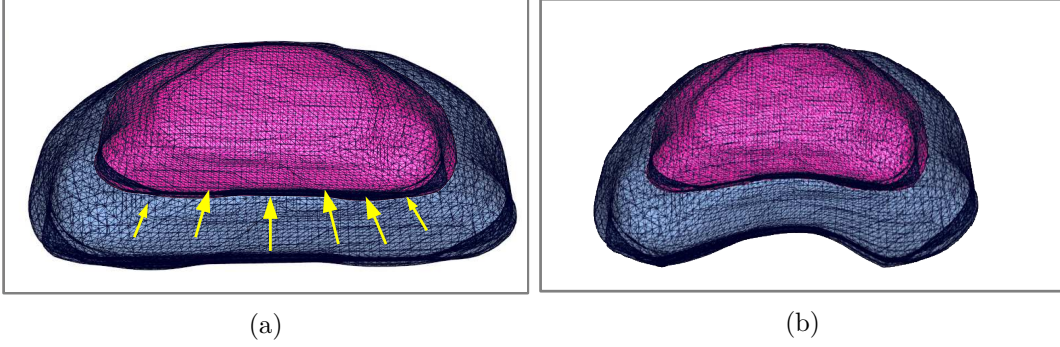


Figure 3.8: FEM of the CG (pink) and PZ (blue). Forces (yellow) are applied to the CG of the prostate (a). The FEM deforms the entire mesh based on these forces, resulting in a deformed model (b).

3.3.4 FEM Deformation of Prostate MRI

In the case of the EBRT-induced shrinkage, the displacements $\mathbf{u}_c$ from each of the M shrinking regions are used as boundary conditions in the FEM, as described in [90]. Boundary conditions essentially set the displacements of several nodes as constant and solve the FEM for the displacements of the remaining nodes (denoted as U). To determine the displacement of each voxel in the image scene ($c \in C$), the nodes surrounding c , $S_c \subset \{1, \dots, N\}$, are defined by the corners of the FEM element containing c . In this work we use hexahedron elements as in [92, 105], and as such, $S_c \in \mathbb{R}^8$. The transformation of c is defined as an interpolation of nodal displacements,

$$T(c) = c + \frac{\sum_{n \in S_c} \|c - v_n\|_2 \cdot u_n}{\sum_{n \in S_c} \|c - v_n\|_2}, \quad (3.25)$$

where $\mathbf{u}_n$ denotes the displacement of node n from the FEM result U . This allows for a deformation of I_{Pre} given the parameterized shrinking regions. The transformed pre-EBRT MRI $T(I_{Pre})$ is defined as,

$$T(I_{Pre}) = \{C_{Pre}, f_{Pre}(T(c))\}. \quad (3.26)$$

Figure 3.9 shows the general flow of DoCD.

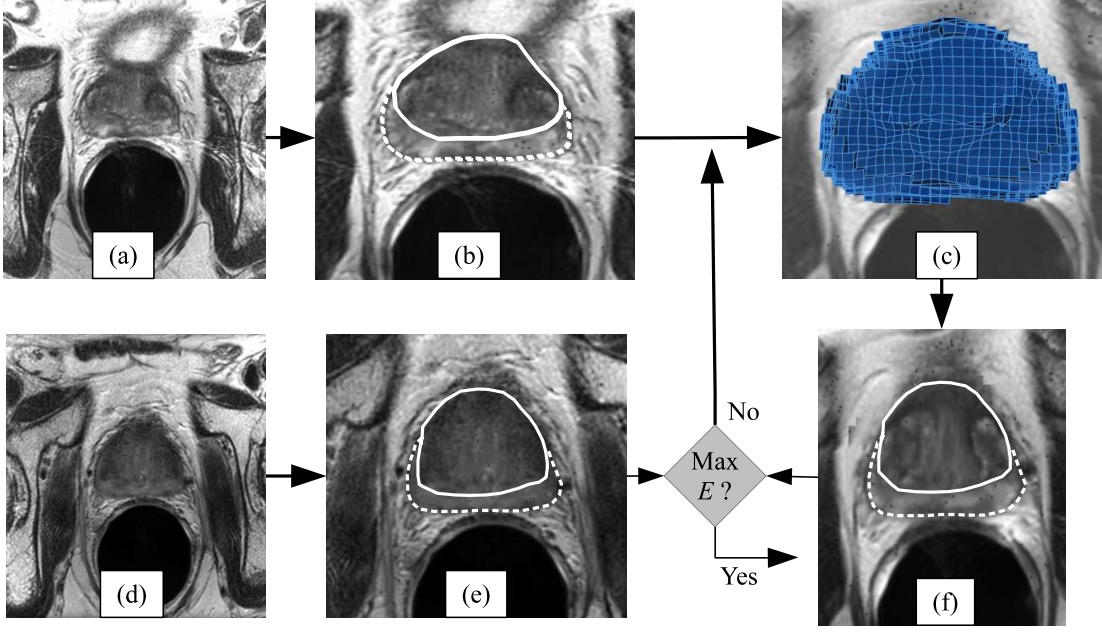


Figure 3.9: Flowchart of DoCD. The pre-EBRT MRI I_{Pre} is shown in (a) and in (b) with the CG and PZ outlines in white solid and dashed lines, respectively. The post-EBRT MRI I_{Post} is shown in (d) and (e). The prostate structures are discretized into an FEM (c) which is used to deform the image. The deformed pre-EBRT $T(I_{Pre})$ is shown in (f). An optimizer induces different deformations until a similarity energy E is maximized.

3.3.5 Optimization of EBRT Shrinking Parameters

We aim to register a pre-EBRT MRI I_{Pre} to a post-EBRT MRI I_{Post} . The goal is to calculate the transformation T , such that,

$$T = \arg \max E(I_{Post}, T(I_{Pre})), \quad (3.27)$$

where T is defined by the magnitude of shrinkage at each node on the surface of the prostate substructures. E is an energy function measuring the degree of overlap, and expressed as,

$$E = \sum_{c \in C} E(c), \quad E(c) = \begin{cases} 1, & \text{if } L_{Post}(c) \equiv L_{Pre}(T(c)), \\ 0, & \text{otherwise.} \end{cases} \quad (3.28)$$

The parameters defining T are modified, and the registration algorithm then proceeds to determine which parameters maximize E , in a manner similar to [96]. A

“particle swarm” optimizer [100] is used, in which 100 random parameters (100 “particles”) are each allowed to converge independently on the maximum E , and the particle with the maximum energy overall is chosen.

Chapter 4

Evaluation of Radical Prostatectomy

4.1 Data Description

Two datasets were used for these experiments: one specifically tailored to evaluate the segmentation methodology, and one to evaluate the prostatectomy volume changes. Some content is taken from [5], on which Robert Toth is the second author.

4.1.1 Segmentation Accuracy Dataset

This datasets consists of 108 prostate endorectal MR images, acquired using T2-weighting protocol and a 3.0 Tesla coil. A detailed description is shown in Table 4.1. The prostate boundaries were manually segmented in 3D by an expert radiologist using the 3D Slicer software [106, 107, 108, 109]. In addition, to help determine inter-expert variability a second expert segmented a subset of the studies. For 17 studies in which a second expert segmented the prostate capsule, the mean Dice Similarity Coefficient value (Equation (4.1)) between the experts' segmentations was 0.899894 with a standard deviation of 0.023272. The raw data for each study was originally $256 \times 256 \times Z$, where $20 < Z \leq 40$. So as not to lose information, the images were upscaled and interpolated so that each image was $256 \times 256 \times 40$ pixels ($P \approx 2.6 \times 10^6$) [1].

Table 4.1: Detailed description of the data used to test the MFLAAM segmentation.

Protocol	T2-weighted, 3.0 Tesla
Image Size (pixels)	$256 \times 256 \times Z$, $20 \leq Z \leq 40$
Field of View (mm)	$140 \times 140 \times Z$, $60 \leq Z \leq 150$
Resolution (mm)	$0.54 \times 0.54 \times Z$, $2.0 \leq Z \leq 3.0$
MRI Acquisition	Fast Spin Echo, Endorectal Coil

4.1.2 Prostatectomy Volume Dataset

From August 2007 to May 2009, 96 consecutive subjects with wholemounted specimens from radical prostatectomy who had undergone preoperative pelvic MR imaging were initially included in our study from the Beth Israel Deaconess Medical Center. Two subjects were excluded for lack of access to MR images. One subject was excluded because MR imaging was performed with a 1.5T magnet. One subject was excluded for lack of endorectal coil use. One subject was excluded because pathologic specimen weight was unavailable. A total of 91 patients (mean age, 59 years; age range, 42-84 years) were included in this data set.

Ninety-one prostates were analyzed with MR images acquired with a 3T wholebody imager (GE Healthcare Technologies, Waukesha, Wis) and an endorectal coil (Medrad, Pittsburgh, Pa) inflated with 60 mL of a 100% weight per volume barium sulfate suspension for improved spatial resolution [110, 111, 112]. T2-weighted MR images were acquired in the axial, coronal, and sagittal planes (repetition time msec/echo time msec, 3300 – 6250/155 – 165; echo train length, 20 – 21; four signals acquired; field of view, 16×16 cm (coronal and sagittal) or 14×14 cm (axial); section thickness, 2.2 – 3.0 mm with no gap). The section thickness varied according to the size of the prostate gland to maintain a consistent imaging time and in-plane resolution [5].

4.2 Experimental Design

4.2.1 Segmentation Accuracy Experiments

Each image was preprocessed to normalize the intensities and remove the bias field [113]. Since the radiologists acquired additional slices past the apex and base, the user manually selected the first and last slices, which were transformed into the appropriate translation and scale in the Z -direction. This served as the only initialization of the model, and hence the MFLAAM segmentation was minimally supervised.

A 5-fold cross validation was performed, in which the data was split into 5 equal partitions. To train, 4/5 of the images were used, and the trained MFLAAM was used to segment the remaining 1/5 of the images, repeated 5 times.

Measures to Evaluate Segmentation Performance

The first measure to evaluate the segmentation result is the Dice Similarity Coefficient (DSC). DSC is volume-based and measures the overlap between two segmentations (higher is better), given as,

$$DSC(C_i, C_\theta) = 2 \cdot \frac{|C_i^{(In)} \cap C_\theta^{(In)}|}{|C_i^{(In)}| + |C_\theta^{(In)}|}. \quad (4.1)$$

The second measure is the Mean Absolute Distance (MAD). MAD measures the average distance between two surfaces (in mm, lower is better), and is calculated as,

$$MAD(C_i, C_\theta) = \frac{1}{|C_\theta^{(On)}|} \cdot \sum_{c_\theta \in C_\theta^{(On)}} \left(\min_{c_i \in C_i^{(On)}} \|c_\theta - c_i\|_2 \right) \quad (4.2)$$

Experiment $\mathcal{E}_1$: Evaluation of Efficiency

This experiment aims to measure runtime efficiency. For this experiment, the number of texture features used was varied from $2 \leq M \leq 7$, and the average time per segmentation was noted, as was the average accuracy in terms of DSC [1].

Experiment $\mathcal{E}_2$: Evaluation of Texture Features

In this experiment, we aimed to determine whether ϕ_j is a useful measure for selecting texture features. The MFLAAM was run using the texture features with the highest ϕ_j scores (Ω_{High}) and lowest ϕ_j scores (Ω_{Low}). Finally, the use of no texture features was explored, where $M = 2$ and $f_{i,2}(k)$ represents the intensity at pixel k . This is analogous to a traditional AAM, which only uses image intensities, and is therefore denoted Ω_{AAM} . A list of models are shown in Table 4.2 [1].

Experiment $\mathcal{E}_3$: Comparison of MFLAAM to Existing Prostate Segmentation Algorithms

This experiment compares the MFLAAM segmentation accuracy in the context of the prostate MRI segmentation schemes by Klein et al. [85], Martin et al. [114, 86],

Table 4.2: Models employed in experiments $\mathcal{E}_2$ and $\mathcal{E}_3$.

Experiment	Model	Model Description
$\mathcal{E}_2$	Ω_{High}	MFLAAM using texture features with high ϕ_j
$\mathcal{E}_2$	Ω_{Low}	MFLAAM using texture features with low ϕ_j
$\mathcal{E}_2$	Ω_{AAM}	MFLAAM with only intensities (no texture features)
$\mathcal{E}_3$	Ω_{ASM}	Multi-Feature ASM [37]
$\mathcal{E}_3$	Ω_{Base}	Ω_{High} results from prostate base
$\mathcal{E}_3$	Ω_{Mid}	Ω_{High} results from prostate midgland
$\mathcal{E}_3$	Ω_{Apex}	Ω_{High} results from prostate apex

Pasquier et al. [87], and Makni et al. [88].

In addition, we show the MFLAAM accuracy for different regions of the prostate. The base is considered the first third of the prostate, the midgland the next third, and the apex the final third. The accuracies are reported independently for each region.

A multi-feature ASM (Ω_{ASM}) was constructed, as described in our previous work [37]. For the Ω_{ASM} , a series of 500 landmarks were placed on the prostate surface in each training image after alignment. Then, a multi-variate, $(M - 1)$ dimensional Gaussian distribution was constructed for each landmark point, serving as a unique appearance model for each of the 500 landmarks. To segment a new image, the location with the highest probability was determined for each landmark point, and the landmark-based shape model was optimally fit to these detected locations, as described in [66].

4.2.2 Prostatectomy Volume Experiments

Prostatectomy Volume Estimation Procedure

Ninety-one prostatectomy specimens (prostate gland with attached seminal vesicles), which were removed during radical prostatectomy, were weighed by a pathologist when fresh. As demonstrated by Rodriguez et al. [115], there is a 0.997 correlation between prostate weight and displaced water volume in milliliters; Varma and Morgan [116] found a similar agreement. Therefore, the specimen weight is used as the true volume of the prostate gland. Rodriguez et al [115] also showed 3.8 g to be the average weight of

seminal vesicles, and this number was subtracted from specimen weight to compensate for the attached seminal vesicles. This calculated weight multiplied by 1.05 g/mL (for prostatic tissue) and served as the reference standard for our study [5, 117].

Experiment $\mathcal{E}_4$: Comparison of Volume Estimation Methods

Total prostate volumes were calculated from T2-weighted axial MR images in a prospective real-time reading fashion as part of the routine clinical interpretation by members of the clinical radiology team (seven fellowship-trained radiologists with 1 to 20 years of experience reading prostate MR images, who are hereafter collectively referred to as reader 1) and retrospectively by a radiologist (with 9 years of experience interpreting prostate MR imaging, hereafter referred to as reader 2) who was not involved in any of the prospective clinical interpretations of reader 1.

Readers calculated the volume V by using the standard ellipsoid formula:

$$V = D_{AP} \cdot D_{ML} \cdot D_{TV} \cdot \pi/6 \quad (4.3)$$

where D_{AP} is the maximum anteroposterior dimension measured on sagittal images, D_{ML} is the maximum craniocaudal dimension measured on sagittal images, and D_{TV} is the maximum transverse dimension measured on axial images.

The MFLAAM was then used to calculate the volume by determining the number of pixels within the prostate shape, and multiplying by the pixel size.

$$V = \left| C_{\theta}^{(In)} \right| \cdot (0.54 \times 0.54 \times 2.2) . \quad (4.4)$$

To establish a surrogate in vivo ground truth, planimetry was performed by two independent readers (reader 3: with less than 1 year of experience; reader 4: with more than 6 years of experience) who did not have prior exposure to the cases. T2-weighted axial MR images of the prostate were analyzed by using a workstation (Advantage 4.0; GE Medical Systems). The prostatic capsule was manually traced by drawing a region on each two-dimensional MR image of the series, which took 5 to 10 minutes per case. Segmentations were initially drawn around the midgland and were then drawn

section by section up to the base and down to the apex. Upon completing the tracing, the software displays the area for each section in square centimeters. The volume was estimated by multiplying the sum of these areas by the section thickness in centimeters.

The Wilcoxon signed rank test was used to compare the mean volume between any two methods. Type I error was adjusted by using the Bonferroni multiple comparison adjustment. The P values were compared with multiple comparison-adjusted type I errors. To assess concordance between two methods, linear regression was used to obtain the individual slope and its 95% confidence interval. To test for the difference between any two of these slopes, linear mixed-effects models [118] with linear contrasts with compound symmetry structure for the variance-covariance were used. In addition, the concordance correlation coefficient and its 95% confidence interval were computed. The percentage of measurements whose between-methods differences were within the limits of agreement from the Bland-Altman plot was also reported. All analyses were performed with SAS software (version 8; SAS Institute, Cary, NC) [5].

4.3 Results and Discussion

4.3.1 Qualitative Results

Figure 4.1 shows qualitative results for two T2-weighted prostate MR images. In both cases, Ω_{High} performed significantly better than both Ω_{Low} and Ω_{AAM} . It can be seen in Figures 4.1(b) and 4.1(d), that all models had trouble segmenting the apex of the prostate, but Ω_{AAM} encountered difficulties with the right side of the prostate. The poor results in the apex are also supported by the results from $\mathcal{E}_3$. Ω_{Low} in Figure 4.1(c) completely missed the peripheral zone, resulting in a DSC value of only 0.62. Examples such as this one lend credence to the necessity for accurate feature selection.

