

AWARD NUMBER: W81XWH-15-1-0346

TITLE: Novel Diffusion-Weighted MRI for High-Grade Prostate Cancer Detection

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CONTRACTING ORGANIZATION: University of Illinois  
Chicago, IL 60612

REPORT DATE: October 2016

TYPE OF REPORT: Annual report

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;

Distribution Unlimited

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# REPORT DOCUMENTATION PAGE

Form Approved<sup>2</sup>  
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<b>1. REPORT DATE</b> October 2016		<b>2. REPORT TYPE</b> Annual Report		<b>3. DATES COVERED</b> 15 Sep 2015 - 14 Sep 2016	
<b>4. TITLE AND SUBTITLE</b>  Novel Diffusion-Weighted MRI for High-Grade Prostate Cancer Detection				<b>5a. CONTRACT NUMBER</b>	
				<b>5b. GRANT NUMBER</b> W81XWH-15-1-0346	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Michael Abern MD; Brandon Caldwell BS; Virgilia Macias MD; Andre Kajdacsy-Balla PhD/MD; Richard Magin PhD; Joe Zhou PhD; Peter Gann ScD/MD  E-Mail: mabern1@uic.edu				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  University of Illinois 820 S Wood St. CSN 515 M/C 955. Chicago, IL. 60612.				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Materiel Command Fort Detrick. Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Matching in-vivo mpMRI to whole embedded RP sections is a challenging technical process given the vast difference in image resolution and scale. This process is critical for evaluating new imaging modalities. Our initial findings illustrate the potential of the stretched exponential model parameters to better characterize high-grade prostate cancer. Additional work is underway to establish the correspondence between the DDC and a-maps with histological sections of the entire prostate gland. Development of a non-invasive quantitative imaging biomarker for high grade PCa will be useful for improving biopsy yield and grade accuracy, accurately identifying men					
<b>15. SUBJECT TERMS</b> FROC, Prostate Cancer, MRI, Diffusion					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b>
<b>a. REPORT</b>	<b>b. ABSTRACT</b>	<b>c. THIS PAGE</b>			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	13	<b>19b. TELEPHONE NUMBER</b> (include area code)

Standard Form 298 (Rev. 8-98)  
Prescribed by ANSI Std. Z39.18

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## INTRODUCTION:

Accurate detection of aggressive prostate cancer (PCa) using existing clinical prediction tools is a challenge. Prostate MRI is promising technology for PCa detection and characterization. However, its accuracy has been sub-optimal especially in the setting of benign prostate inflammation or hyperplasia. We have developed a more sophisticated computational model of diffusion weighted MRI (FROC-DWI) that produces quantitative information regarding tissue architecture in-vivo. We hypothesize that the use of FROC-DWI in men with clinical suspicion for PCa will differentiate high grade PCa from indolent PCa and benign prostate pathology and therefore improve biopsy detection of aggressive PCa.

## KEYWORDS:

FROC, Prostate Cancer, MRI, Diffusion

## ACCOMPLISHMENTS:

### What were the major goals of the project?

The major goal of the project is to generate a fractional order diffusion weighted (FROC) MRI signature that differentiates high grade prostate cancer (PCa) from low grade PCa and benign prostate tissues. The quantitative parameters of the FROC signature will be compared with histologic tissue architecture using RP specimens from our biorepository archive. The FROC diffusion parameters  $\beta$ ,  $\mu$ , and  $D$  will be correlated with stromal and epithelial architecture of areas of benign and malignant prostate tissue and a predictive model will be created to differentiate Gleason pattern 4 or higher PCa from other tissue types.

**Aim 1:** Generate a FROC MRI signature that differentiates high grade PCa from low grade PCa and benign prostate tissues

**Aim 2:** Validate the FROC MRI signature in a prospective patient cohort undergoing RP

### What was accomplished under these goals?

#### Aim 1 accomplishments:

- Brandon Caldwell has been hired as a research specialist, and has undergone necessary training to manage the regulatory functions of the project.
- The computing workstation for the project has been procured and all necessary software obtained including Leica Aperio suite, MatLab, DICOM viewer, R.