In the second row of Figure 4.1, all models (Ω_{High} , Ω_{Low} , Ω_{AAM}) performed relatively well. All 3 models encountered difficulties near the levator ani muscles on the left side of the prostate, but this was exacerbated in the Ω_{AAM} (Figure 4.1(i)). However, the Ω_{High} still performed slightly better than Ω_{Low} , especially near the apical region closest to the endorectal coil. Figure 4.1 represents the types of errors typically

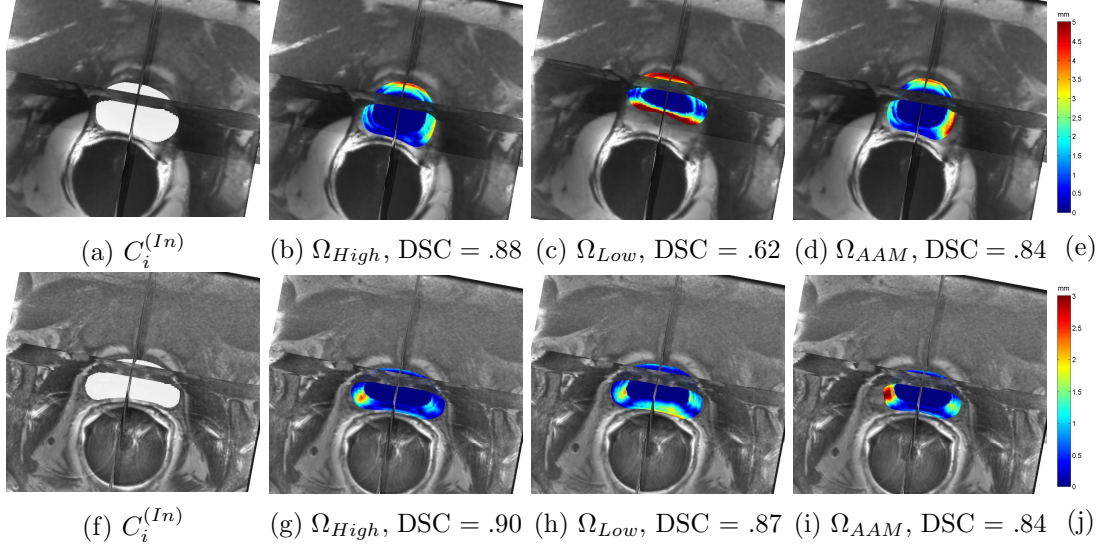


Figure 4.1: Each row represents the results for one T2-w prostate MRI. The ground truth $C_i^{(In)}$ is shown in (a) in (f). The prostate segmentation results obtained via Ω_{High} are shown in the (b) and (g), the corresponding results from Ω_{Low} are shown in (c) and (h), and Ω_{AAM} in (d) and (i). For (b)-(d) and (g)-(i), the T2-weighted MR image is shown in the background, and the segmentation result is shown as a colored surface (heatmap). Hot colors represent large errors while cooler colors represent small errors between the corresponding model and associated ground truth segmentation. For (b)-(d), red represents an error of 5 mm, while in (g)-(i) red represents 3 mm.

seen in the three models tested in Experiment $\mathcal{E}_2$ (Ω_{High} , Ω_{Low} , Ω_{AAM}) and shows the usefulness of accurate feature selection with the MFLAAM.

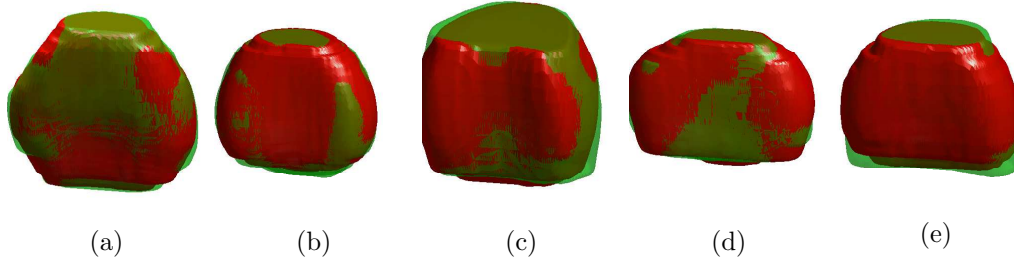


Figure 4.2: Isosurface renderings of the prostate capsule segmentations are shown for I_1 (a) through I_5 (e), in which the ground truth $C_i^{(In)}$ is shown in green and the segmentation $C_\theta^{(In)}$ from Ω_{High} is shown in red.

4.3.2 Experiment $\mathcal{E}_1$: Evaluation of Efficiency

The results from experiment $\mathcal{E}_1$ are displayed in Figure 4.3. The runtimes range from just under 2 minutes per volume to approximately 8 minutes per volume (Figure 4.3(b)). However, no additional improvement in accuracy was noted after the inclusion of the fifth texture feature (Figure 4.3(a)). This suggests that after the first four texture features, minimal correlation exists with the shape information, or that the subsequent texture features chosen by the feature selection scheme had a low signal to noise ratio. Overall, we believe that 3 texture features offer a reasonable trade-off between accuracy and efficiency. Consequently, we chose to use $M = 4$ for experiments $\mathcal{E}_2$ and $\mathcal{E}_3$ [1].

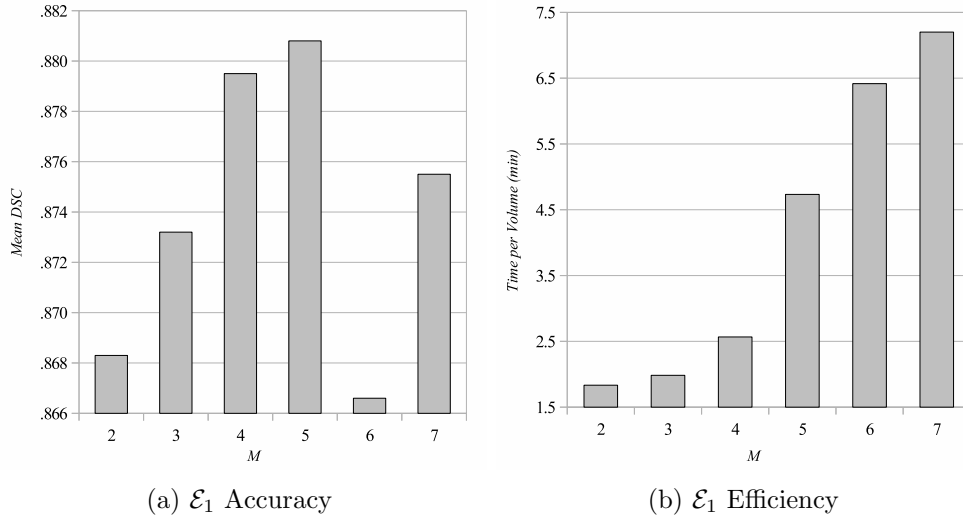


Figure 4.3: Results from experiment $\mathcal{E}_1$, which aimed to explore model efficiency. The mean accuracies (a) and runtimes (b) for the MFLAAM are displayed for different number of texture features. $M = 2$ represents just one texture feature, while $M = 7$ represents six texture features.

4.3.3 Experiment $\mathcal{E}_2$: Evaluation of Texture Features

The first 3 rows of Table 4.3 show the quantitative results for the Ω_{High} , Ω_{Low} , and Ω_{AAM} . We report separate p values from a 1-tailed paired Student's t-test for the DSC values between $\{\Omega_{High}, \Omega_{Low}\}$, $\{\Omega_{High}, \Omega_{AAM}\}$, and $\{\Omega_{AAM}, \Omega_{Low}\}$. A histogram of the DSC values from Ω_{High} over 108 studies is shown in Figure 4.4.

The value of using ϕ_j as a feature selection measure for the MFLAAM can clearly be seen, as Ω_{High} performed significantly better than Ω_{AAM} ($p = .0473$). When comparing Ω_{High} to Ω_{Low} , the results were even more pronounced, with $p = .000171$. Comparing Ω_{Low} to Ω_{AAM} resulted in Ω_{AAM} being significantly better ($p = .0081$). This suggests that the MFLAAM has the potential to perform significantly better than a traditional AAM when the appropriate texture features are selected and used in conjunction with the model [1].

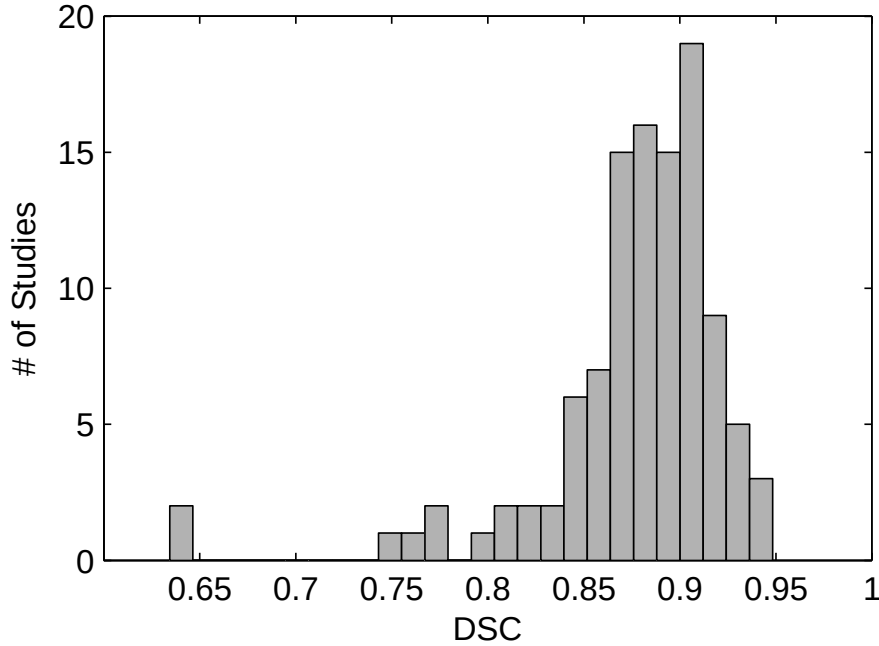


Figure 4.4: A histogram of the DSC results for Ω_{High} is shown for all 108 studies. The mean and median DSC values equal 0.88 with a standard deviation of 0.05.

4.3.4 Experiment $\mathcal{E}_3$: Comparison of MFLAAM to Existing Prostate Segmentation Algorithms

The bottom 5 rows of Table 4.3 show the results from the Ω_{ASM} as well as other prostate MR segmentation algorithms. The number of prostate volume studies tested in [85, 86, 87, 88, 114] range from 12 to 50 studies, with varying degrees of manual intervention, ranging from completely automated to fully interactive initialization of the segmentation. By comparison, our model is being evaluated on 108 studies and requires only very minimal user interaction. It should be noted that since each of the comparative results operated on different datasets, a direct comparison is impossible. This would involve applying a set of algorithms to the same benchmark dataset, utilizing the same ground truth annotations.

The results show that in a quantitative evaluation involving more than twice the number of patient studies used in either of [85, 86, 87, 88, 114], our model yielded a consistent median and average Dice accuracy of .88. This is at least as high, if not higher, than any other state of the art prostate segmentation methods. In addition, our mean absolute distance between surfaces was approximately 1.5 mm, compared to [86], where an error of 2.41 mm was reported.

Ω_{ASM} performed poorly, possibly due to many false positive locations in the image which had a similar appearance to the prostate boundary, and took a much longer time to run on a full 3D volume compared to the MFLAAM. The results for different regions of the prostate showed that the MFLAAM performed extremely well in the base and midgland, but most of the inaccuracies were localized to the apex [1].

Table 4.3: Quantitative results in terms of mean, median, and standard deviations of accuracy for $\mathcal{E}_2$ and $\mathcal{E}_3$. Accuracy values for the MFLAAM are reported separately for the base (Ω_{Base}), midgland (Ω_{Mid}), and apex (Ω_{Apex}). Comparison with other state of the art prostate MR segmentation systems in terms of the number of volumes used in the study, the efficiency (in seconds per volume), and the level of user interaction required, ordered by year are also listed. The best results for each measure for each experiment are bolded.

Exper.	Reference	Volumes	DSC			MAD			Time (s)	Interaction
			Mean	Median	Std.	Mean	Median	Std.		
$\mathcal{E}_2$	Ω_{High}	108	.8766	.8848	.0497	1.51 mm	1.35 mm	.781 mm	154	minimal
	Ω_{Low}	108	.8158	.8673	.1663	2.25 mm	1.56 mm	2.53 mm	154	minimal
	Ω_{AAM}	108	.8599	.8804	.0903	1.64 mm	1.37 mm	.986 mm	110	minimal
$\mathcal{E}_3$	Ω_{ASM}	108	.5898	.6196	.1750	4.85 mm	4.41 mm	3.20 mm	180	none
	Ω_{Base}	108	.8808	.8903	.0596					
	Ω_{Mid}	108	.9141	.9238	.0420					
	Ω_{Apex}	108	.8424	.8672	.0907					
	Pasquier 2007 [87]	24	.879		.04				1200 [88]	medium
	Klein 2008 [85]	50		.85 - .88					900 [88]	none
	Makni 2009 [88]	12	.91		.0260				76 [88]	none
	Martin 2010 [86]	36	.84	.87		2.41 mm			240 [86]	unknown

Table 4.4: Prostate volume as estimated with clinical and MFLAAM methods..

Method	Reader	Mean (mL)	Median (mL)	Range (mL)
Ellipsoid	Reader 1	40.81 ± 21.38	35.40	14.57 – 128.11
Ellipsoid	Reader 2	42.80 ± 21.14	38.58	13.23 – 155.77
Planimetry	Reader 3	41.11 ± 21.44	35.22	12.72 – 139.13
Planimetry	Reader 4	44.81 ± 23.20	39.22	14.70 – 151.94
MFLAAM	N/A	42.62 ± 20.89	37.75	12.54 – 133.41
Prostatectomy	N/A	50.38 ± 19.94	45.36	23.31 – 138.81

4.3.5 Experiment $\mathcal{E}_4$: Comparison of Volume Estimation Methods

Distribution of Volumes

Table 4.4 shows the mean 6 standard deviation, median, and range for prostate volume with each of the six methods. The distributions show asymmetry, with the medians consistently smaller than the means, indicating slight skewness of the right tail. The mean and median prostate volumes with the four MR imaging methods and MFLAAM are consistently smaller than those with the pathologic reference standard. This indicates a potential underestimation of the prostate volume with the MR imaging and MFLAAM methods. The variability in the distribution of these five methods is similar to that of the pathologic reference standard. The P values from Table 1 for comparison of these five methods with the pathologic reference standard indicate that the underestimation is indeed significant (15.8%, $P = .0001$). The first column in Table 4.5 also shows the mean amount and variability of underestimation [5].

Volume Estimates with Ellipsoid

The ellipsoid estimate by reader 1 was the least correlated with the prostatectomy volume (slope, 0.805; 95% CI: 0.707, 0.903). The estimate by reader 2 had a slope of 0.864 (95% CI: 0.786, 0.942) when compared with the prostatectomy. Reader 1 had slopes of 0.910 and 0.987 when compared with planimetry from readers 3 and 4, respectively. When compared with each other, calculations by readers 1 and 2 had a slope of 0.897 (95% CI: 0.810, 0.983). The underestimation of the prostate volume

as compared with the prostatectomy volume was similar for readers 1 and 2 (-9.56 vs -7.58). Reader 2 also had a higher concordance correlation coefficient (0.857 vs. 0.779) and percentage of measurements within the limits of agreement (95.6% vs 92.3%) [5].

Volume Estimates with Planimetry

The slope of the regression model for planimetry volume in comparison to the prostatectomy specimen was 0.864 for reader 3 and 0.804 for reader 4. When the two planimetry data sets were compared, the slope of the line was 1.074 (95% CI: 1.046, 1.101). Reader 4 had a higher concordance correlation coefficient (0.897 vs 0.843) and a similar percentage of measurements within the Bland-Altman limits of agreement (95.6% vs 94.5%) compared with reader 3. The mean underestimation of the prostatectomy volume was smaller in reader 4 than in reader 3 (-5.57 vs -9.26) [5].

Volume Estimates with MFLAAM

Prostatectomy prostate volume was underestimated by a mean -7.76 ± 7.69 with the MFLAAM. The MFLAAM yielded the slope closest to 1.0 when compared with the pathologic reference standard (slope, 0.888; [95% CI: 0.800, 0.976]; concordance correlation coefficient, 0.867) 4.5. MFLAAM prostate volume were compared with planimetry prostate volume; the results were not significant for readers 3 or 4 ($P = .265$ and $.027$, respectively) with the adjusted type I error level of $.004$. The concordance correlation coefficient between MFLAAM and the pathologic reference standard was 0.867, with 93.4% of the measured differences within the Bland-Altman limits of agreement [5].

4.3.6 Discussion of Prostatectomy Volume Estimation

The best estimates of prostatectomy prostate volume were obtained with the MFLAAM algorithm and planimetry as performed by reader 4. Furthermore, the MFLAAM planimetry-determined volumes showed substantial overlap in slopes and confidence intervals, suggesting MFLAAM is an appropriate surrogate for planimetry. Though readers 1 and 2 showed strong agreement with one another (slope, 0.897; 95% CI:

0.810, 0.983), the differing slopes suggest that ellipsoid volume measurements have a user dependence. It is also possible that there is dependency on the interpretive circumstance, since reader 1 prostate volumes were generated during clinical interpretations, whereas reader 2 prostate volumes were generated in a dedicated research mode, isolate from the distractions encountered in clinical practice. It is interesting that the ellipsoid based prostate volumes showed a stronger relationship to planimetry prostate volumes than to prostatectomy prostate volumes, whereas MFLAAM volumes showed a stronger relationship to prostatectomy volumes. When the ellipsoid prostate volumes were compared with the *in vivo* ground truth of planimetry volumes, the regression line slopes were closer to 1.0, indicating a stronger relationship with *in vivo* images than with prostatectomy specimens [5].

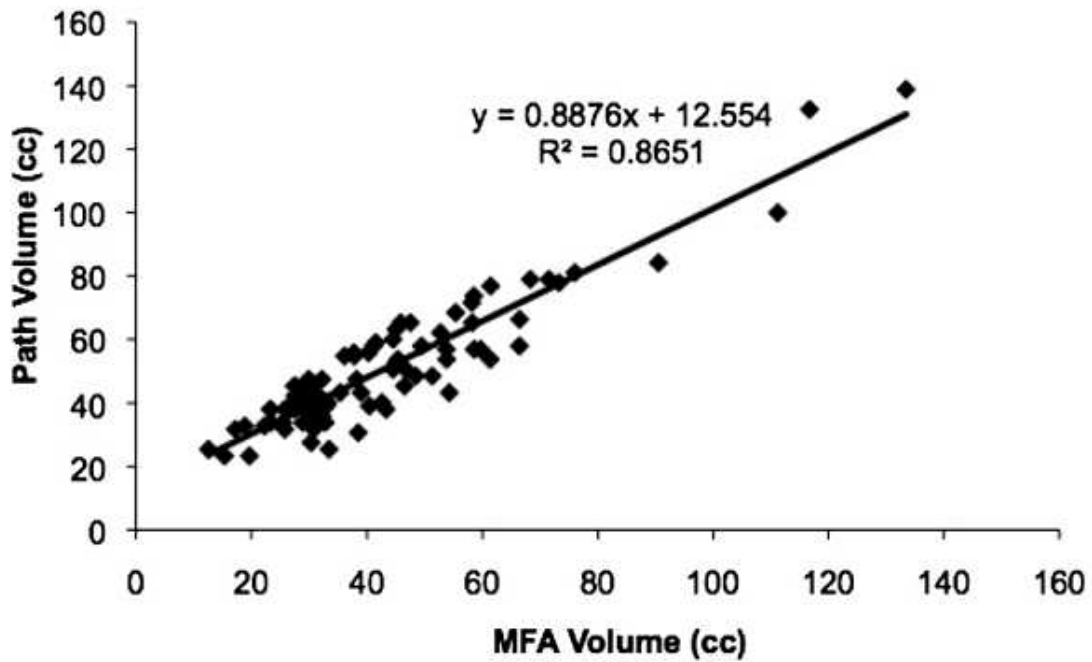


Figure 4.5: MFLAAM volume estimates (x-axis) compared to prostatectomy (y-axis).