- IRB approval has been acquired for this aim
- While 25 subjects were proposed in the grant narrative, we identified 22 retrospective subjects to be eligible for analysis as determined by adequate pathologic processing and MR images deemed to be of adequate quality by the study team.
- The histology samples have been requested from the UIC biorepository for digitization
- All MR images have been collected and prepared for image processing and analysis
- MR images have been de-identified and prepared in MatLab for quantitative analysis by the bioengineering co-investigators
- The histology specimens have all been retrieved and digitized so the grades of cancers can be outlined by the pathology co-investigators
- The UIC IRB has approved the continuing review of the protocol on 3/29/16
- 3 cases have had digital pathology annotation and MR image computation.
- Quality control testing of the MR imaging files has been completed.
- An abstract was presented to the IMPaCT conference for August 4-5 2016
- An abstract was presented to the ISMRM Workshop for September 11-16 2016

### **Aim 2 accomplishments:**

- The prospective experimental imaging protocol has been designed and approved by the collaborating radiology and bioengineering collaborators.
- The prospective prostatectomy sectioning protocol has been developed and approved by the IRB.
- The IRB protocol has been completed for Aims 2 and 3. Based on IRB and cancer center review, it was recommended to separate these into two separate protocols as the patients in aim 3 will be randomized. The IRB for aim 2 is completed and approved.
- The first subject enrollment under the prospective prostatectomy section (whole mount) has been scheduled for 10/14/16

### **What opportunities for training and professional development has the project provided?**

Dr. Abern, the PI, proposed a training plan as part of this grant. He has initiated several of the objectives.

- His enrolled in the Masters of Science in Clinical and Translational Science program offered by the University of Illinois School of Public Health. He has completed HPA 472 (Clinical Research Methods 1) with a grade of A. He is currently enrolled in HPA 473 (Clinical Research Methods 2).

- Dr. Gann has been teaching his course, Molecular Epidemiology and Biomarker Development (EPID512) , in a one-on-one fashion during weekly meetings
- He has attended the biweekly Works-in-Progress Seminar that includes participation from the Mentor's lab (Dr. Gann) as well as several other senior faculty members (including Dr. Gail Prins, Dr. Larissa Nonn) focusing on PCa.
- He attended the DOD IMPACT conference, which allowed for discussions and collaboration with several other DOD funded investigators.
- He will be attending the Prostate Cancer Foundation annual conference October 27-29, 2016.

### **How were the results disseminated to communities of interest?**

Presentations were given at the DOD IMPACT conference, and an abstract was prepared for the International Society of Magnetic Resonance Meeting in Lisbon, Portugal to be presented by one of the collaborators Meltem Uyanik and Dr. Richard Magin(both are attached in the appendix materials).

### **What do you plan to do during the next reporting period to accomplish the goals?**

#### **Aim 1:**

- Complete the imaging processing for the model development cohort
- Complete the statistical analysis of the model development cohort
- Prepare the data for publication in a peer-reviewed journal

#### **Aim 2:**

- Enroll all patients proposed for the prospective cohort (validation)
- Complete the imaging processing for the model validation cohort
- Complete the statistical analysis of the model validation cohort
- Prepare the data for publication in a peer-reviewed journal

#### **Aim 3:**

- Obtain IRB approval for Aim 3

**IMPACT:****What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

**What was the impact on other disciplines?**

The development of a whole mount prostatectomy grossing protocol will be beneficial for the Research Histology and Tissue Imaging Core at UIC.

The development of a methodology of digital prostate cancer annotation and mapping will provide a valuable resource for future projects.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

Nothing to report.

**CHANGES/PROBLEMS:****Changes in approach and reasons for change**

We have decided to make a change in our histological analysis. Due to inconsistencies in prostate grossing, we are no longer going to reconstruct the prostate from the four quadrants typically cut during grossing. Instead, we have developed a whole mount protocol to better match histology with MR data.

**Actual or anticipated problems or delays and actions or plans to resolve them**

There is a lack of consistency with regard to gross processing of the prostatectomy specimens in the biorepository. We have designed a zonal model of tumor location as a means to compare the tumor locations on the MR and histology images. For Aim 2, the prospective protocol, a strict grossing protocol has been IRB approved with the assistance of Dr. Andre Balla.

There were data quality issues with our 22 subjects for Aim 1. Since Aim 1 was retrospective and a development aim not requiring power analysis, we will proceed to analyze and report the data of sufficient quality that we have for Aim 1.

There were some issues in obtaining a process for sectioning the radical prostatectomy specimens on large format slides for analysis. We are testing a work-around using our institution's Research Histology Core to section, embed, and stain these large format slides.

**Changes that had a significant impact on expenditures**

Nothing to report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

**Significant changes in use or care of human subjects**

Nothing to report.

**Significant changes in use or care of vertebrate animals.**

Nothing to report.

**Significant changes in use of biohazards and/or select agents**

Nothing to report.

**PRODUCTS:**

**Publications, conference papers, and presentations**

**Journal publications.**

Nothing to report.

**Books or other non-periodical, one-time publications.**

Nothing to report.

**Other publications, conference papers, and presentations.**

1. Michael Abern MD, Brandon Caldwell BS, Virgilia Macias MD, Winnie Mar MD, Karen Xie MD, Andre Kajdacsy-Balla PhD/MD, Richard Magin PhD, Joe Zhou PhD, Peter Gann ScD/MD; *High Grade Prostate Cancer Characterization Using Fractional Order Calculus Diffusion Weighted MRI*; 2016; Abstract and poster for PCRPaCT Conference; Accepted; Yes (federally supported)
2. Meltem Uyanik MS, Michael Abern MD, Brandon Caldwell BS, Muge Karaman PhD, Winnie Mar MD, Joe Zhou PhD, Richard L. Magin PhD;

*Prostate Cancer Classification Using a Stretched Exponential Model of Diffusion*; 2016; Abstract and poster for ISMRM Workshop; Accepted; No

**Website(s) or other Internet site(s)**

Nothing to report.

**Technologies or techniques**

Nothing to report.

**Inventions, patent applications, and/or licenses**

Nothing to report.

**Other Products**

Nothing to report.

**PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

Name: Michael Abern, MD  
 Project Role: PI  
 Researcher Identifier: mabern  
 Nearest person month worked:  $12 \times 0.4 = 4.8$   
 Contribution to Project: Dr. Abern has acted as the project lead

Name: Peter Gann, MD  
 Project Role: Co-mentor  
 Researcher Identifier: pgann  
 Nearest person month worked:  $12 \times 0.1 = 1.2$   
 Contribution to Project: Dr. Gann has contributed as mentor for the histologic analytic aspects of the project, and has conducted bi-weekly meetings with the PI

Name: Andre Balla, MD/PhD  
 Project Role: Pathology consultant  
 Researcher Identifier: aballa  
 Nearest person month worked:  $12 \times 0.05 = 0.6$   
 Contribution to Project: Dr. Balla has consulted regarding the tissue preparation of the prostatectomy specimens for Aim 2

Name: Virgilia Macias, MD  
 Project Role: Pathology consultant  
 Researcher Identifier: vmacias

Nearest person month worked:  $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Macias has assisted in screening the retrospective pathology samples for adequacy for analysis

Name: Xiaohong “Joe” Zhou, PhD

Project Role: Co-mentor

Researcher Identifier: xjzhou

Nearest person month worked:  $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Zhou has contributed by holding bi-weekly meetings with the PI and consulting regarding the MR processing for aim 1, and for the scan protocol for aim 2

Name: Brandon Caldwell

Project Role: Study Coordinator

Nearest person month worked:  $12 \times 0.50 = 6$

Contribution to Project: Mr. Caldwell has contributed to the study via IRB management and submissions, Cancer Center compliance and research design.

Name: Richard Magin, PhD

Project Role: Mathematical image analysis team

Researcher Identifier: rmagin

Nearest person month worked:  $12 \times 0.05 = 0.6$

Contribution to Project: Dr. Magin has contributed as the designer of the FROC model and supervisor of the MR image processing

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

**What other organizations were involved as partners?**

Nothing to report.

## **SPECIAL REPORTING REQUIREMENTS**

### **COLLABORATIVE AWARDS:**

Nothing to report.

### **QUAD CHARTS:**

Nothing to report.