Table 4.5: Linear regression data for clinical and MFLAAM volume measurements. The mean volumes are ± 6 standard deviations. Bonferroni-adjusted type I error set at .003 (.05 divided by 15 comparisons). For the concordance coefficient, the data in parentheses are 95% confidence intervals. For the final columns, the limits were the upper and lower bounds from the Bland-Altman plot.

Comparison	Mean difference	P Value	Regression	95% C.I. of Slope	Concordance Correlation Coefficient	Measurements within Limits of Agreement
Ellipsoid vs prostatectomy:						
Reader 1	-9.56 ± 10.88	.0001	$y = 0.805x + 17.51$	0.707, 0.903	0.779(0.707, 0.852)	.923
Reader 2	-7.58 ± 8.49	.0001	$y = 0.864x + 13.39$	0.786, 0.942	0.857(0.807, 0.907)	.956
Planimetry vs. prostatectomy:						
Reader 3	-9.26 ± 7.92	.0001	$y = 0.864x + 14.85$	0.793, 0.935	0.843(0.792, 0.9895)	.945
Reader 4	-5.57 ± 8.34	.0001	$y = 0.804x + 14.32$	0.741, 0.867	0.897(0.858, 0.835)	.956
MFLAAM vs. prostatectomy:						
	-7.76 ± 7.69	.0001	$y = 0.888x + 12.55$	0.800, 0.976	0.867(0.821, 0.913)	.934
MFLAAM vs. Ellipsoid:						
Reader 1	$+1.79 \pm 12.36$	.225	$y = 0.849x + 4.65$	0.730, 0.967	0.828(0.763, 0.893)	.956
Reader 2	-0.18 ± 10.29	.700	$y = 0.891x + 4.82$	0.791, 0.990	0.882(0.836, 0.928)	.934
Ellipsoid vs. planimetry:						
Reader 1 vs. reader 3	-0.30 ± 9.22	.756	$y = 0.910x + 3.975$	0.822, 0.998	0.908(0.872, 0.944)	.934
Reader 1 vs. reader 4	-4.00 ± 9.61	.105	$y = 0.987x + 1.081$	0.893, 1.081	0.894(0.853, 0.935)	.967
Reader 2 vs. reader 3	$+1.68 \pm 5.34$	.381	$y = 0.983x - 0.935$	0.930, 1.036	0.966(0.952, 0.980)	.934
Reader 2 vs. reader 3	-2.01 ± 5.35	.0001	$y = 1.070x - 0.990$	1.019, 1.121	0.967(0.954, 0.981)	.923
Planimetry vs MFLAAM:						
Reader 3	-1.50 ± 9.38	.265	$y = 0.879x + 6.475$	0.791, 0.967	0.900(0.861, 0.939)	.934
Reader 4	$+2.19 \pm 9.70$	.027	$y = 0.818x + 5.955$	0.739, 0.896	0.900(0.861, 0.939)	.934
Planimetry:						
Reader 3 vs. reader 4	-3.69 ± 3.25	.162	$y = 1.074x + 0.661$	1.046, 1.101	0.976(0.967, 0.985)	.956
Ellipsoid:						
Reader 1 vs. reader 2	-1.98 ± 9.17	.222	$y = 0.897x + 6.190$	0.810, 0.983	0.904(0.866, 0.942)	.945

Since the reference standard for comparison is uncertain, it remains a choice whether to prefer a method that aligns better with prostatectomy or *in vivo* planimetry volumes. However, the lower bound slope of the best-performing volume estimation method (MFLAAM) versus the prostatectomy reference standard can be as low as 0.800, indicating up to a 20% underestimation of prostate volume. All methods showed a similar and consistent underestimation of prostate volume when compared with the prostatectomy reference standard. The clinical implications of this underestimation and inaccuracy should be further investigated.

We recognize that there may be volume changes that occur *in vivo* in MR imaging with an endorectal coil; however, there are also potential volume changes in the *ex vivo* specimens that occur prior to weight measurement. Both of these may be implicated in the increased strength of association between MR imaging ellipsoid volumes and planimetry-generated volumes.

A surrogate *in vivo* ground truth, planimetry, was used in our study to approximate changes that may occur *ex vivo* and for comparison with the volume estimates derived from MR images with an endorectal coil. Heijmink et al [119] showed a significant difference in prostate volume (mean of 18% decrease) when MR images were acquired with an endorectal coil compared with those acquired with a body-array coil. In that study, the anteroposterior dimension was, on average, reduced by 15.7% with an endorectal coil. Such shape and volume changes may be influenced by water loss or physical vasoconstriction from the pressure of the inflated endorectal balloon [119]. Our results show an average underestimation across the five volume measurements of 15.8% when compared with prostatectomy specimens, which is consistent with the findings of Heijmink et al. As a point in favor of imaging with an endorectal coil, the signal-to-noise benefit enables higher spatial resolution for a given imaging time and, therefore, may yield a more accurate delineation of gland borders.

The small differences in MR imaging planimetry results between readers 3 and 4 may be related to experience in determining the prostate gland borders. The results of reader 3 likely benefited from the fact that reader 4 designated the inferior-most and superior-most sections for reader 3. In general, inaccuracies in planimetry may be

related to volume averaging and difficulty in delineating prostate borders, especially at the apex.

We subtracted 3.8 g from each specimen weight to adjust for seminal vesicle contributions to prostate volumes. This produced a shift in data and did not affect the correlation. Despite the strong correlation between specimen weight and true volume, seminal vesicle size can vary substantially between patients, resulting in a small source of error in our study. We recognize concerns about the use of prostatectomy specimens as the reference standard considering the potential *ex vivo* blood loss and the inclusion of periprostatic tissue [120]. Future prospective studies with more precise pathologic analysis (removal of seminal vesicles and periprostatic tissue, immediate weight measurement) may yield additional information on the accuracy of *in vivo* volume estimates with MFLAAM and MR imaging [5].

4.4 Concluding Remarks

We have presented a novel methodology for extending the traditional Active Appearance Model (AAM) framework to include multiple texture features, as well as a landmark-free framework for generating a statistical shape model. We have shown that the amount of information lost by using principal component analysis on a series of texture features, and combining those texture features with a shape model, is minimal compared to a traditional AAM. This is a significant improvement over current state of the art statistical shape models. Our segmentation algorithm employs an advanced feature selection algorithm, and our final MFLAAM yields both accurate and consistent segmentation results, tested over a large cohort of data. In terms of accuracy, level of interaction, efficiency, and consistency over a large number of volumes, the MFLAAM can outperform most other prostate MRI segmentation algorithms.

When comparing the MFLAAM to other clinical prostate volume estimations in the context of radical prostatectomy, we note that no significant differences between methods were demonstrated. However, the trend points toward MFLAAM as having the slope closest to one compared with the prostatectomy reference standard; therefore,

it seems reasonable that MFLAAM can perform at least as well as other methods and should be considered on the basis of its expected practicality in clinical practice. In conclusion, prostate volume estimates with MFLAAM's on axial T2-weighted MR images yield strong approximations of prostatectomy specimen-determined volumes and can serve as a surrogate for MR imaging planimetry determined volumes, offering the prospect for accurate volume determinations in clinical practice.

Chapter 5

Evaluation of External Beam Radiation Treatment

5.1 Experimental Design

5.1.1 PZ/CG Segmentation Experiments

This content is primarily derived from [2], on which Robert Toth is the first author.

Data Description

Our data consists of 40 prostate endorectal MR images, acquired using T2-weighting protocol and a 3.0 Tesla coil. Each image was 512×512 pixels in the x, y directions with a variable number of slices. The prostate capsule, PZ, and CG boundaries were manually segmented in 3D by an expert radiologist using the 3D Slicer software [107, 108, 109]. The raw data for each study was preprocessed to normalize the intensities and remove the bias field [113]. In addition, the variance of each levelset and each intensity image was normalized to a value of 1. Due to the fact that MR imagery of the prostate is used for staging of prostate cancer in the US, and not for screening, all 40 studies have biopsy-confirmed prostate cancer present. A full description of our dataset and associated parameters is shown in Table 5.1 [2].

Table 5.1: Detailed description of the data used to test the MFLAAM.

# of Studies	40 Studies
Protocol	3.0 Tesla, T2-weighted
MRI Acquisition	Fast Spin Echo, Endorectal Coil
Image Size (pixels)	$512 \times 512 \times Z$, $20 < Z < 50$
Field of View (mm)	$140 \times 140 \times Z$, $60 < Z < 150$
Resolution (mm)	$0.27 \times 0.27 \times 3.0$

Implementation Details

The MFLAAM was implemented in C++ using the ITK framework [121]. The MFLAAM was run on a machine with 8 cores (each 2.67 GHz) and 32 GB of memory running Debian Linux, compiled using GCC (version 4.7.1). The segmentation process was performed in a multi-resolution fashion, with $P \approx 10^6$ at the coarsest resolution and $P \approx 10^7$ in the finest resolution. Segmenting the prostate, CG, and PZ on a $140 \text{ mm} \times 140 \text{ mm} \times 140 \text{ mm}$ image took approximately 200 seconds. For all experiments, $\alpha = 0.95$ was used, similar to [67].

Hierarchical Prostate Segmentation

Two specific categories of experiments were performed: non-hierarchical experiments ($\mathcal{E}_1, \mathcal{E}_3, \mathcal{E}_5$) and hierarchical experiments ($\mathcal{E}_2, \mathcal{E}_4, \mathcal{E}_6$). The non-hierarchical experiments used only the imaging information to simultaneously segment the prostate, CG, and PZ. Therefore, for $K = \emptyset$, as only the intensities were used to segment the objects. The hierarchical experiments used the imaging information, as well as the known segmentation of the prostate, to segment the CG and PZ, and thus $K = \{\text{Prostate}\}$. Due to the fact that CG and PZ are embedded within the prostate itself, using a segmentation of the prostate boundary forces the MFLAAM to only consider the desired region of interest. This is also similar to the approach taken in [122], which assumed the prostate was already segmented prior to segmenting the PZ and CG.

Cross Validation Experiments

For both the hierarchical experiments and the non-hierarchical experiments, both a leave-one-out cross validation, and a 30-run, 5-fold cross validation were performed. For the leave one out experiments ($\mathcal{E}_1, \mathcal{E}_2$), for each image I_n , the MFLAAM was trained using the other 39 studies. For each run of 5-fold cross validation experiments ($\mathcal{E}_3 - \mathcal{E}_6$), the dataset was randomly split into 5 groups of 8 studies per group. Each study in a given group was segmented using an MFLAAM trained from the 32 studies in the other 4 groups, resulting in a segmentation for each study. This was repeated

30 times, resulting in 30 segmentations for each study. The goal of the cross validation experiment is to determine the generalizability of the MFLAAM to different training sets, by determining how well each study was segmented given different training sets, and the variance of the results over the various training sets.

The segmentation result $C_{m,\theta}^{(in)}$ was compared to the ground truth segmentation $C_{m,n}^{(in)}$ using the Dice similarity coefficient (DSC).

$$DSC\left(C_{m,n}^{(in)}, C_{m,\theta}^{(in)}\right) = 2 \cdot \frac{\left|C_{m,\theta}^{(in)} \cap C_{m,n}^{(in)}\right|}{\left|C_{m,\theta}^{(in)}\right| + \left|C_{m,n}^{(in)}\right|}. \quad (5.1)$$

In addition, the Mean Absolute Distance (MAD) between the surfaces was reported, calculated as,

$$MAD\left(C_{m,n}^{(in)}, C_{m,\theta}^{(in)}\right) = \frac{1}{\left|C_{m,\theta}^{(on)}\right|} \cdot \sum_{c \in C_{m,\theta}^{(on)}} \left(\min_{d \in C_{m,n}^{(on)}} \|c - d\|_2 \right) \quad (5.2)$$

where $C^{(on)}$ represents pixels on the surface of the object, and the MAD values are reported in mm.

The results from the prostate, PZ, and CG segmentations from the non-hierarchical experiments ($\mathcal{E}_1, \mathcal{E}_3, \mathcal{E}_5$) are presented, in addition to the PZ, and CG segmentation results from the hierarchical experiments ($\mathcal{E}_2, \mathcal{E}_4, \mathcal{E}_6$). The segmentation results in the midgland of the prostate are presented separately for the area-based DSC values (the boundary-based MAD is not easily defined for separate regions). This was done due to poor boundary contrast in the base and apex of the prostate, preventing accurate segmentations in these regions.

The cross validation experiments resulted in 30 values for each of the 40 studies (1200 total values). Experiments $\mathcal{E}_3$ and $\mathcal{E}_4$ present the results over all 1200 values for the non-hierarchical and hierarchical experiments respectively. To determine the generalizability over different training sets, the median value was computed over the 40 values for each run. The results over the 30 different median values (1 for each run) are presented as $\mathcal{E}_5$ and $\mathcal{E}_6$. Table 5.2 summarizes the different experiments performed [2].

Table 5.2: Description of the leave-one-out and cross validation experiments performed to quantitatively test the MFLAAM. The difference between $\mathcal{E}_3/\mathcal{E}_4$ and $\mathcal{E}_5/\mathcal{E}_6$ is that with $\mathcal{E}_3/\mathcal{E}_4$ we calculate the results over all 1200 trials ($30 \text{ runs} \times 40 \text{ studies}$), while with $\mathcal{E}_5/\mathcal{E}_6$ we calculate the median value for each of 30 runs and calculate the results over all 30 runs to determine the generalizability of the MFLAAM over different training sets.

Experiment	Hierarchical	Runs	Folds	Total # of Trials
$\mathcal{E}_1$	No	1	40	40
$\mathcal{E}_2$	Yes	1	40	40
$\mathcal{E}_3$	No	30	5	1200
$\mathcal{E}_4$	Yes	30	5	1200
$\mathcal{E}_5$	No	30	5	30
$\mathcal{E}_6$	Yes	30	5	30

5.1.2 EBRT Registration Experiments

Data Description

A retrospective cohort of 30 CaP patients had T2-weighted MRI acquired both before and after EBRT. The cohort included patients from between 1991 and 2011 and the selection criteria included patients from UCSF who had both pre-, post-EBRT T2-weighted MRI but no androgen deprivation therapy. In each study, the T2-weighted MRI was acquired using either a 1.5 Tesla or 3.0 Tesla GE MRI scanner. The image sizes were approximately $140 \times 140 \times 140$ mm, and the voxel sizes ranged from $0.27 \times 0.27 \times 2.2$ mm/voxel to $0.54 \times 0.54 \times 3.0$ mm/voxel. A summary is shown in Table 5.3.

Table 5.3: Detailed description of the data used to test DoCD.

# of Patients	30
Protocol	T2-weighted, 3.0 Tesla
Field Strength	1.5 or 3.0 Tesla
Image Size (pixels)	$(256 \times 256 \times 19)$ to $(512 \times 512 \times 35)$
Field of View (mm)	$140 \times 140 \times Z$, $60 < Z < 150$
Resolution (mm)	$(0.54 \times 0.54 \times 3.0)$ to $(0.27 \times 0.27 \times 2.2)$
MRI Acquisition	Fast Spin Echo, Endorectal Coil
Hormonal Therapy	No

Quantitative Measures for Evaluating Registration Accuracy

As in [123, 124], segmentations of the prostatic structures were used to drive the registration. Similar to [90], the center of mass (CoM) of the prostate, and the mean absolute distance (MAD) between the surfaces, were used to evaluate the accuracy of the registration. A registration is considered accurate if the residual error is less than the largest voxel dimension (in our case 3.0 mm) [90]. Moreover, the Dice similarity coefficient [125], which measures the overlap between two volumes (1.0 is a perfect overlap), was also used to evaluate the registration accuracy.

In addition, between 3 and 11 anatomical fiducials (median of 6) were manually identified by an expert corresponding to structures, such as the urethra or calcifications as in [126], visible on both pre-EBRT and post-EBRT imagery. The root-mean-square (RMS) displacement between the fiducials (in mm) was then calculated following the registration, which gives a more unbiased estimate of the registration errors within the prostate. The following measures were used to evaluate the accuracy of the registration comparing $\mathcal{C}_{Post}$, and $T(\mathcal{C}_{Pre})$.

1. Dice coefficient [125] for prostate, CG (0.0 to 1.0, higher is better).
2. Center of Mass (CoM) displacements [90] (mm, lower is better).
3. Mean Absolute Distance (MAD) for surfaces [90] (mm, lower is better).
4. Root Mean Square (RMS) differences between the manually identified fiducials within the prostate [126] (mm, lower is better).

Comparative Strategies

The following strategies were compared against DoCD:

1. An FEM which does not explicitly exploit EBRT domain knowledge.
2. Rigid alignment, in which only translations and rotations (no change in volume) are allowed.
3. Affine alignment, which adds X, Y, and Z scaling terms to a rigid transformation to account for global changes in volume and shearing effects.

We have adopted an implementation of a “traditional” biomechanical FEM (simply referred to as FEM) which contains just as many degrees of freedom as DoCD, is also deformable, and yet does not exploit specific EBRT domain knowledge. The model is based on the FEM in [90] which was used to align prostate surfaces. Young’s modulus was set to 20 kPa, Poisson’s ratio to 0.49, and an iterative closest points algorithm [90] was used to align the prostate surfaces. No information on the internal anatomy of the prostate, nor any specific radiation-induced shrinking effects, was used.

In addition, a rigid registration (translation plus rotation) was used as a comparative strategy in [124] for a deformable registration of pre-EBRT MRI and CT. Rigid was therefore used as a comparative strategy in this study. Moreover, we also compared our strategy to an affine registration, which extends rigid registration by allowing scaling and shearing in each of the 3 dimensions. A comparison with affine will allow us to determine the usefulness of using a linear scaling term to model the EBRT induced shrinkage since rigid does not allow scaling. A statistical test of the results was performed. The null hypothesis was that the mean error between DoCD and the comparative strategy was equivalent for a given strategy.

5.2 Results and Discussion

5.2.1 PZ/CG Segmentation Results

This content is primarily derived from [2], on which Robert Toth is the first author. The quantitative results for the prostate, CG, and PZ for experiments E_1 through E_6 are shown in Figure 5.1. The segmentation of the capsule boundary resulted in a mean *DSC* accuracy of 0.81, and a mean *MAD* value of 1.8 mm. When only considering the midgland of the prostate, the mean *DSC* value for the prostate increased to 0.89, reflecting the tapering off of the gland towards the base and apex [2].