**APPENDICES:**

# Introduction

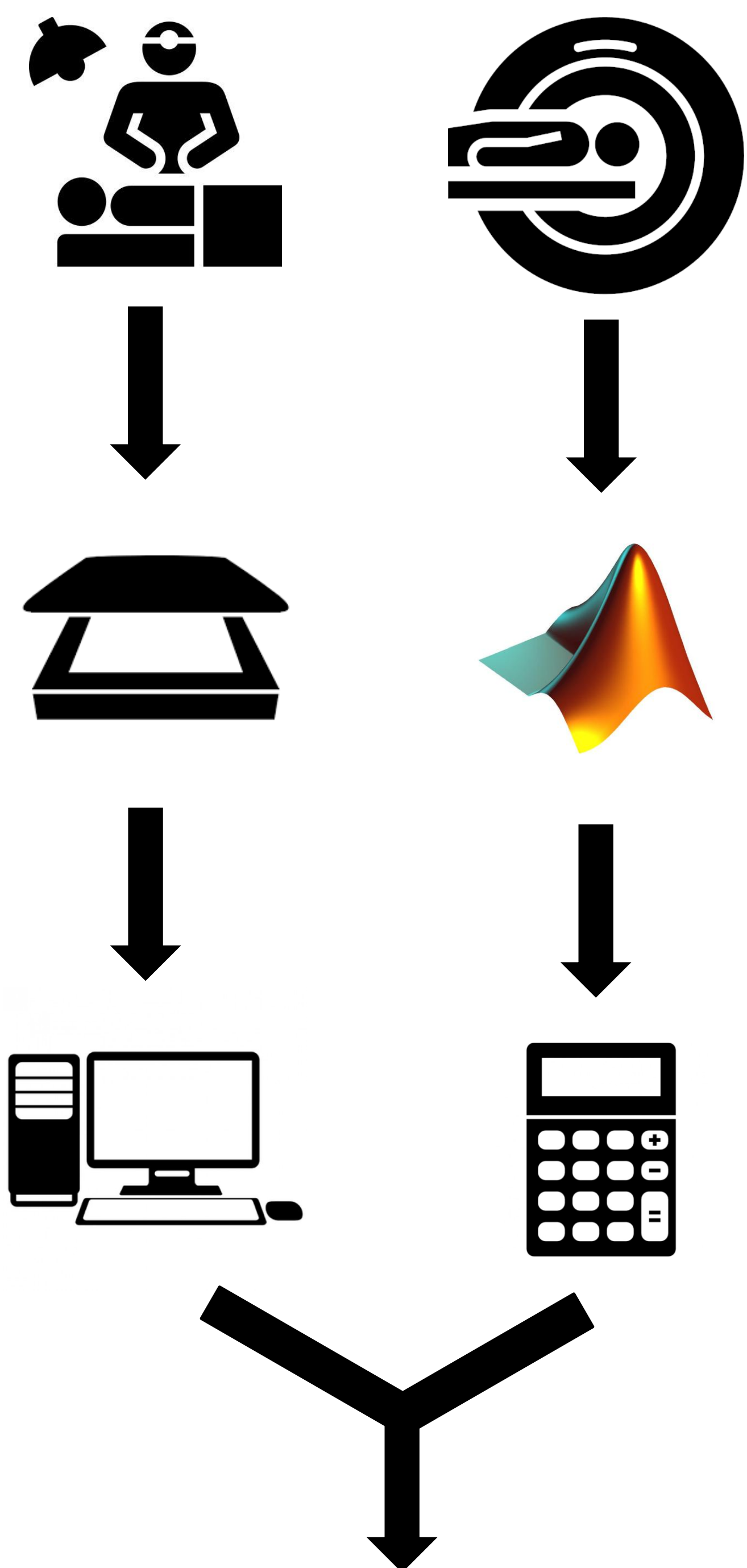
- Accurate detection of aggressive prostate cancer (PCa) using existing clinical prediction tools is a challenge.
- Prostate MRI is a promising technology for PCa detection and characterization; however, its accuracy has been sub-optimal, especially in the setting of benign prostate inflammation or hyperplasia[1].
- High-grade PCa has a greater extent of tissue heterogeneity that may not be adequately captured using current computational models
- We have developed a more sophisticated computational model of diffusion weighted MRI (FROC-DWI) that produces quantitative information regarding tissue architecture in-vivo.
- In order to quantify the degree of tissue heterogeneity, Bennet et al. [2] proposed a stretched-exponential model,  $S = S_0 \exp[-(\beta \times DDC)^\alpha]$ , where DDC is the distributed diffusion coefficient,  $\alpha$  ( $0 < \alpha < 1$ ) is a heterogeneity index that characterizes the multi-exponential nature of diffusion-related signal decay [3].
- We hypothesize that the use of FROC-DWI in men with clinical suspicion for PCa will differentiate high grade PCa from indolent PCa and benign prostate pathology therefore improving biopsy detection of aggressive PCa.

# Methods

- A cohort of patients that underwent in-vivo 3T multiparametric MRI (mpMRI) including FROC-DWI prior to radical prostatectomy was identified

- Whole embedded RP sections were digitized at 20X magnification using a digital scanner (Scanscope CS, Aperio Technologies)

- All tumor foci were annotated by Gleason pattern by a board certified genitourinary pathologist (Aperio Imagescope 11.2.0.780, Leica Biosystems)



- MRI DWI images were acquired at multiple B values (50, 500, 1000, 1500, 2000).