The hierarchical segmentation results E_2 , in which it is assumed that the prostate segmentation already exists, as in [122], resulted in a mean *DSC* value of 0.79 for the CG, and 0.68 for the PZ, with mean *MAD* values of 1.4 mm and 1.0 mm for the CG, and PZ, respectively. When only considering the midgland, the mean *DSC* values were 0.84, and 0.76 for the CG and PZ, respectively. However, when only using the imaging information (non-hierarchical experiment E_1), the mean *DSC* values for the CG and PZ were 0.72 and 0.60 respectively.

Qualitative results from two studies are shown in Figures 5.2 and 5.3. The region in green represents the ground truth segmentations and red represents the segmentation results. The *DSC* values for the prostate, CG, and PZ, were .88, .86, and .76 respectively in Figure 5.2. The *DSC* values for the prostate, CG, and PZ, were .90, .71, and .73 respectively in Figure 5.3. In addition, the reconstruction is shown in Figures 5.2(c) and 5.3(c), which demonstrates that the intensities in a previously unseen study can be reasonably well reconstructed [2].

5.2.2 PZ/CG Segmentation Discussion

The closest related work is [122], which reported mean *DSC* values of 0.89 and 0.80 for the CG and PZ segmentations respectively on multi-spectral (T2-weighted and dynamic contrast enhanced), 1.5 Tesla prostate MRI. When using the ground truth prostate segmentations to drive the CG and PZ segmentations, similar to [122], resulted in *DSC* accuracies of 0.79 and 0.68 for the CG and PZ for the MFLAAM. However, it should

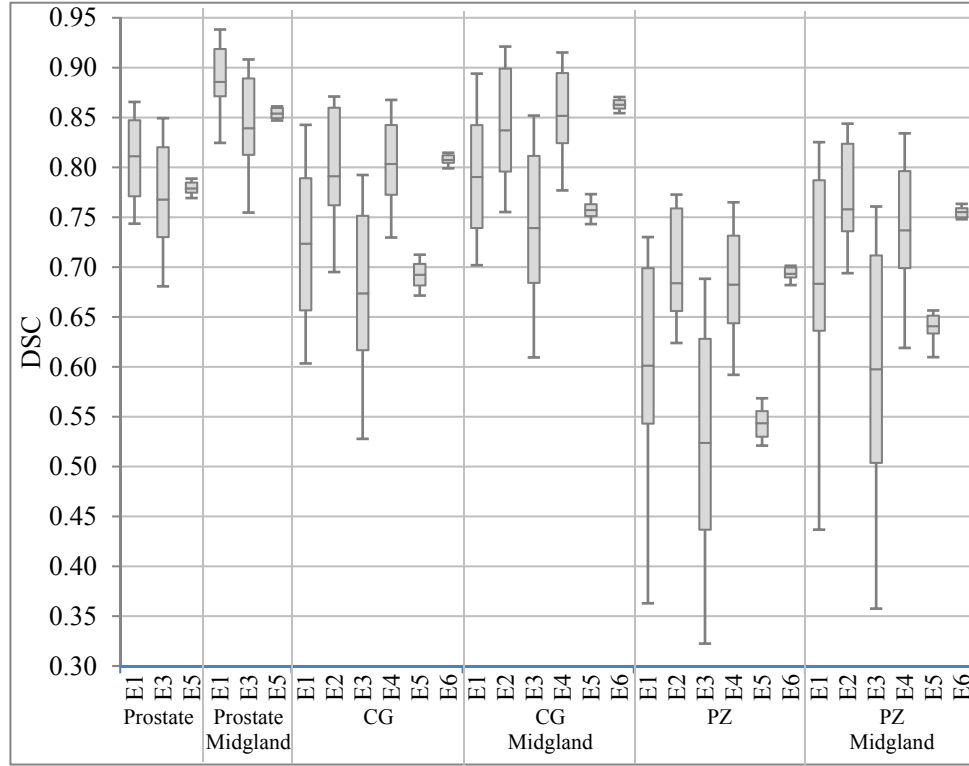
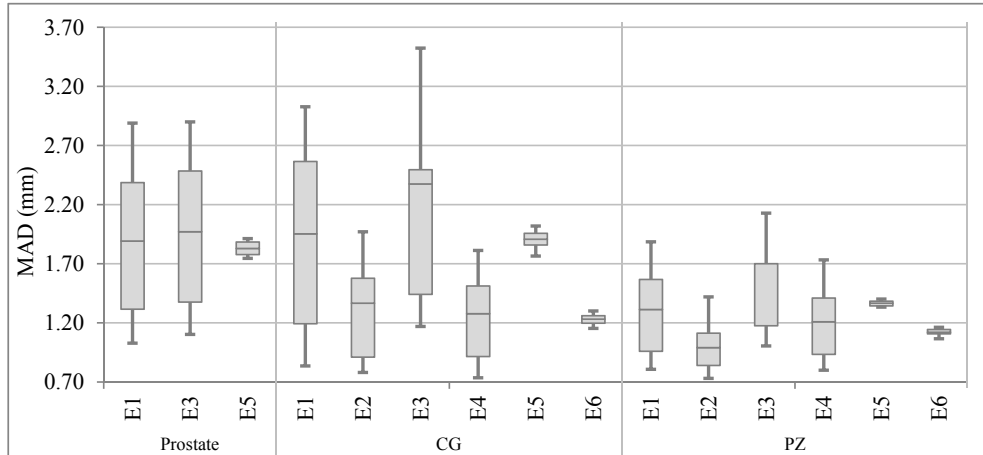
(a) Prostate, CG, PZ *DSC* Values(b) Prostate, CG, PZ *MAD* Values

Figure 5.1: Quantitative segmentation results from experiments $\mathcal{E}_1$ through $\mathcal{E}_6$ for 40 studies segmenting the prostate, CG, and PZ. The mean is given by a solid gray line, the 25th – 75th percentiles are shown as a shaded gray rectangle, and the 10th – 90th percentiles are shown as error bars.

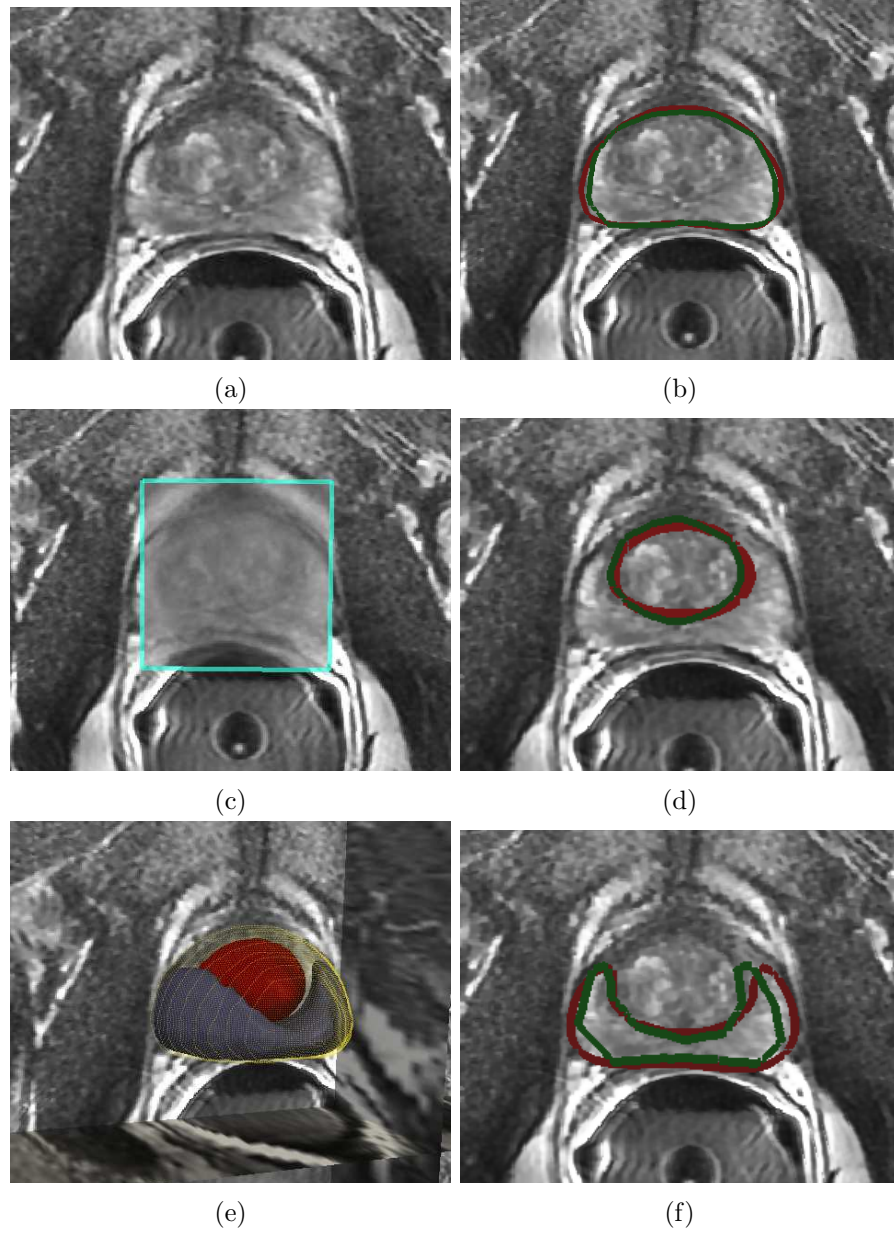


Figure 5.2: (a) illustrates the intensities F_θ of a midgland prostate slice from a 3D, T2-w, endorectal MR image. (c) represents the reconstruction $R(\hat{F}_{T^*})$ resulting from the MFLAAM. (e) illustrates a 3D rendering of the the prostate in light yellow, CG in red, and PZ in dark purple. In (b), (d), and (f), the MFLAAM segmentations are shown in red while the ground truth segmentations are shown in green. (b) illustrates the prostate, with $DSC = 0.878$. (d) represents the CG, with $DSC = 0.861$. (f) illustrates the PZ, with $DSC = 0.764$.

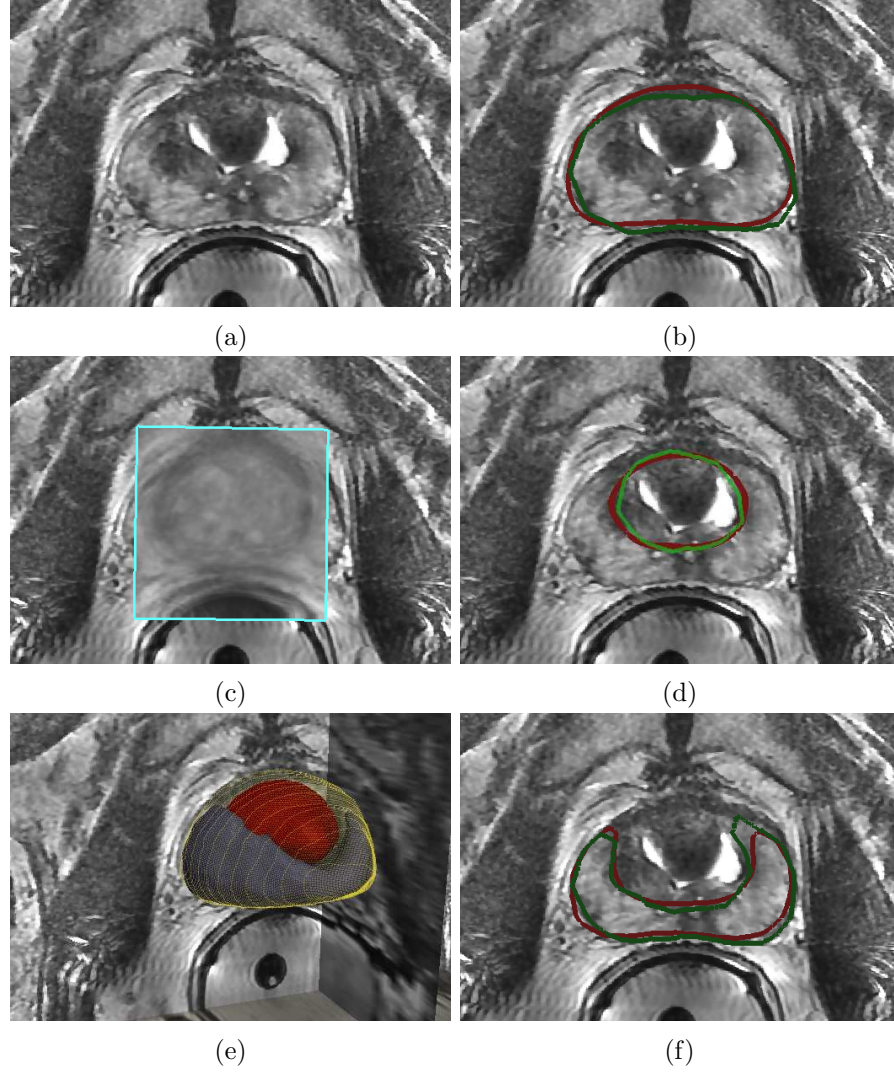


Figure 5.3: (a) illustrates the intensities F_θ of a midgland prostate slice from a 3D, T2-w, endorectal MR image. (c) represents the reconstruction $R(\hat{F}_{T^*})$ resulting from the MFLAAM. (e) illustrates a 3D rendering of the the prostate in light yellow, CG in red, and PZ in dark purple. In (b), (d), and (f), the MFLAAM segmentations are shown in red while the ground truth segmentations are shown in green. (b) illustrates the prostate, with $DSC = 0.90$. (d) represents the CG, with $DSC = 0.81$. (f) illustrates the PZ, with $DSC = 0.73$.

be noted that those reported DSC values in [122] were from a combined STAPLE segmentation of three expert ground truths. When considering only one of the ground truths in [122], the mean DSC values decreased to 0.82 and 0.71 respectively. This is a more appropriate and fairer comparison to the results presented in this work, and also reflects the difficulty of getting accurate expert segmentations for the CG and PZ from prostate MRI. In addition, the data used in [122] contained 31 studies (as compared to the 40 we employed in this study).

Moreover, the algorithm in [122] was specifically designed to intelligently take into account data from multiple modalities such as T1 contrast enhanced and diffusion weighted images, to complement the T2-weighted MR imagery. This allowed the algorithm to extract more accurate CG and PZ boundaries by leveraging additional information that may not be present in T2-weighted MRI. It is not clear how well the algorithm in [122] would perform if only T2-weighted MRI images were available (as in the current dataset). In addition, it is also unclear how well the MFLAAM would perform if other MRI protocols were used in addition to, or instead of, T2-weighted intensities, so a direct comparison is difficult. However, it is important to note that while T2-weighted MRI is routinely performed at all sites where prostate MRI is performed, multi-parametric MRI is only done in a subset of those imaging facilities. Hence our algorithm could be employed on data from a larger number of centers.

To the best of our knowledge, this is the first work exploring a fully automated CG and PZ segmentation algorithm, as [122] only reported results using the ground truth prostate segmentations as the inputs to the algorithm.

In all the cases, the 5-fold cross validation experiments performed worse than the leave-one-out experiments, mainly due to the 20% fewer studies used to train the MLA (32 versus 39 training studies), suggesting the need for a large training cohort. However, the median DSC and MAD values between cross validation runs were remarkably consistent, suggesting very little variance between different training sets [2].

5.2.3 EBRT Registration Results

Qualitative Estimation of Location of DoCD Registration Errors

Qualitative results of the location of DoCD registration errors are shown in Figures 5.4 and 5.5. In each panel of Figure 5.4, the post-EBRT MRI $\mathcal{C}_{Post}$ is shown along with the deformed pre-EBRT MRI $T(\mathcal{C}_{Pre})$. In addition, renderings of the prostate and CG surfaces are shown, in which hot colors represent regions of large error, while cool colors represent regions of low error. Most errors were sub-millimeter. A comparison of DoCD with Rigid, Affine, and FEM registration schemes, in terms of surface errors on the prostate, is shown in Figure 5.5.

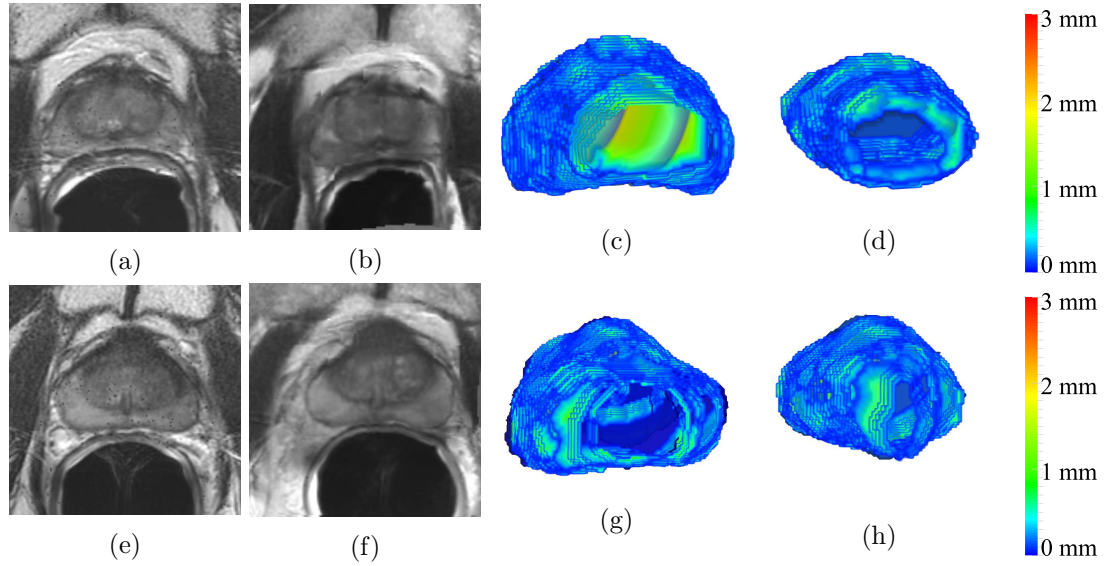


Figure 5.4: Qualitative results showing the location of DoCD registration errors for two studies (one study per row). The post-EBRT MRI $\mathcal{C}_{Post}$ was used as the fixed image, and is shown in ((a)) and ((e)). The deformed pre-EBRT MRI $T(\mathcal{C}_{Pre})$ is shown in ((b)) and ((f)). In ((c)) and ((g)), the surfaces of the post-EBRT prostate are shown in 3D, and colored based on the deformation error. For every voxel on the surface, the closest distance to the prostate on $T(\mathcal{C}_{Pre})$ is calculated and colored, such that blue represents 0 mm (no error) and red represents an error of 3 mm. The same renderings are shown for the CG in ((d)) and ((h)).