- One each image, the prostatic capsule and regions of interest were annotated by a board certified genitourinary radiologist With extensive MRI expertise (MatLab R2015b, MathWorks).

- The quantitative FROC-DWI parameters  $\beta$ ,  $\mu$ , and  $\Delta$  were calculated on a voxel basis. The data was fit pixel by pixel for selected slices to the mono-exponential and the stretched-exponential models using a nonlinear least squares fitting algorithm in MatLab.

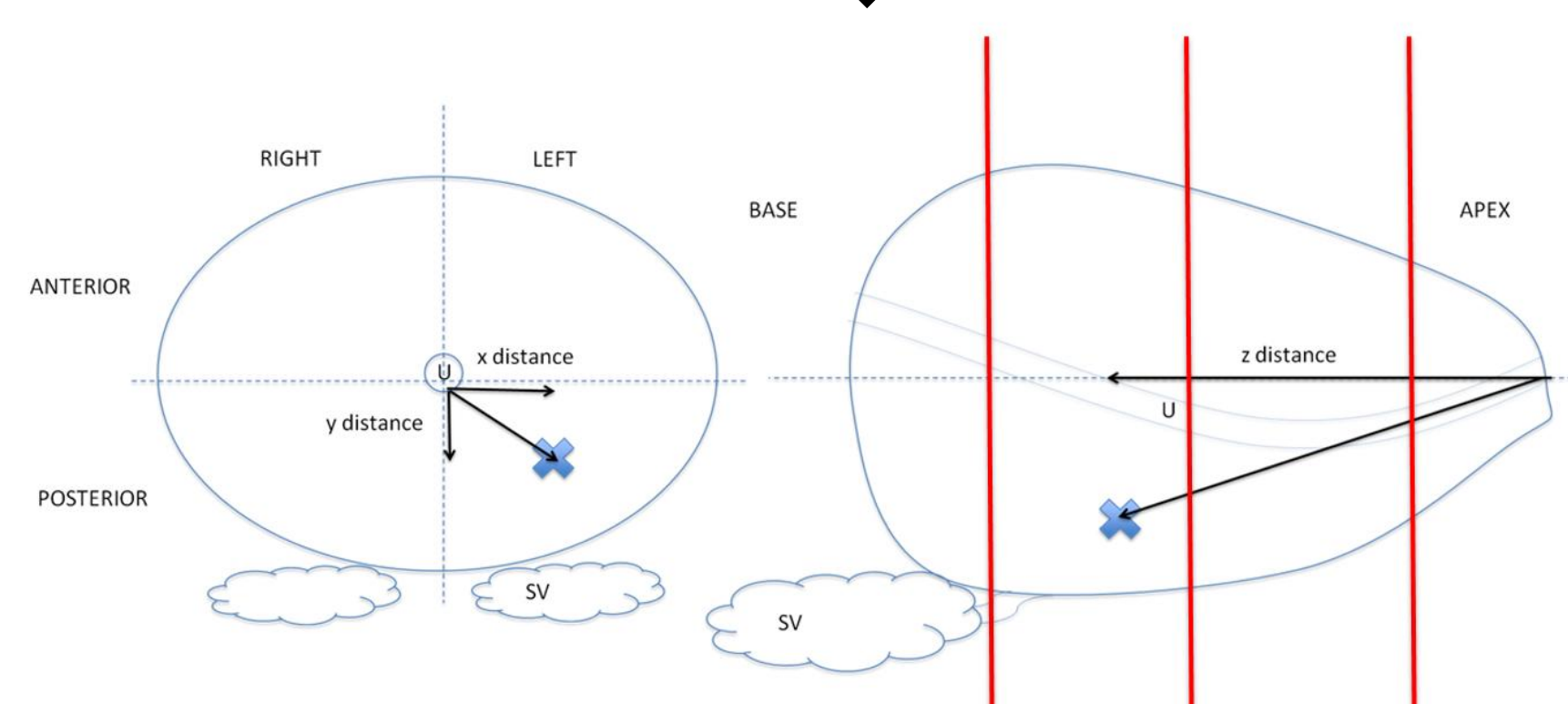


Figure 1: Flow of analysis from raw collection to consolidation

- A 16-zone scheme was devised for matching the MRI to the RP sections based on the orientation to the urethra (anterior/posterior, left/right, level from base to apex).