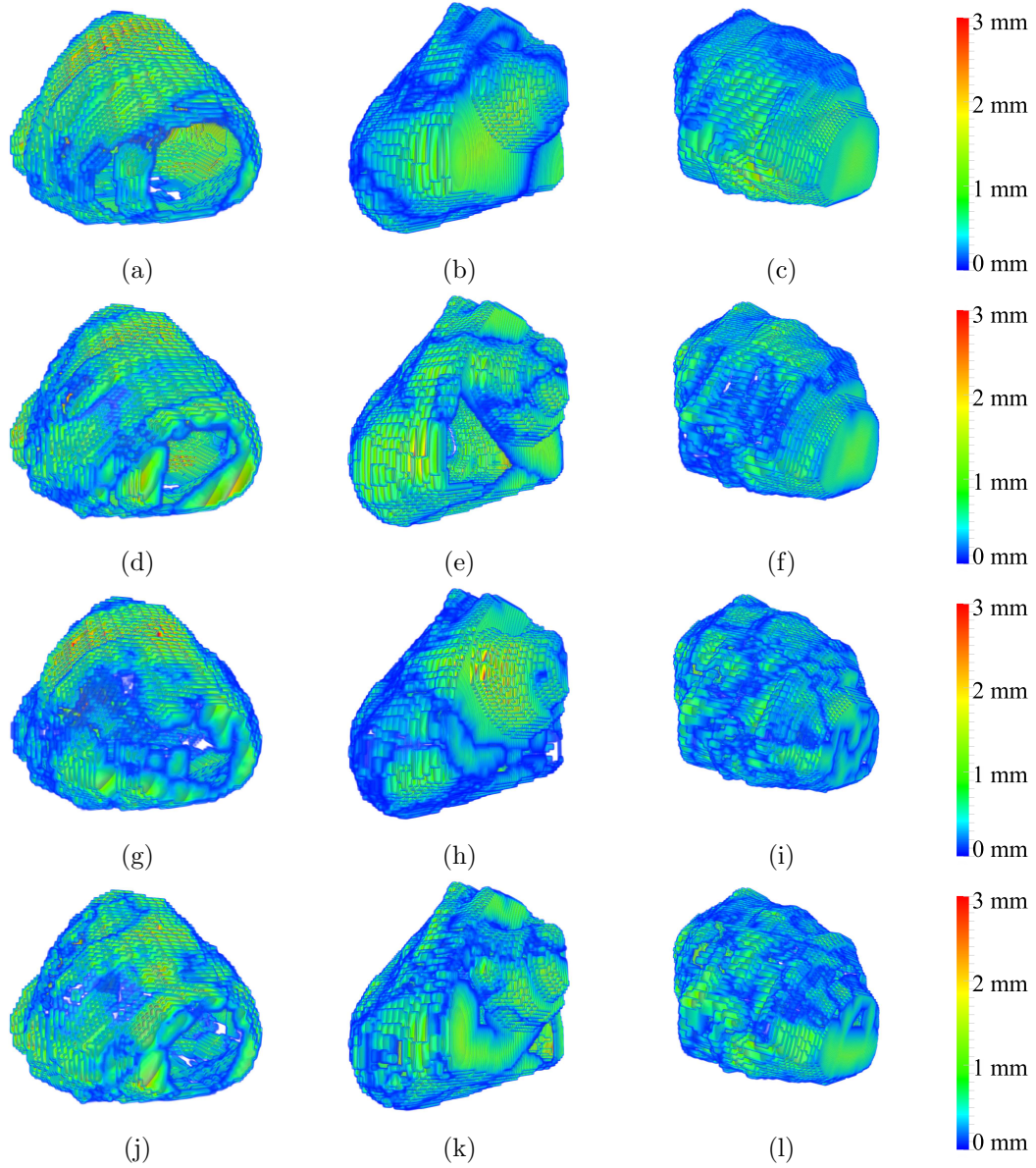


Figure 5.5: Qualitative results comparing the locations of registration misalignments for DoCD and the comparative strategies are shown for three studies (one study per column). Shown are the misalignment locations for Rigid (first row), Affine (second row), FEM (third row), and DoCD (fourth row) schemes. In each image, the prostate surface is colored depending on the surface error at that location, where hot colors represent regions of large error and cool colors represent regions of small error. The errors range from 0 mm (blue) to 3 mm (red) (see Figure 5.4).

Quantitative Evaluation of DoCD versus Comparative Registration Schemes

Quantitative registration errors are shown in Figure 5.6. DoCD outperformed the rigid, affine, and FEM registration schemes in terms of Dice, MAD, CoM and fiducial errors. DoCD yielded mean Dice coefficients for the prostate and CG of 0.896 and 0.902 respectively (median of 0.916 and 0.911). The mean MAD of the prostate and CG surfaces were 0.665 mm and 0.397 mm respectively (median of 0.642 mm and 0.379 mm). The mean CoM displacements of the prostate and CG were 1.104 mm and 0.617 mm respectively (median of 0.598 mm and 0.540 mm). The mean RMS fiducial displacement was 2.994 mm for DoCD (median of 2.894 mm). Results from a Student's t-test are shown in Table 5.4. The null hypothesis was rejected for all results except the prostate surface MAD and CoM of the traditional FEM.

Table 5.4: Results of a 2-tailed paired Student's t-test (p is shown), with statistically significant results indicated by asterisks ($p < .05^*$, $p < .01^{**}$). DoCD was compared to each method in terms of the center of mass (CoM) displacements, the mean absolute distance (MAD) between surfaces, the Dice similarity coefficient, and the root mean square (RMS) error between fiducials.

DoCD vs:	Rigid	Affine	FEM
Prostate Dice	$1.84 \times 10^{-09}^{**}$	$1.32 \times 10^{-06}^{**}$	$1.81 \times 10^{-02}^*$
CG Dice	$8.87 \times 10^{-11}^{**}$	$8.02 \times 10^{-08}^{**}$	$7.11 \times 10^{-07}^{**}$
Prostate MAD	$8.18 \times 10^{-10}^{**}$	$3.62 \times 10^{-09}^{**}$	8.02×10^{-02}
CG MAD	$2.95 \times 10^{-09}^{**}$	$2.69 \times 10^{-09}^{**}$	$3.18 \times 10^{-06}^{**}$
Prostate CoM	$3.60 \times 10^{-04}^{**}$	$9.40 \times 10^{-04}^{**}$	1.29×10^{-01}
CG CoM	$2.30 \times 10^{-03}^{**}$	$1.02 \times 10^{-02}^*$	$3.27 \times 10^{-04}^{**}$
Fiducials RMS	$5.62 \times 10^{-05}^{**}$	$1.18 \times 10^{-02}^*$	$2.80 \times 10^{-10}^*$

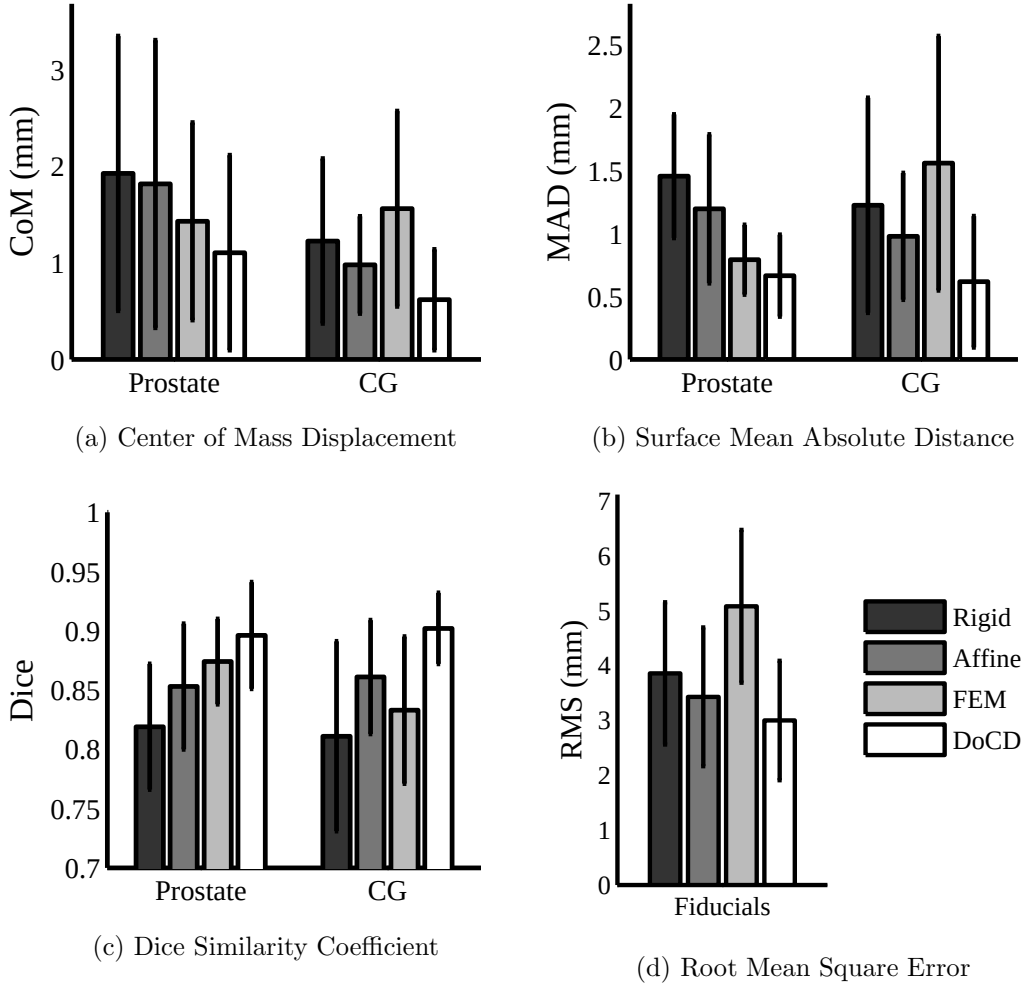


Figure 5.6: Quantitative results comparing the rigid (90% grey), affine (60% grey), traditional FEM [90] (30% grey) and DoCD (white) registration algorithms in terms of the center of mass (CoM) between objects ((a)), the mean absolute distance (MAD) between surfaces ((b)), the Dice similarity coefficient between volumes ((c)), and the RMS distance between fiducials ((d)). The height of the bars represent the mean over 30 studies, and the standard deviations are shown as black error bars.

5.2.4 EBRT Registration Discussion

Comparison of DoCD to Linear Registration

The difference in accuracy between rigid and affine schemes demonstrates the importance of the scaling term for EBRT images. However, while the affine registration yielded better results than rigid registration, the local morphologic deformations modeled by DoCD statistically significantly outperformed the affine registration in terms of

Dice, COM, and MAD measures. Nonetheless, a perfect alignment of the prostate and CG surfaces would have yielded a “perfect” Dice measure of 1.0, and “perfect” CoM & MAD errors of 0.0 mm, yet could yield completely unrealistic deformations within the prostate. This underlies the necessity of evaluating the registration accuracy with manually identified fiducials within the prostate. The statistically significant improvements noticed in the Dice, CoM, and MAD evaluation measures are also apparent in the fiducial errors, suggesting that DoCD is better able to capture the internal deformations occurring after EBRT. In addition, in 16 of the 30 cases, the fiducial displacements were within the inter-slice resolution of the MRI.

Comparison of DoCD to Traditional FEM

Even though both DoCD and the traditional FEM accurately deformed the prostate surface (as demonstrated in the prostate Dice values), there was a minor significant improvement in the prostate Dice values in DoCD. This suggests the importance of explicitly incorporating the EBRT induced shrinkage, represented by the low Poisson’s ratio in DoCD. However, there were no significant differences in the CoM and MAD values between DoCD and the FEM.

The traditional FEM yielded noticeably poor results in the CG evaluation, even compared to the rigid and affine results. The most noticeable results, however, are in the fiducial displacements, in which the FEM was outperformed by all comparative strategies. The fact that the FEM had better prostate Dice, MAD, and CoM values than rigid and affine, and yet poorer CG and fiducial values, suggests that while the FEM aligned the prostate surfaces quite well, it did not accurately model the internal changes to the prostate as a result of EBRT. Our DoCD method, comparatively, was able to align the prostate surfaces well, in addition to the internals of the prostate, thus showing the importance of the domain knowledge incorporated into the model.

5.3 Concluding Remarks

Radiation treatment aims to destroy cancerous cells with ionizing radiation, and pre- and post-EBRT treatment MRI can potentially be used to determine treatment related changes in the gland. However, to quantify these changes, the pre- and post-EBRT MR images must first be segmented and then registered.

To segment the internal structures of the prostate (the PZ and CG) the MFLAAM was extended to simultaneously segment multiple shapes. The multi-shape MFLAAM presented uses the texture features, as well as the existing prostate segmentation, to drive the simultaneous segmentations of the PZ and CG. This is accomplished using knowledge of the shapes of various objects, and how those shapes correlate with textures. The algorithm was tested on 40 T2-weighted, 3D, endorectal, 3.0 Tesla, prostate MRI images containing ground truth segmentations of the prostate, central gland (CG), and peripheral zone (PZ). Most existing prostate segmentation algorithms only segment the prostate boundary, and yet CG and PZ segmentations are critical for cancer detection and treatment planning. When using the intensities and known prostate segmentations, mean DSC values of 0.79 and 0.68 were reported for the CG and PZ, respectively.

Once the PZ and CG were segmented, a domain-constrained deformable model (DoCD) was employed to register the pre-, post-EBRT MRI. Challenges of such a registration technique arise from the significant changes to gland morphology following radiation treatment, specifically local gland shrinkage arising from a reduction in tumor volume, as well as atrophy of benign tissue. In this work we presented DoCD, a biomechanical model for simulating the effects of radiation on the internal substructures of the prostate. DoCD has been applied to register images from 30 patients who have undergone external beam radiation therapy (EBRT) for prostate cancer. Qualitative and quantitative results demonstrate the efficacy of this model. Each patient had internal fiducials manually identified for evaluating the accuracy. DoCD achieved a root mean square fiducial error of 2.994 mm, which was statistically significantly better a traditional biomechanical model (mean of 5.071 mm).

Chapter 6

Evaluation of Focal Laser Ablation Treatment

6.1 Focal Laser Ablation Registration Methodology

6.1.1 Notation and Overview

A 3D MRI scene $I = (C, f(c))$ is defined by a collection of voxels $c = (x_c, y_c, z_c)$, $\forall c \in C$, and MRI intensity information for each voxel, $f(c) \in \mathbb{R}$, $\forall c \in C$. The pre-FLA MRI is denoted as I_{Pre} and the post-FLA MRI is denoted as I_{Post} . An image scene deformed by transformation T is defined as,

$$T(I) = (C, f(T(c))), \quad (6.1)$$

where $T(c)$ represents the transformation of voxel c . $T(C)$ represents the collection of transformed voxels, $T(C) = \{T(c) \mid \forall c \in C\}$.

Following treatment, we assume the prostate undergoes transformations due to different patient alignment within the MRI machine (T_1), transformations due to changes in surround tissue (T_2), and FLA-induced transformations (T_3). Therefore,

$$C_{Post} = T_1(T_2(T_3(C_{Pre}))). \quad (6.2)$$

It follows that,

$$T_3(C_{Pre}) = \hat{T}_2(\hat{T}_1(C_{Post})), \quad (6.3)$$

where $\hat{T}$ represents the inverse transformation. The following sections outline the procedure for calculating the inverse transformations $\hat{T}_1$, $\hat{T}_2$, thereby removing the effects of those transformations. This leaves only the FLA-induced morphologic changes to

the prostate, T_3 . In addition, once $\hat{T}_1$, $\hat{T}_2$, and T_3 are known, the MRI parameters can be compared between $T_3(I_{Pre})$ and $\hat{T}_1(\hat{T}_2(I_{Post}))$, which represents spatially aligned, pre-, post-FLA MRI.

6.1.2 Linear Alignment $\hat{T}_1$

The first step in accounting for the FLA induced deformation is to linearly align the pre-, post-FLA MRI. A linear transform is defined by translation, rotation, and scaling, in each of the three dimensions. The mutual information (MI) between the pre-, post-MRI is used as the metric to guide the linear registration. A gradient descent optimizer is used to determine which transformation yields the maximum MI , defined as,

$$\hat{T}_1 = \arg \max_T MI(T(I_{Post}), I_{Pre}). \quad (6.4)$$

6.1.3 Modelling Changes from Surrounding Tissue $\hat{T}_2$

Even after taking account patient motion and position within the MRI between visits (defined by $\hat{T}_1$), changes in tissues surrounding the prostate, such as the bladder and rectum, can cause deformations to the gland. To model how the bladder and rectum deform, an FEM is created by defining forces at the surface of these structures. The direction and magnitude of the forces are defined by deforming the bladder and rectum on $\hat{T}_1(I_{Post})$ towards the bladder and rectum on I_{Pre} . Figure 6.1 shows the process of removing the deformations due to the bladder and rectum from the images. The FEM calculates the deformation for the entire image given the forces at the surface of the bladder and rectum. These deformations are applied to the prostate, yielding only the deformations due to the FLA remaining. The FEM based deformations (from the bladder and rectum on post- to pre-FLA) is denoted as,

$$\hat{T}_2 = FEM_{BR}(\hat{T}_1(I_{Post}), I_{Pre}), \quad (6.5)$$

where $FEM_{BR}(a, b)$ represents the FEM-induced deformations due to deforming the bladder and rectum from a to b .

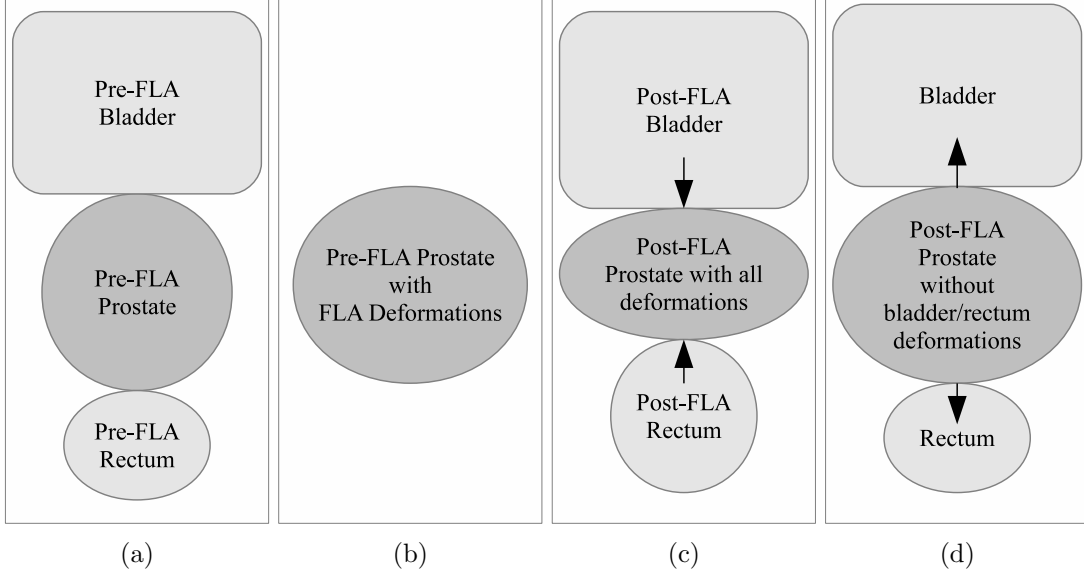


Figure 6.1: (a) represents the pre-FLA prostate, bladder, and rectum I_{Pre} . Following the FLA treatment, the prostate is deformed, represented in (b) as $T_3(I_{Pre})$, which we aim to recover in this work. However, there are changes to the bladder and rectum between the acquisition of the pre-FLA MRI (a) and post-FLA MRI (c) (I_{Post}), represented in this example by forces angled towards the center of the prostate in (c). To recover only the FLA-induced changes to the prostate, a FEM determines which forces will deform the post-FLA bladder/rectum to the pre-FLA bladder/rectum. This is shown by forces in (d) angled away from the prostate, yielding $\hat{T}_2(\hat{T}_1(I_{Post}))$. Notice that the prostate in (d) is most similar to the prostate in (b).