# Results

- Nine cases with whole embedded RP sections and complete mpMRI with DWI were identified.
- We have created an image resolution matching technique for the annotated RP sections to the mpMRI.
- Several quantitative models of the FROC parameters will be fit with the present data to a standard. This model will be validated prospectively using a new cohort of patients.
- Figures 2-8 showcase data from a patient for whom the apparent diffusion coefficient (ADC) maps are similar, but the  $\alpha$ -map exhibits greater contrast.
- Figure 3 contains annotations by a pathologist under current protocol while Figure 4 shows a new scheme and subsequent masking in MatLab.
- The pure tri-color scheme demarks only the most prevalent grade of tumor present in the prostate. This was implemented in MatLab, thus simplifying annotations and masking.
- The  $\alpha$  parameter was shown by Berbian-Santos et al. [3] to capture a distribution of diffusion coefficients.
- In Figure 8, the stretched exponential model is seen to more closely fit the observed data.

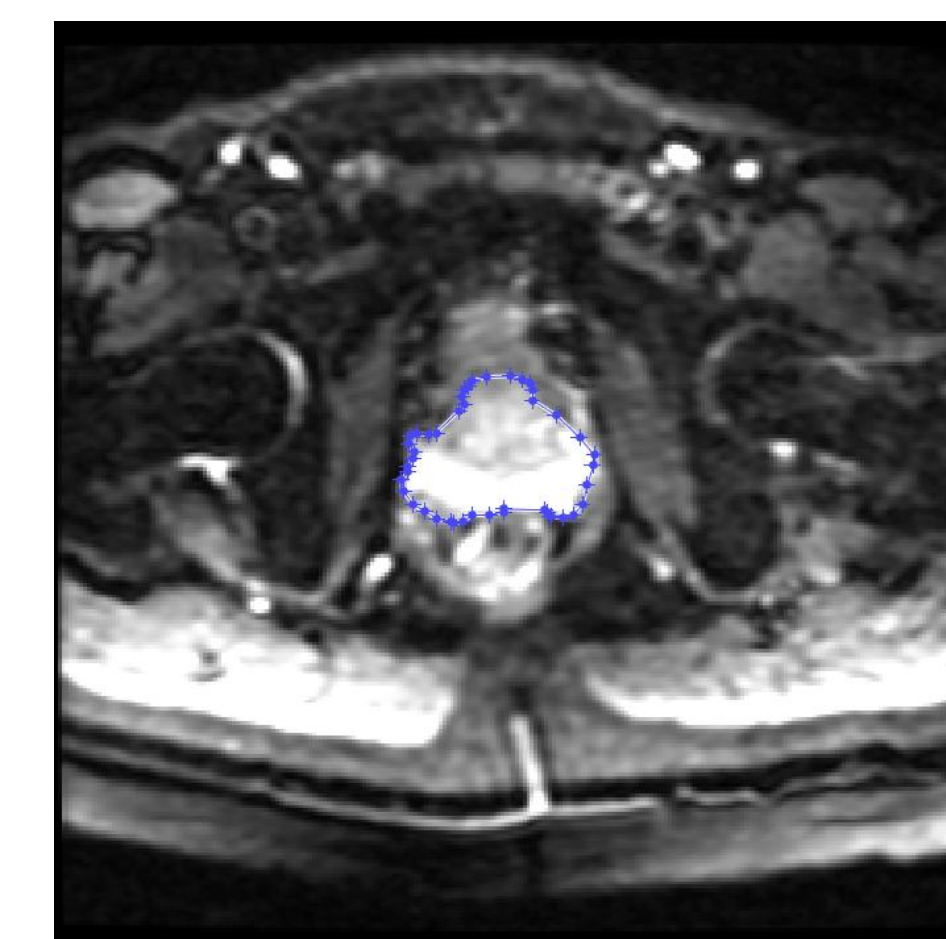


Figure 2: Outlined prostate in MatLab on b50 DWI from mid-base region of prostate.

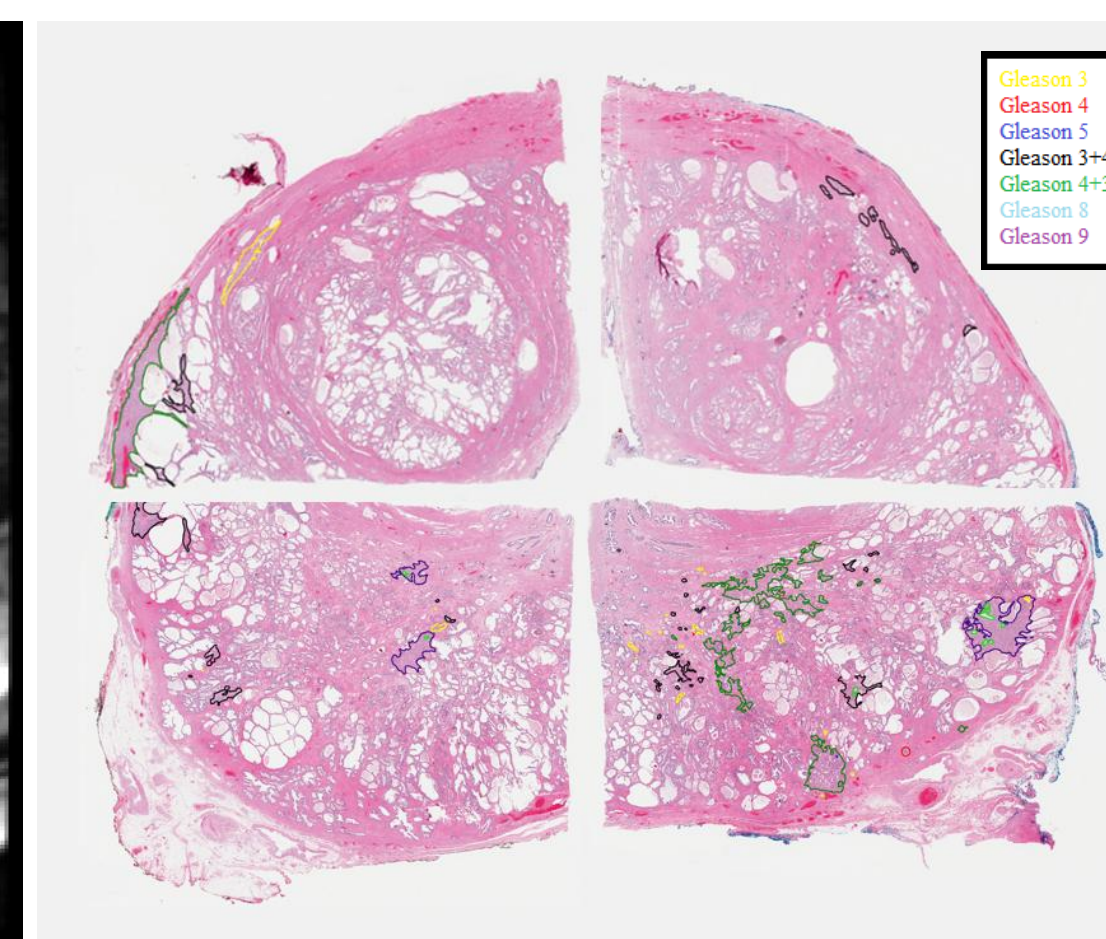


Figure 3: Annotated prostate at approximate level of MRI. Prospectively, this will be done in true whole mount and with a pure tri-color scheme.