6.1.4 FLA Induced Prostate Deformations T_3

$\hat{T}_2(\hat{T}_1(I_{Post}))$ represents the post-FLA image with the deformations due to the bladder and rectum removed. To model the FLA induced changes to the prostate, a FEM of the prostate is generated, and the prostate on $\hat{T}_2(\hat{T}_1(I_{Post}))$ is deformed to best first the prostate on I_{Pre} . This deformation is denoted as T_3 , defined as,

$$T_3 = FEM_P(I_{Pre}, \hat{T}_2(\hat{T}_1(I_{Post}))). \quad (6.6)$$

where $FEM_P(a, b)$ represents the FEM-induced deformations due to deforming the prostate from a to b . T_3 represents the morphological changes solely due to the FLA. $T_3(I_{Pre})$ and $\hat{T}_2(\hat{T}_1(I_{Post}))$ represent spatially aligned pre-, post-FLA MRI respectively.

6.2 Experimental Design

6.2.1 Data Description

A retrospective cohort of 10 CaP patients had T2-weighted MRI acquired both before and after FLA. The cohort included patients from between 2008 and 2011. In each study, the T2-weighted MRI was acquired using a 3.0 Tesla MRI scanner without an endorectal coil. None of the patients in this cohort had androgen deprivation therapy. The image sizes were approximately $140 \times 140 \times 140$ mm, and the voxel sizes ranged from $0.27 \times 0.27 \times 2.2$ mm/voxel to $0.54 \times 0.54 \times 3.0$ mm/voxel.

6.2.2 Testing Accuracy of T_2 via Synthetic Deformations

$\hat{T}_2$ aims to remove the deformations on the prostate due to surrounding tissues. In this experiment, T_2 is synthetically generated (defined as $\tilde{T}_2$) in order to quantify the accuracy of the inversion. If $\hat{T}_2$ perfectly recovered the deformations due to the bladder and rectum, then $\hat{T}_2 = \left(\tilde{T}_2\right)^{-1}$

An FEM model of the bladder and rectum was created for the pre-FLA image on one study I_{Pre} , and known forces at the surface were induced to generate a synthetic transformation $\tilde{T}_2$. The forces were chosen to deform the pre-FLA bladder and rectum towards the post-FLA bladder and rectum for the same study. This yields a synthetic post-FLA $\tilde{I}_{Post}$. Let C_{Pre}^P represent the pre-FLA prostate voxels, and $\tilde{C}_{Post}^P = \tilde{T}_2(C_{Pre}^P)$ represents the synthetically deformed post-FLA prostate voxels. The Dice similarity coefficient [125] between C_{Pre}^P and $\hat{T}_2(\tilde{C}_{Post}^P)$ was used to determine the accuracy of the inversion, where a Dice of 100% indicates $\hat{T}_2 = \left(\tilde{T}_2\right)^{-1}$.

6.2.3 FLA Induced Deformations

For each step in the registration process, one image is fixed as the reference, and another image is considered the moving image, outlined in Table 6.1. The first two steps bring I_{Post} into the frame of reference of I_{Pre} , after which the FLA-induced changes to the prostate are calculated to deform the pre-FLA MRI onto the post-FLA MRI in which all external deformations have been removed. The final deformation, T_3 represents the

Table 6.1: Description of the registration steps for the experiments. Specifically which images were used as fixed and moving in each of the steps in the registration process. The final result is the FLA-induced morphological changes (T_3) as well as spatially aligned pre-, post-FLA images.

Registration Step	Fixed Image	Moving Image	Moved Image
1. Linear	I_{Pre}	I_{Post}	$\hat{T}_1(I_{Post})$
2. Bladder/Rectum	I_{Pre}	$\hat{T}_1(I_{Post})$	$\hat{T}_2(\hat{T}_1(I_{Post}))$
3. Prostate FLA	$\hat{T}_2(\hat{T}_1(I_{Post}))$	I_{Pre}	$T_3(I_{Pre})$

morphological changes in the prostate due to the FLA treatment. This is compared to the location of treatment in order to determine if the FLA-induced morphological changes at the site of necrosis.

6.3 Results and Discussion

The synthetic experiments outlined in Section 6.2.2 resulted in a mean Dice score of $93\% \pm 2\%$, suggesting that the FEM was able to accurately recover the bladder and rectum deformations. Figure 6.2 shows the qualitative results of T_2 in Figure 6.2(b) and the result of the recovered deformation $\hat{T}_2$ in Figure 6.2(c). In this case, the change in the rectum (pale blue, below) was the primary driving force in pushing the prostate (teal) upwards, near the apex. The pulling effect caused by bringing the rectum back to its original position caused the inverse deformation in the prostate, yielding a high overlap with the original prostate in Figure 6.2(c).

Figure 6.3 shows the prostate volume before and after FLA treatment. The median pre-FLA volume was 51.0 ml and the median post-FLA volume was 47.7 ml, a decrease of 5.1%. This decrease suggests that the necrosis caused by the FLA treatment caused shrinking effects within the prostate. However, in Patient #1, which had the largest prostate, the volume actually increased. Future work will aim to determine if the change in volume is correlated to treatment outcome.

Figure 6.4 shows the registration result for three patients in order to determine where the morphological changes in the prostate occurred. Each patient is shown as a

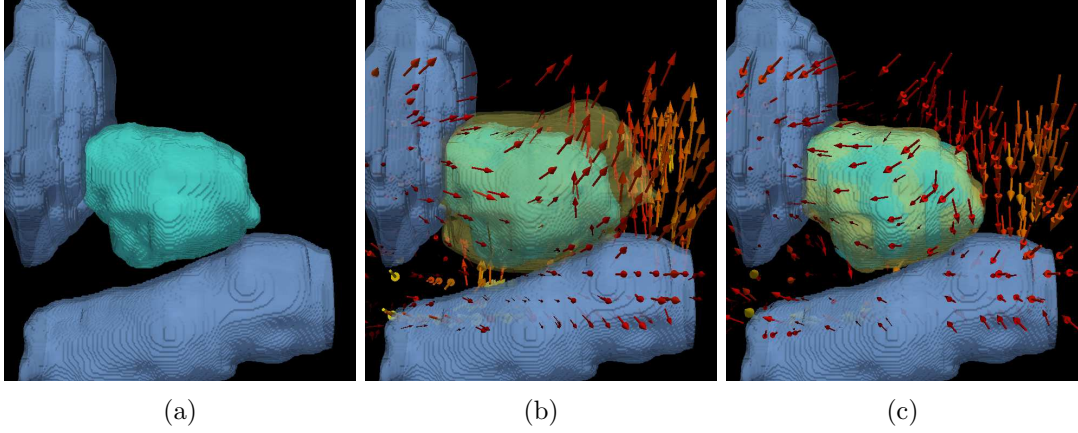


Figure 6.2: (a) represents the bladder and rectum in pale blue, and prostate in teal. (b) represents the result of the synthetic deformation T_2 . The deformed prostate is shown in yellow, and the arrows represent the direction of the transform (in this case mostly due to the rectum). (c) represents the result of the recovered deformation $\hat{T}_2$. The deformed prostate is shown in yellow, and the high level of overlap with the original, undeformed prostate, can be seen.

column. The first row shows I_{Pre} , the second row shows a live image of the ablation needle during treatment, and the third row shows I_{Post} . The slight change in volume in the prostate can be visible in I_{Post} . The registration result T_3 is shown in the fourth row. The arrows represent the direction of the morphological changes, and in all cases they point inwards towards the centroid of the prostate close to the site of ablation. In addition, the heatmap shows the magnitude of morphological changes ($\|T_3(c) - c\|_2$), where red represents a small change and white represents a large change. These results show that the slight decrease in volume of the prostate occurred at the site of ablation, suggesting that the FLA-induced necrosis caused a change in prostate morphology. Future work will follow these patients and attempt to correlate the location and degree of morphological changes with patient outcome.

Figure 6.5 shows the registration result of a given patient, with spatially aligned pre-FLA ($T_3(I_{Pre})$, Figure 6.5(a)) and post-FLA ($T_3(I_{Pre})$, Figure 6.5(a)) MRI. This particular patient had two sites of ablation, shown by the MRI images during treatment in Figures 6.5(c) and 6.5(d). The changes in MRI intensity values are shown as a colored heatmap in Figures 6.5(e) and 6.5(f). Hot colors represent areas of large changes and cooler colors represent areas of small changes. The first thing to notice is that there

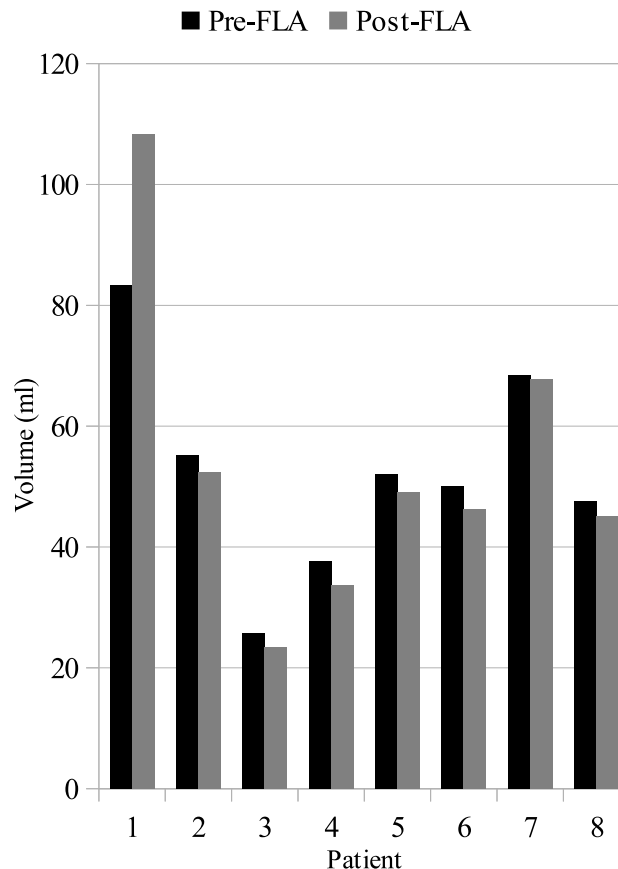


Figure 6.3: The volume of eight patients pre-, post-FLA. The median change was a 5% decrease in volume.

are some hot regions at the top of the prostate due to minor registration edge artifacts. This was caused by a very slight misalignment of the prostate boundaries at that region. However, at the two FLA locations, there is significant necrosis following treatment, showing up as dark regions in Figure 6.5(b), and as hot colors in Figures 6.5(e) and 6.5(f). This result paves the way for quantifying the effect of radiation treatment, and allows for a quantifiable way to track patients over time. Future work will aim to determine if the magnitude and location of changes in MRI parameters are correlated with patient outcome.

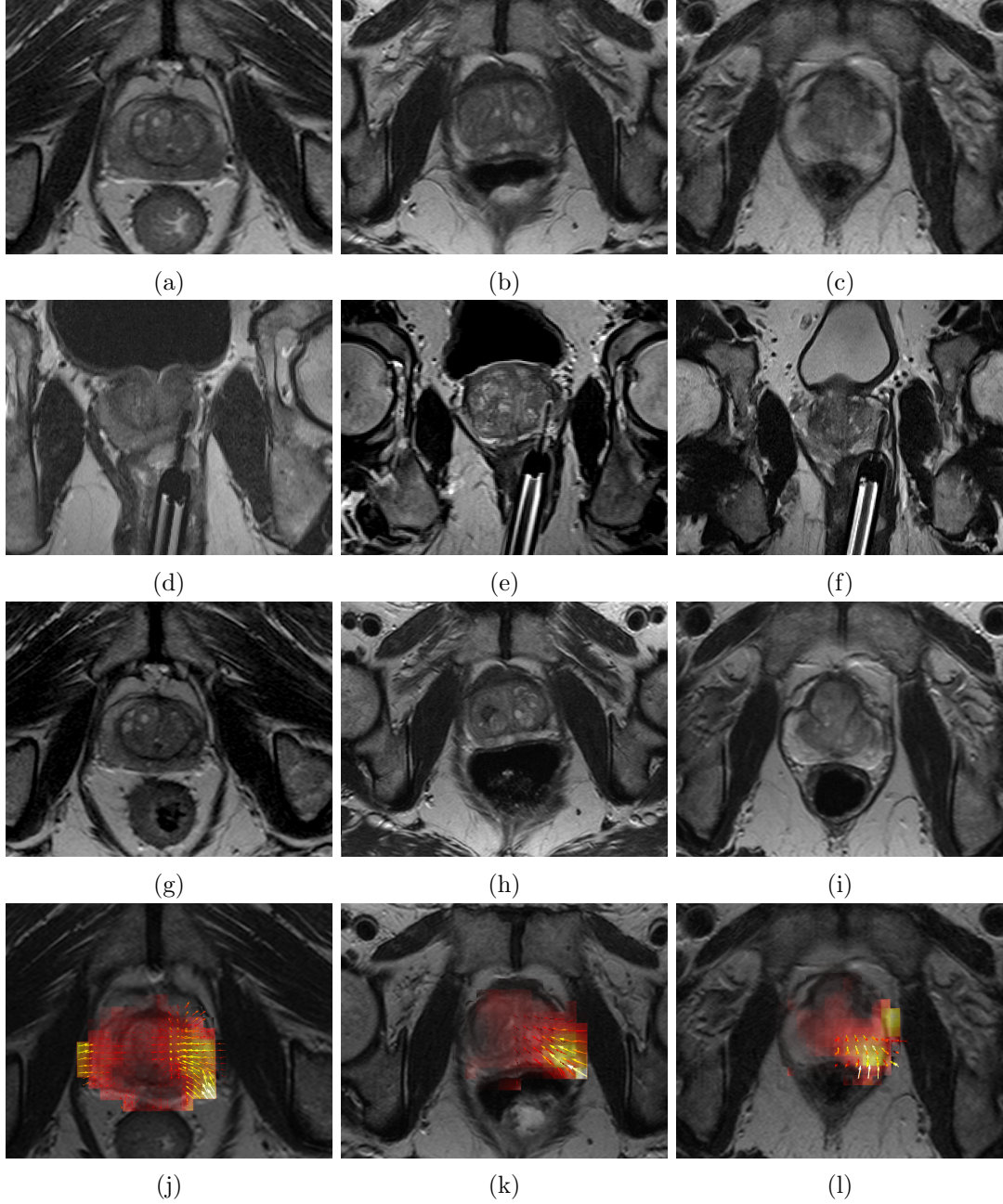


Figure 6.4: Results of morphological changes for three patients (one per column). The first row represents I_{Pre} . The second row represents an image of the location for the laser during treatment, in all cases shown in the bottom right corner of the prostate. The third row represents I_{Post} . The fourth row represents a heat map of the FLA-induced deformations T_3 . White represents regions of large deformations, while transparent red represents regions of small deformations. Small arrows represent the direction of the deformation (in all cases pointing towards the centroid of the prostate) after removing deformations due to patient alignment (T_1) and surrounding tissues (T_2). It can be seen that in all patients, the areas with the the largest deformations were also the FLA treatment locations.

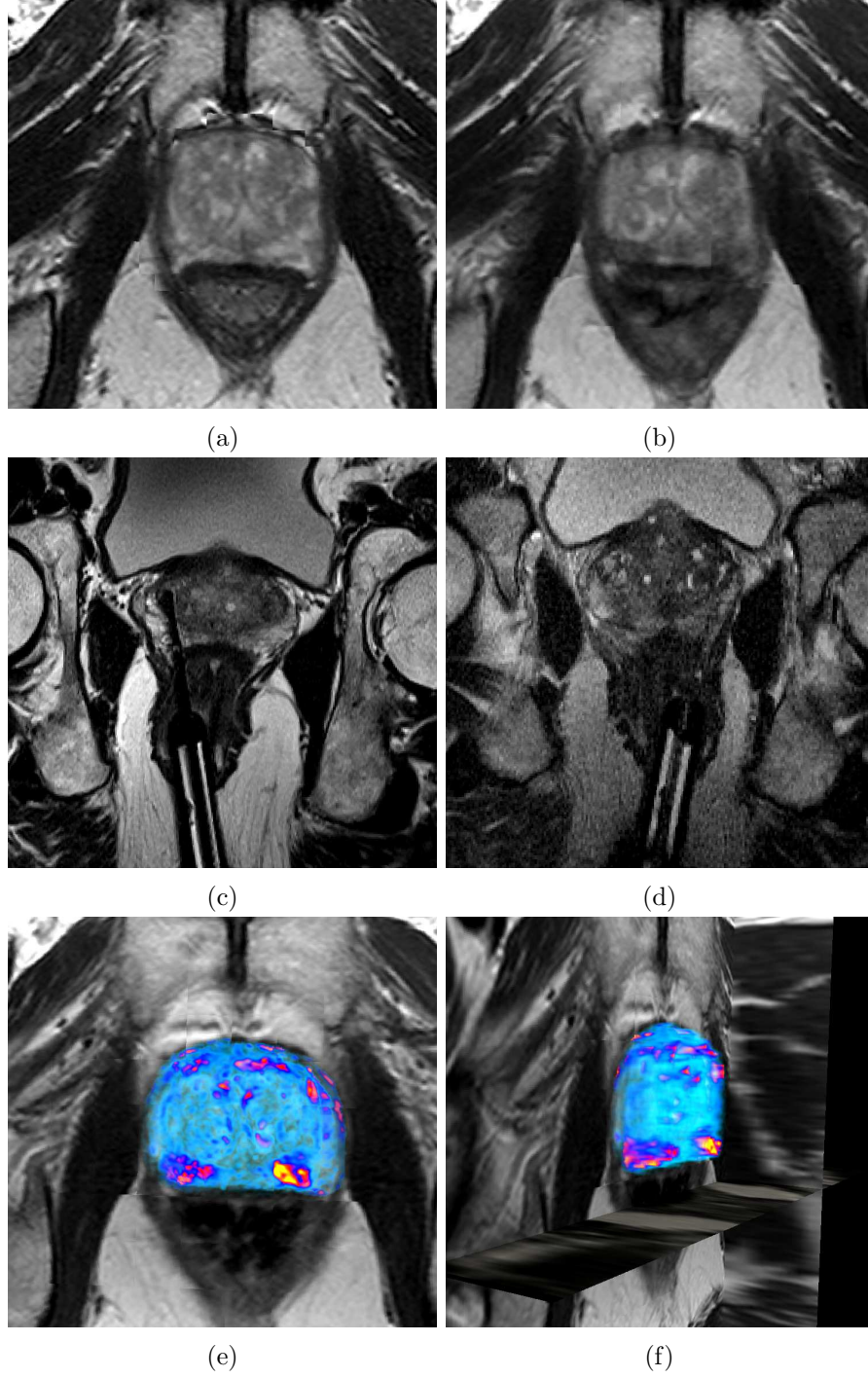


Figure 6.5: (a) and (b) show the registered pre-, post-FLA images $T_3(I_{Pre})$ and $\hat{T}_2(\hat{T}_1(I_{Post}))$ respectively. For this patient, two different FLA needle locations were used, shown in (c) and (d). After registration, the difference between the MRI intensity values are shown as colored values in 2D (e) and 3D (f), where cool colors represent regions of small differences, and hot colors represent regions of large differences. The hot colors at the top of the prostate are likely due to edge artifacts, yet the hot colors at the bottom of the prostate are correlated with the needle locations.

6.4 Concluding Remarks

Focal laser ablation (FLA) treatment aims to destroy cancerous cells with highly focused laser, in order to cause necrosis to the affected tissue. It combines the aggressive benefits of radiation treatments (the ability to destroy cancers cells) without the harmful side effects (due to its localization). However, to quantify these changes, the pre- and post-FLA MR images must first be spatially aligned via image registration. Challenges of such a registration technique arise from the significant changes to gland morphology following radiation treatment due to (1) patient alignment, (2) changes due to surrounding organs such as the bladder rectum, and (3) changes due to the FLA itself. In order to isolate the FLA-induced morphological changes, the changes from (1) and (2) are first modeled and removed. Then, a finite element model determines the FLA-induced changes to the prostate. This results in (a) FLA-induced morphological changes to the prostate, and (b) spatially aligned pre-, post-FLA imagery. In this work we present results which suggest that the FLA treatment causes a minor decrease in prostate volume, focused specifically at the site of ablation. In addition, after spatially aligning the images, changes to MRI intensity values are clearly visible at the site of ablation. Both these results lend themselves to quantifying the degree of FLA-induced changes to the prostate, which can be used to track a patient over time. Future work will explore the correlation between morphological and intensity changes within the prostate, with patient outcome.

Chapter 7

Concluding Remarks and Future Directions

In this work we have presented a suite of novel segmentation and registration methods for quantitative evaluation of prostate cancer treatment using MRI. Specific goals accomplished include, (a) evaluation of radical prostatectomy via quantification of prostate volume, (b) evaluation of EBRT via modeling EBRT-induced shrinking effects post-treatment, and (c) evaluation of FLA treatment via a biomechanical model aimed to isolate FLA-induced changes to the prostate.

This work represents the first method to combine multiple shape models with a texture model for 3D image segmentation (MFLAAM). In terms of accuracy, level of interaction, efficiency, and consistency over a large number of volumes, the MFLAAM outperforms most other prostate MRI segmentation algorithms. MFLAAM prostate volume estimates yield strong approximations of prostatectomy determined volumes, offering the prospect for accurate, automatic volume determinations in clinical practice.

This work also represents the first attempt to model treatment-specific morphological changes to the prostate via the use of a domain-constrained, deformable (DoCD) biomechanical model. Explicitly modeling the shrinking effects of the internal substructures of the prostate allows for a more accurate registration of pre-, post-treatment prostate MRI than current state of the art registration methods. This novel domain-constrained registration model was validated over 30 EBRT and 10 FLA patients with pre-, post-treatment MRI. Future work will aim to use DoCD to quantify the specific changes in prostate morphology and MRI parameters over time, and correlate those changes with patient outcomes. This will lend itself towards creation of a predictive model, so that early changes detected from prostate MRI following treatment could be used to predict long term treatment efficacy and patient outcome.

References

- [1] R. Toth and A. Madabhushi. Multi-feature landmark free active appearance models: Application to prostate MRI segmentation. *Medical Imaging, IEEE Transactions on*, 38(8):1638–1650, Aug 2012.
- [2] R. Toth, J. Ribault, J.C. Gentile, D. Sperling, and A. Madabhushi. Simultaneous segmentation of prostatic zones using active appearance models with multiple coupled levelsets. *Computer Vision and Image Understanding*, 117(9):1051–1060, Sep 2013.
- [3] R. Toth, B. Traughber, R. Ellis, J. Kurhanewicz, and A. Madabhushi. Registering pre-, post-radiation treatment prostate imagery using domain-specific biomechanical model. *Neurocomputing*, Special Issue on Image Guided Interventions:Accepted Pending Changes, 2013.
- [4] R. Toth, J. Bulman, A. Patel, B.N. Bloch, E.M. Genega, N.M. Rofsky, R.E. Lenkinski, and A. Madabhushi. Integrating an adaptive region based appearance model with a landmark free statistical shape model: Application to prostate MRI segmentation. *SPIE Medical Imaging*, 7962, 2011.
- [5] J.C. Bulman, R. Toth, A.D. Patel, N.B. Bloch, MacMahon C.J., Ngo L., A. Madabhushi, and N.M. Rofsky. Automated computer-derived prostate volumes from MRI data: Comparison to radiologist-derived mri volumes and pathology specimen volumes. *Radiology*, 262(1):144–151, Jan 2012.
- [6] S. Viswanath, R. Toth, M. Rusu, D. Sperling, H. Lepor, J. Futterer, and A. Madabhushi. Quantitative evaluation of treatment related changes on multiparametric MRI after laser interstitial thermal therapy of prostate cancer. *SPIE Medical Imaging*, 8671:8671F, 2013.
- [7] A. Heidenreich, G. Aus, M. Bolla, S. Joniau, V.B. Matveev, H.P. Schmid, and F. Zattoni. Eau guidelines on prostate cancer. *European Urology*, 53(1):68–80, Jan 2008.
- [8] K.L. Blackwell, D.G. Bostwick, R.P. Myers, H. Zincke, and J.E. Oesterling. Combining prostate specific antigen with cancer and gland volume to predict more reliably pathological stage: the influence of prostate specific antigen cancer density. *Journal of Urology*, 151(6):1565–1570, 1994.
- [9] S.Y. Eskicorapci, F. Guliyev, B. Akdogan, H.S. Dogan, A. Ergen, and H. Ozen. Individualization of the biopsy protocol according to the prostate gland volume for prostate cancer detection. *Journal of Urology*, 173(5):1536–1540, May 2005.
- [10] P.M. Pierorazio, M.D. Kinnaman, M.S. Wosnitzer, M.C. Benson, J.M. McKiernan, and E.T. Goluboff. Prostate volume and pathologic prostate cancer outcomes after radical prostatectomy. *Urology*, 70(4):696–701, Oct. 2007.

- [11] J.M. Kaminski, A.L. Hanlon, E.M. Horwitz, W.H. Pinover, R.K. Mitra, and G.E. Hanks. Relationship between prostate volume, prostate-specific antigen nadir, and biochemical control. *International Journal of Radiation Oncology and Biological Physics*, 52(4):888–892, Mar 2002.
- [12] C.G. Roehrborn, P. Boyle, D. Bergner, T. Gray, M. Gittleman, T. Shown, A. Melman, R.B. Bracken, R.V. White, A. Taylor, D. Wang, and J. Waldstreicher. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: Results of a four-year, randomized trial comparing finasteride versus placebo. *Adult Urology*, pages 662–670, 1999.
- [13] C.H. Bangma, A.Q.H.J. Niemer, D.E. Grobbee, and F.H. Schroder. Transrectal ultrasonic volumetry of the prostate: In vivo comparison of different methods. *The Prostate*, 28:107–110, 1996.
- [14] S.C. Hoffelt, L.M. Marshall, M. Garzotto, A. Hung, J. Holland, and T.M. Beer. A comparison of ct scan to transrectal ultrasound measured prostate volume in untreated prostate cancer. *International Journal of Radiation Oncology and Biological Physics*, 57(1):29–32, 2003.
- [15] L.M. Eri, H. Thomassen, B. Brennhovd, and L.L. Hheim. Accuracy and repeatability of prostate volume measurements by transrectal ultrasound. *Nature*, 5(4):273–278, Dec. 2002.
- [16] P.J. Littrup, C.R. Williams, T.K. Egglin, and R.A. Kane. Determination of prostate volume with transrectal us for cancer screening. part 11. accuracy of in vitro and in vivo techniques. *Radiology*, 52:49–53, 1991.
- [17] G.J. Matthews, J. Motta, and J.A. Fracchia. The accuracy of transrectal ultrasound prostate volume estimation: Clinical correlations. *Journal of Clinical Ultrasound*, 24:501–505, 1996.
- [18] M.S. Nathan, K. Seenivasagam, Q. Mei, J.E.A. Wickham, and R.A. Miller. Transrectal ultrasonography: Why are estimates of prostate volume and dimension so inaccurate? *British Journal of Urology*, 77(3):401–407, Mar 1996.
- [19] S.B. Park, J.K. Kim, S.H. Choi, H.N. Noh, E.K. Ji, and K.S. Cho. Prostate volume measurements by trus using heights obtained by transaxial and midsagittal scanning: Comparison with specimen volume following radical prostatectomy. *Korean Journal of Radiology*, pages 110–113, 2000.
- [20] A. Tewari, R. Indudhara, K. Shinohara, E. Schallow, M. Woods, R. Lee, C. Anderson, and P. Narayan. Comparison of transrectal ultrasound prostatic volume estimation with magnetic resonance imaging volume estimation and surgical specimen weight in patients with benign prostatic hyperplasia. *Journal of Clinical Ultrasound*, 24:169–174, May 1996.
- [21] C.W. Jeong, H.K. Park, S.K. Hong, S. Byun, H.J. Lee, and S.E. Lee. Comparison of prostate volume measured by transrectal ultrasonography and MRI with the actual prostate volume measured after radical prostatectomy. *Urologia Internationalis*, 81(2):179–185, Aug. 2008.

- [22] J. Sosna, N.M. Rofsky, S.M. Gaston, W.C. DeWolf, and R.E. Lenkinski. Determinations of prostate volume at 3-tesla using an external phased array coil : Comparison to pathologic specimens. *Academic Radiology*, 10(8):846–853, 2003.
- [23] P.J. MacMahon, A. Kennedy, D.T. Murphy, M. Maher, and M.M. McNicholas. Modified prostate volume algorithm improves transrectal us volume estimation in men presenting for prostate brachytherapy. *Radiology*, 250:273–280, Jan. 2009.
- [24] P.S. Myschetzky, R.E. Suburu, B.S. Jr. Kelly, M.L. Wilson, S.C. Chen, and F. Lee. Determination of prostate gland volume by transrectal ultrasound: correlation with radical prostatectomy specimens. *Scand J Urol Nephrol Suppl.*, 137:107 – 111, 1991.
- [25] J. Bonilla, E. Stoner, P. Grino, B. Binkowitz, and A. Taylor. Intra- and interobserver variability of MRI prostate volume measurements. *The Prostate*, 31(2):98–102, 1997.
- [26] R.G. Aarnink, J.J.M.C.H. de la Rosette, F.M.J. Debruyne, and H. Wijkstra. Reproducibility of prostate volume measurements from transrectal ultrasonography by an automated and a manual technique. *British Journal of Urology*, 78(2):219–223, Aug 1996.
- [27] Y. Zhu, R. Zwigelaar, and S. Williams. Prostate segmentation: a comparative study. In *MIUA*, pages 129–132, 2003.
- [28] B. Chiu, G.H. Freeman, M.M.A. Salama, and A. Fenster. Prostate segmentation algorithm using dyadic wavelet transform and discrete dynamic contour. *Physics of Medical Biology*, 49(21):4943–4960, Nov 2004.
- [29] J. Costa, H. Delingette, S. Novellas, and N. Ayache. Automatic segmentation of bladder and prostate using coupled 3D deformable models. In *MICCAI*, pages 252–260, 2007.
- [30] H. M. Ladak, F. Mao, Y. Wang, D.B. Downey, D.A. Steinman, and A. Fenster. Prostate boundary segmentation from 2d ultrasound images. *Medical Physics*, 27(8):1777–1788, Aug 2000.
- [31] N. Hu, D.B. Downey, A. Fenster, and H.M. Ladak. Prostate boundary segmentation from 3D ultrasound images. *Medical Physics*, 30(7):1648–1659, 2003.
- [32] S.D. Pathak, V. Chalana, D.R. Haynor, and Y. Kim. Prostate segmentation algorithm using dyadic wavelet transform and discrete dynamic contour. *Medical Imaging, IEEE Transactions on*, 19(12):1211–1219, December 2000.
- [33] L. Gong, S.D. Pathak, D.R. Haynor, P.S. Cho, and Y. Kim. Parametric shape modeling using deformable superellipses for prostate segmentation. *Medical Imaging, IEEE Transactions on*, 23(3):340–349, Mar 2004.
- [34] F.A. Cosio. Automatic initialization of an active shape model of the prostate. *Medical Image Analysis*, 12(4):469–483, Aug 2008.

- [35] Z. Gao, D. Wilkins, L. Eapen, C. Morash, Y. Wassef, and L. Gerig. A study of prostate delineation referenced against a gold standard created from the visible human data. *Radiotherapy and Oncology*, 85(2):239–246, Nov 2007.
- [36] Y. Gao, R. Sandhu, G. Fichtinger, and A. Tannenbaum. A coupled global registration and segmentation framework with application to magnetic resonance prostate imagery. *IEEE Trans Med Imaging*, 2010.
- [37] R. Toth, B.N. Bloch, E. Genega, N. Rofsky, R. Lenkinski, M. Rosen, and A. Madabhushi. Accurate prostate volume estimation using active shape models on T2-weighted MRI. *Academic Radiology*, 18(2):745–754, Jun 2011.
- [38] S.K. Warfield, K.H. Zou, and W.M. Wells. *Validation of Image Segmentation and Expert Quality with an Expectation-Maximization Algorithm*, volume 2488, pages 298–306. Springer Berlin Heidelberg, 2002.
- [39] S. K. Warfield, K. H. Zou, and W. M. Wells. Simultaneous truth and performance level estimation (staple): an algorithm for the validation of image segmentation. *Medical Imaging, IEEE Transactions on*, 23(7):903–921, Jul 2004.
- [40] J.W. Shay and I.B. Roninson. Halcancer of senscence in carcinogenesis and cancer therapy. *Oncogene*, 23:2919–2933, 2004.
- [41] S.R. Denmeade, X.S. Lin, and J.T. Isaacs. Role of programmed (apoptotic) cell death during the progression and therapy for prostate cancer. *The Prostate*, 28(4):251–265, 1996.
- [42] P.B. Gaudin, M.J. Zelefsky, S.A. Leibel, Z. Fulks, and V.E. Reuter. Histopathologic effects of three-dimensional conformal external beam radiation therapy on benign and malignant prostate tissues. *The American Journal of Surgical Pathology*, 23(9):1021–1045, Sep 1999.
- [43] A.C. Westphalen, F.V. Coakley, M.3rd. Roach, C.E. McCulloch, and J. Kurhanewicz. Locally recurrent prostate cancer after external beam radiation therapy: diagnostic performance of 1.5-T endorectal MR imaging and MR spectroscopic imaging for detection. *Radiology*, 256(2):485–492, Aug 2010.
- [44] G.A. Viani, E.J. Stefano, and S.L. Afonso. Higher-than-conventional radiation doses in localized prostate cancer treatment: A meta-analysis of randomized, controlled trials. *Int. J. of Rad. Onc. Bio. Phys.*, 74(5):1405–1418, 2009.
- [45] M.J. Zelefsky, L. Ben-Porat, H.I. Scher, H.M. Chan, P.A. Fearn, Z.Y. Fuks, S.A. Leibel, and E.S. Venkatraman. Outcome predictors for the increasing psa state after definitive external-beam radiotherapy for prostate cancer. *Journal of Clinical Oncology*, 23(4):826–831, Feb 2005.
- [46] S.F. Slovin, A.S. Wilton, G. Heller, and H.I. Scher. Time to detectable metastatic disease in patients with rising prostate-specific antigen values following surgery or radiation therapy. *Clinical Cancer Research*, 11(24):8669–8673, Dec 2005.
- [47] O.F. Donati, Vargas H.A. Jung, S.I., D.H. Gultekin, J. Zheng, C.S. Moskowitz, H. Hricak, M.J. Zelefsk, and O. Akin. Multiparametric prostate mr imaging

with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: Are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? *Radiology*, 268(1), Jul 2013.

- [48] J.J. Ftterer. Imaging of recurrent prostate cancer. *Radiologic Clinics of North America*, 50(6):1075–1083, Nov 2012.
- [49] C. Roy, F. Foudi, J. Charton, M. Jung, H. Lang, C. Saussine, and D. Jacqmin. Functional mri sequences in detection of local recurrence of prostate carcinoma after radical prostatectomy or external-beam radiotherapy. *Genitourinary Imaging*, 200(4):W361–W368, 2013.
- [50] Diffusion-weighted imaging of local recurrent prostate cancer after radiation therapy: Comparison with 22-core three-dimensional prostate mapping biopsy. *Magnetic Resonance Imaging*, 30(8):1091–1098, Oct 2012.
- [51] A.C. Westphalen, G.D. Reed, P.P. Vinh, C. Sotto, D. Vigneron, and J. Kurhanewicz. Multiparametric 3T endorectal MRI after external beam radiation therapy for prostate cancer. *Journal of Magnetic Resonance Imaging*, 36(2):430–437, Aug 2012.
- [52] O. Rouvire. Imaging techniques for local recurrence of prostate cancer: For whom, why and how? *Diagnostic and Interventional Imaging*, 93:279–290, 2012.
- [53] O. Rouvire, L. Sbihi, A. Gelet, and J.Y. Chapelon. Salvage high-intensity focused ultrasound ablation for prostate cancer local recurrence after external-beam radiation therapy: Prognostic value of prostate mri. *Clinical Radiology*, 68:661–667, 2013.
- [54] W.D. Foltz, A. Wu, P. Chung, C. Catton, A. Bayley, M. Milosevic, R. Bristow, P. Warde, A. Simeonov, D.A. Jaffray, M.A. Haider, and C. Menard. Changes in apparent diffusion coefficient and T2 relaxation during radiotherapy for prostate cancer. *Journal of Magnetic Resonance Imaging*, 37(4):909–916, Apr 2013.
- [55] J.J. Ftterer and J.O. Barentsz. 3T MRI of prostate cancer. *Applied Radiology*, 38(1):25–32, Jan 2009.
- [56] A. Erbersdobler, H. Augustin, T. Schlomm, and R. Henke. Prostate cancers in the transitionj zone: Part 1; pathological aspects. *BJU International*, 94(9):1221–1225, Dec 2004.
- [57] O. Rouvire, O. Valette, S. Grivolat, C. Colin-Pangaud, R. Bouvier, J.Y. Chapelon, A. Gelet, and D. Lyonnet. Recurrent prostate cancer after external beam radiotherapy: Value of contrast-enhanced dynamic mri in localizing intraprostatic tumor - correlation with biopsy findings. *Adult Urology*, 63(5):922–927, May 2004.
- [58] P. Colin, S. Mordon, P. Nevoux, M.F. Marqa, A. Ouzzane, P. Puech, G. Bozzini, B. Leroux, A. Villers, and N. Betrouni. Focal laser ablation of prostate cancer: Denition, needs, and future. *Advances in Urology*, 2012:589160–589169, 2012.
- [59] A. Oto, I. Sethi, G. Karczmar, R. McNicholas, M.K. Ivancevic, W.M. Stadler, S. Watson, and S. Eggener. MR imaging-guided focal laser ablation for prostate cancer: Phase i trial. *Radiology*, 267:932–940, Jun 2013.

- [60] S. Eggener, G. Salomon, P.T. Scardino, J. De la Rosette, T.J. Polascik, and S. Brewster. Focal therapy for prostate cancer: Possibilities and limitations. *European Urology*, 58:57–64, Mar 2010.
- [61] O. Raz, M.A. Haider, S.R.H. Davidson, U. Lindner, E. Hlasny, R. Weersink, M.R. Gertner, W. Kucharczyk, S.A. McClusky, and J. Trachtenberg. Real-time magnetic resonance imaging guided focallaser therapy in patients with low-risk prostate cancer. *European Urology*, 58(1):173–177, Jul 2010.
- [62] U. Lindner, N. Lawrentschuk, R.A. Weersink, S.R.H. Davidson, O. Raz, E. Hlasny, D.L. Langer, M.R. Gertner, T. van der Kwast, M.A. Haider, and J. Trachtenberg. Focal laser ablation for prostate cancer followed by radical prostatectomy: Validation of focal therapy and imaging accuracy. *European Urology*, 57:1111–1114, 2010.
- [63] U. Lindner, J. Trachtenberg, and N. Lawrentschuk. Focal therapy in prostate cancer: Modalities, findings and future considerations. *Nature Reviews in Urology*, 7:562–571, Sep 2010.
- [64] F.A. Jolesz, A. Nabavi, and R. Kikinis. Integration of interventional MRI with computer-assisted surgery. *Journal of Magnetic Resonance Imaging*, 13(1):69–77, Jan 2001.
- [65] S. Viswanath, B.N. Bloch, E. Genega, N. Rofsky, R. Lenkinski, J. Chappelow, R. Toth, and A. Madabhushi. A comprehensive segmentation registration and cancer detection scheme on 3 tesla in vivo prostate DCE MRI. *Medical Image Computing and Computer Assisted Intervention*, 1:662–669, 2008.
- [66] T.F. Cootes, C.J. Taylor, D.H. Cooper, and J. Graham. Active shape models - their training and application. *Computer Vision and Image Understanding*, 61(1):38–59, Jan 1995.
- [67] T.F. Cootes, G.J. Edwards, and C.J. Taylor. Active appearance models. *Pattern Analysis and Machine Intelligence, IEEE Transactions on*, 23(6):681–685, 2001.
- [68] G.J. Edwards, A. Lanitis, C.J. Taylor, and T.F. Cootes. Statistical models of face images - improving specificity. In *In British Machine Vision Conference*, pages 765–774, 1996.
- [69] M. de Bruijne, B. van Ginneken, M.A. Viergever, and W.J. Niessen. Adapting active shape models for 3D segmentation of tubular structures in medical images. In C.J. Taylor and J.A. Noble, editors, *Information Processing in Medical Imaging*, volume 2732 of *Lecture Notes in Computer Science*, pages 136–147. Springer, Mar 2003.
- [70] R.H. Davies. *Learning Shape: Optimal Models for Analysing Shape Variability*. PhD thesis, University of Manchester, 2002.
- [71] T. Heimann and H.P. Meinzer. Statistical shape models for 3D medical image segmentation: a review. *Medical Image Analysis*, 13(4):543–563, Aug 2009.

- [72] M. Styner, K. Rajamani, L.P. Nolte, G. Zsemlye, G. Székely, C. Taylor, and R. Davies. Evaluation of 3D correspondence methods for model building. In *IPMI*, volume 2732, pages 63–75. Springer Berlin / Heidelberg, 2003.
- [73] D.D. Morris and T. Kanade. Image-consistent surface triangulation. *Computer Vision and Pattern Recognition*, 1:1332, 2000.
- [74] R. Toth, J. Chappelow, M. Rosen, S. Pungavkar, A. Kalyanpur, and A. Madabhushi. Multi-attribute, non-initializing, texture reconstruction based asm (mantra). In *MICCAI*, volume 1 of *Lecture Notes in Computer Science*, pages 653–661, 2008.
- [75] M.E. Leventon, W.E.L. Grimson, and O. Faugeras. Statistical shape influence in geodesic active contours. In *Computer Vision and Pattern Recognition*, volume 1, pages 316–323, Jun 2000.
- [76] Y. Jeong, R.J. Radke, and D.M. Lovelock. Bilinear models for inter- and intra-patient variation of the prostate. *Physics of Medical Biology*, 55(13):3725–3739, 2010.
- [77] A. Tsai, W. Wells, C. Tempany, E. Grimson, and A. Willsky. Mutual information in coupled multi-shape model for medical image segmentation. *Medical Image Analysis*, 8(4):429–445, Dec 2004.
- [78] S. Hu and D.L. Collins. Joint level-set shape modeling and appearance modeling for brain structure segmentation. *NeuroImage*, 36(3):672–683, Jul 2007.
- [79] A. Akhondi-Asl and H. Soltanian-Zadeh. Effect of number of coupled structures on the segmentation of brain structures. *Journal of Signal Processing Systems*, 54:215–230, 2009.
- [80] D. Seghers, D. Loeckx, F. Maes, D. Vandermeulen, and P. Suetens. Minimal shape and intensity cost path segmentation. *Medical Imaging, IEEE Transactions on*, 26(8):1115–1129, Aug 2007.
- [81] B. van Ginneken, A.F. Frangi, J.J. Staal, B. Romeny, and M.A. Viergever. Active shape model segmentation with optimal features. *Medical Imaging, IEEE Transactions on*, 21(8):924–933, Aug 2002.
- [82] R. Larsen, M.B. Stegmann, S. Darkner, S. Forchhammer, T.F. Cootes, and B.K. Ersboll. Texture enhanced appearance models. *Computer Vision and Image Understanding*, 106(1):20–30, Apr 2007.
- [83] S. Ghose, A. Oliver, R. Marti, X. Llado, J. Freixenet, J.C. Vilanova, and F. Meriaudeau. Prostate segmentation with texture enhanced active appearance model. In *Signal-Image Technology and Internet-Based Systems (SITIS), 2010 Sixth International Conference on*, volume 0, pages 18–22. IEEE Computer Society, 2010.
- [84] N. Baka, J. Milles, E.A. Hendriks, A. Suinesiaputra, M.J. Herold, J.H.C. Reiber, and B.P.F. Lelieveldt. Segmentation of myocardial perfusion MR sequences with multi-band active appearance models driven by spatial and temporal features. *SPIE Medical Imaging*, 6914, Mar 2008.

- [85] S. Klein, U.A. van der Heide, I.M. Lips, M. van Vulpen, M. Staring, and J.P.W. Pluim. Automatic segmentation of the prostate in 3D MR images by atlas matching using localized mutual information. *Medical Physics*, 35(4):1407–1417, Apr. 2008.
- [86] S. Martin, V. Daanen, and J. Troccaz. Automated segmentation of the prostate in 3D MR images using a probabilistic atlas and a spatially constrained deformable model. *Medical Physics*, 37(4):1579–1590, Apr 2010.
- [87] D. Pasquier, T. Lacornerie, M. Vermandel, J. Rousseau, E. Lartigau, and N. Betrouni. Automatic segmentation of pelvic structures from magnetic resonance images for prostate cancer radiotherapy. *International Journal of Radiation Oncology and Biological Physics*, 68(2):592–600, 2007.
- [88] N. Makni, P. Puech, R. Lopes, and A.S. Dewalle. Combining a deformable model and a probabilistic framework for an automatic 3D segmentation of prostate on MRI. *International Journal of Computer Assisted Radiology and Surgery*, 4:181–188, 2009.
- [89] S. Chen, D.M. Lovelock, and R.J. Radke. Segmenting the prostate and rectum in ct imagery using anatomical constraints. *Medical Image Analysis*, 15(1):1–11, Feb 2011.
- [90] K.K. Brock, A.M. Nichol, C. Menard, J.L. Moseley, P.R. Warde, C.N. Catton, and D.A. Jaffray. Accuracy and sensitivity of finite element model-based deformable registration of the prostate. *Medical Physics*, 35(9):4019–4025, Sep 2008.
- [91] Y. Chi, J. Liang, and D. Yan. A material sensitivity study on the accuracy of deformable organ registration using linear biomechanical models. *Medical Physics*, 33(2):421–433, Feb 2006. Finite Element Model.
- [92] J.R. Crouch, S.M. Pizer, E.L. Chaney, Y. Hu, G.S. Mageras, and M. Zaider. Automated finite-element analysis for deformable registration of prostate images. *Medical Imaging, IEEE Transactions on*, 26(10):1379–1391, Oct 2007. Finite Element Model.
- [93] J.M. Hensel, C. Menard, P.W.M. Chung, M.F. Milosevic, A. Kirilova, J.L. Moseley, M.A. Haider, and K.K. Brock. Development of multiorgan finite element-based prostate deformation model enabling registration of endorectal coil magnetic resonance imaging for radiotherapy planning. *International Journal of Radiation Oncology and Biological Physics*, 68(5):1522–1528, 2007.
- [94] M.B. Boubaker, M. Haboussi, J.F. Ganghoffer, and P. Aletti. Finite element simulation of interactions between pelvic organs: Predictive model of the prostate motion in the context of radiotherapy. *Journal of Biomechanics*, 42:1862–1868, 2009.
- [95] A. Mohamed, C. Davatzikos, and R. Taylor. A combined statistical and biomechanical model for estimation of intra-operative prostate deformation. *Medical Image Computing and Computer Assisted Intervention*, 2489:452–460, 2002. Finite Element Model.

- [96] E. Zacharaki, C.S. Hogue, D. Shen, B. Biros, and C. Davatzikos. Non-diffeomorphic registration of brain tumor images by simulating tissue loss and tumor growth. *Neuroimage*, 46(3):762–774, Jul 2009.
- [97] S.K. Kyriacou, C. Davatzikos, S.J. Zinreich, and R.N. Bryan. Nonlinear elastic registration of brain images with tumor pathology using a biomechanical model. *Medical Imaging, IEEE Transactions on*, 18(7):580–592, Jul 1999. Finite Element Model.
- [98] B. Karacali and C. Davatzikos. Simulation of tissue atrophy using a topology preserving transformation model. *Medical Imaging, IEEE Transactions on*, 25(5):649–652, May 2006.
- [99] J.P. Lewis. Fast normalized cross correlation, 1995.
- [100] M.P. Wachowiak, R. Smolikova, Y. Zheng, J.M. Zurada, and A.S. Elmaghraby. An approach to multimodal biomedical image registration utilizing particle swarm optimization. *Evolutionary Computing, IEEE Transactions on*, 8(3):289–301, 2004.
- [101] M.J.D. Powell. An efficient method for finding the minimum of a function of several variables without calculating derivatives. *The Computer Journal*, 7(2):155–162, 1964.
- [102] R.A. Kirsch. Computer determination of the constituent structure of biological images. *Computers and Biomedical Research*, 4(3):315–328, Jun 1971.
- [103] R.C. Gonzalez and R.E. Woods. *Digital Image Processing*. Prentice Hall, 2008.
- [104] H.A. van der Vorst. Bi-CGSTAB: A fast and smoothly convergin variant of Bi-CG for the solution of nonsymmetric linear systems. *SIAM J. Sci and Stat. Comput.*, 13(2):631–644, 1992.
- [105] S.E. Benzley, E. Perry, K. Merkley, B. Clark, and G. Sjaardama. A comparison of all hexagonal and all tetrahedral finite element meshes for elastic and elastoplastic analysis. In *In Proceedings, 4th International Meshing Roundtable*, pages 179–191, 1995.
- [106] <http://www.slicer.org>.
- [107] S. Pieper, B. Lorensen, W. Schroeder, and R. Kikinis. The na-mic kit: Itk, vtk, pipelines, grids and 3D slicer as an open platform for the medical image computing community. In *Proceedings of the 3rd IEEE International Symposium on Biomedical Imaging: From Nano to Macro*, pages 698–701, Apr 2006.
- [108] S. Pieper, M. Halle, and R. Kikinis. 3D slicer. In *Proceedings of the 1st IEEE International Symposium on Biomedical Imaging: From Nano to Macro*, pages 632–635, 2004.
- [109] D. Gering, A. Nabavi, R. Kikinis, W. Grimson, N. Hata, P. Everett, F. Jolesz, and W. Wells. An integrated visualization system for surgical planning and guidance using image fusion and interventional imaging. In *MICCAI*, volume 2, pages 809–819, 1999.

- [110] T.A. Masterson and K. Touijer. The role of endorectal coil mri in preoperative staging and decision-making for the treatment of clinically localized prostate cancer. *MAGMA*, 21(6):371–377, Nov 2008.
- [111] L. Wang, M. Mullerad, H.N. Chen, S.C. Eberhardt, M.W. Kattan, P.T. Scardino, and H. Hricak. Prostate cancer: incremental value of endorectal mr imaging findings for prediction of extracapsular extension. *Radiology*, 232:133–139, Jul 2004.
- [112] Y. Rosen, B.N. Bloch, R.E. Lenkinski, R.L. Greenman, R.P. Marquis, and N.M. Rofsky. 3T MR of the prostate: reducing susceptibility gradients by inflating the endorectal coil with a barium sulfate suspension. *Magnetic Resonance in Medicine*, 57(5):898–904, May 2007.
- [113] M.S. Cohen, R.M. Dubois, and M.M. Zeineh. Rapid and effective correction of rf inhomogeneity for high field magnetic resonance imaging. *Human Brain Mapping*, 10(4):204211, 2000.
- [114] S. Martin, V. Daanen, and J. Troccaz. Atlas-based prostate segmentation using an hybrid registration. *International Journal of Computer Assisted Radiology and Surgery*, 3:485–492, 2008.
- [115] E. Jr. Rodriguez, D. Skarecky, N. Narula, and T.E. Ahlering. Prostate volume estimation using the ellipsoid formula consistently underestimates actual gland size. *Journal of Urology*, 179(2):501–503, Feb 2008.
- [116] M. Varma and J.M. Morgan. The weight of the prostate gland is an excellent surrogate for gland volume. *Histopathology*, 57(1):55–58, Jul 2010.
- [117] H. Ohlson, P. Ekman, and H. Ringertz. Assessment of prostatic size with computed tomography. methodologic aspects. *Acta Radiol Diagn (Stockh)*, 23(3A):219–223, 1982.
- [118] N.M. Laird and J.H. Ware. Random-effects models for longitudinal data. *Biometrics*, 38(4):963–974, Dec 1982.
- [119] S.W. Heijmink, T.W. Scheenen, E.N. van Lin, A.G. Visser, L.A. Kiemeney, J.A. Witjes, and J.O. Barentsz. Changes in prostate shape and volume and their implications for radiotherapy after introduction of endorectal balloon as determined by MRI at 3T. *International Journal of Radiation Oncology, Biology, Physics*, 73(5):1446–1453, Apr 2009.
- [120] A. Rahmouni, A. Yang, C.M. Tempany, T. Frenkel, J. Epstein, P. Walsh, P.K. Leichner, C. Ricci, and E. Zerhouni. Accuracy of in-vivo assessment of prostatic volume by mri and transrectal ultrasonography. *Journal of Computer Assisted Tomography*, 16(6):935–940, Nov 1992.
- [121] T.S. Yoo, M.J. Ackerman, W.E. Lorensen, W. Schroeder, Aylward S. Chalana, V., D. Metaxas, and R. Whitaker. Engineering and algorithm design for an image processing api: A technical report on itk - the insight toolkit. In ed. Westwood, editor, *Proc. of Medicine Meets Virtual Reality*. IOS Press Amsterdam, Jan 2002.

- [122] N. Makni, A. Iancu, P. Puech, O. Colot, S. Mordon, and N. Betrouni. Zonal segmentation of prostate using multispectral magnetic resonance images. *Medical Physics*, 38:6093–6105, 2011.
- [123] J. Lian, L. Xing, S. Hunjan, C. Dumoulin, J. Levin, A. Lo, R. Watkins, K. Rohling, R. Giaquinto, D. Kim, D. Spielman, and B. Daniel. Mapping of the prostate in endorectal coil-based MRI/MRS and CT: A deformable registration and validation study. *Medical Physics*, 31(11):3087–3084, Nov 2004.
- [124] W.H. Greene, S. Chelikani, K. Purushothaman, J.P.S. Knisely, Z. Chen, X. Papademetris, L.H. Staib, and J.S. Duncan. Constrained non-rigid registration for use in image-guided adaptive radiotherapy. *Medical Image Analysis*, 13:809–817, 2009.
- [125] L.R. Dice. Measures of the amount of ecologic association between species. *Ecology*, 263:297–302, 1945.
- [126] T. De Silva, A. Fenster, D.W. Cool, L. Gardi, C. Romagnoli, J. Samarabandu, and A.D. Ward. 2D-3D rigid registration to compensate for prostate motion during 3d TRUS-guided biopsy. *Medical Physics*, 40:022904–1 – 022904–13, 2013.