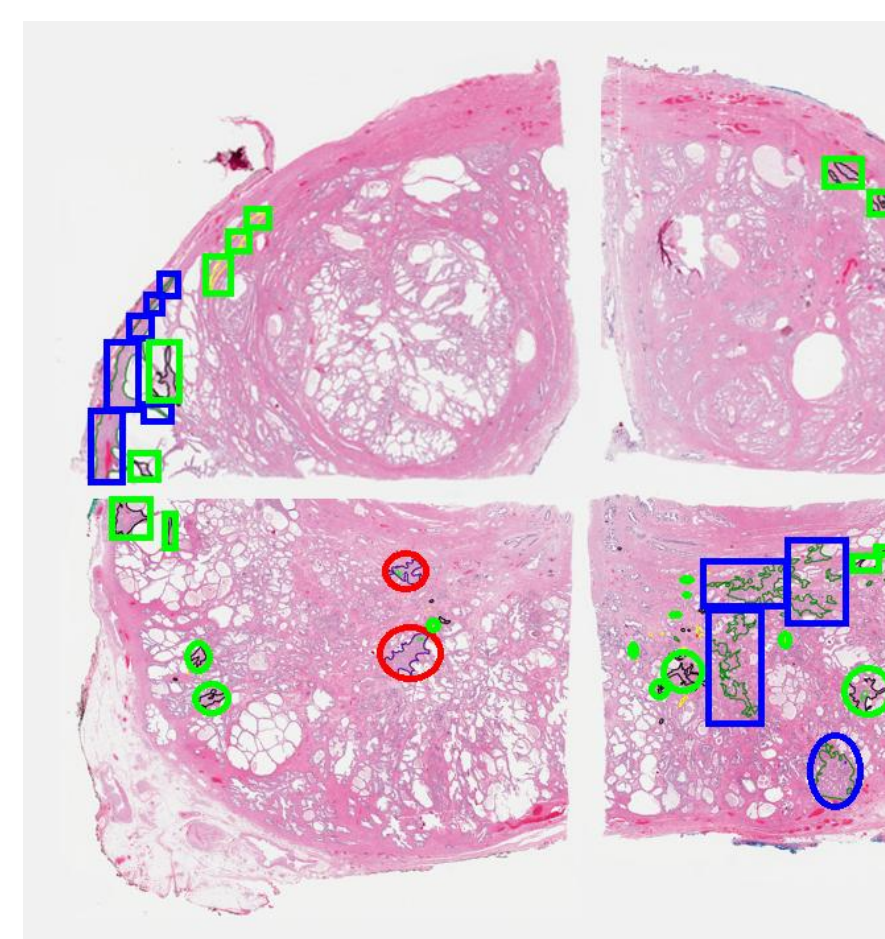


Figure 4: Prepping annotations for masking. This step will be unnecessary under prospective annotation protocol and there will be 1:1 correspondence with the pathologist's annotations.

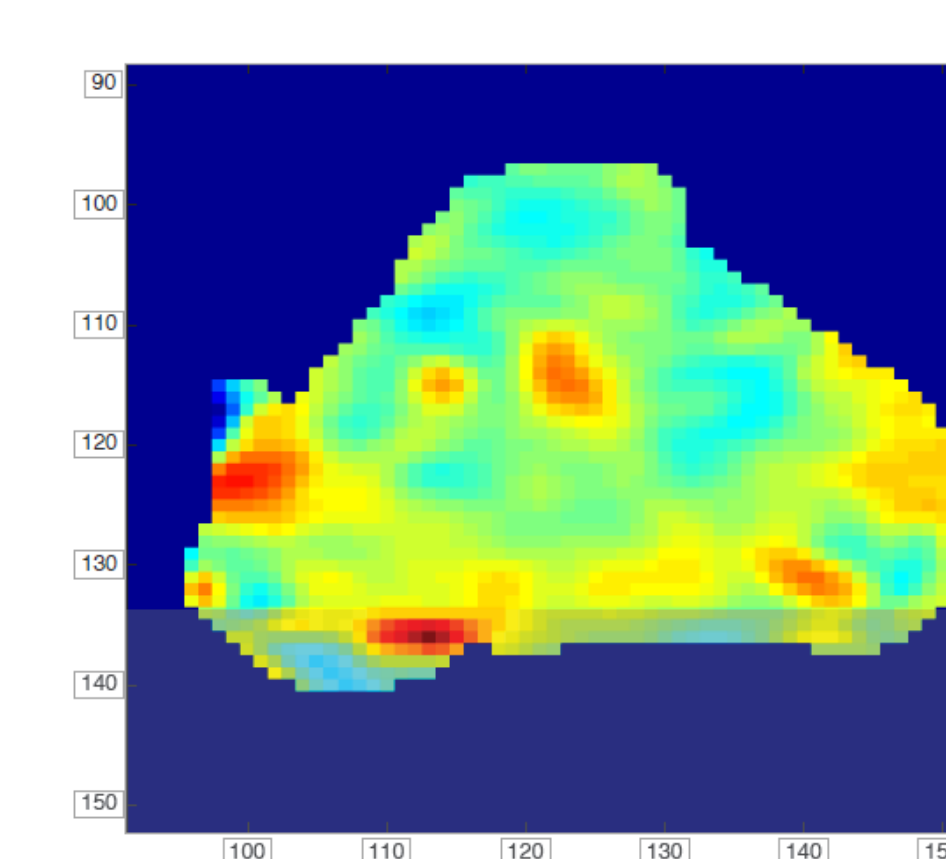


Figure 6: The ADC map for the prostate from mono-exponential model.

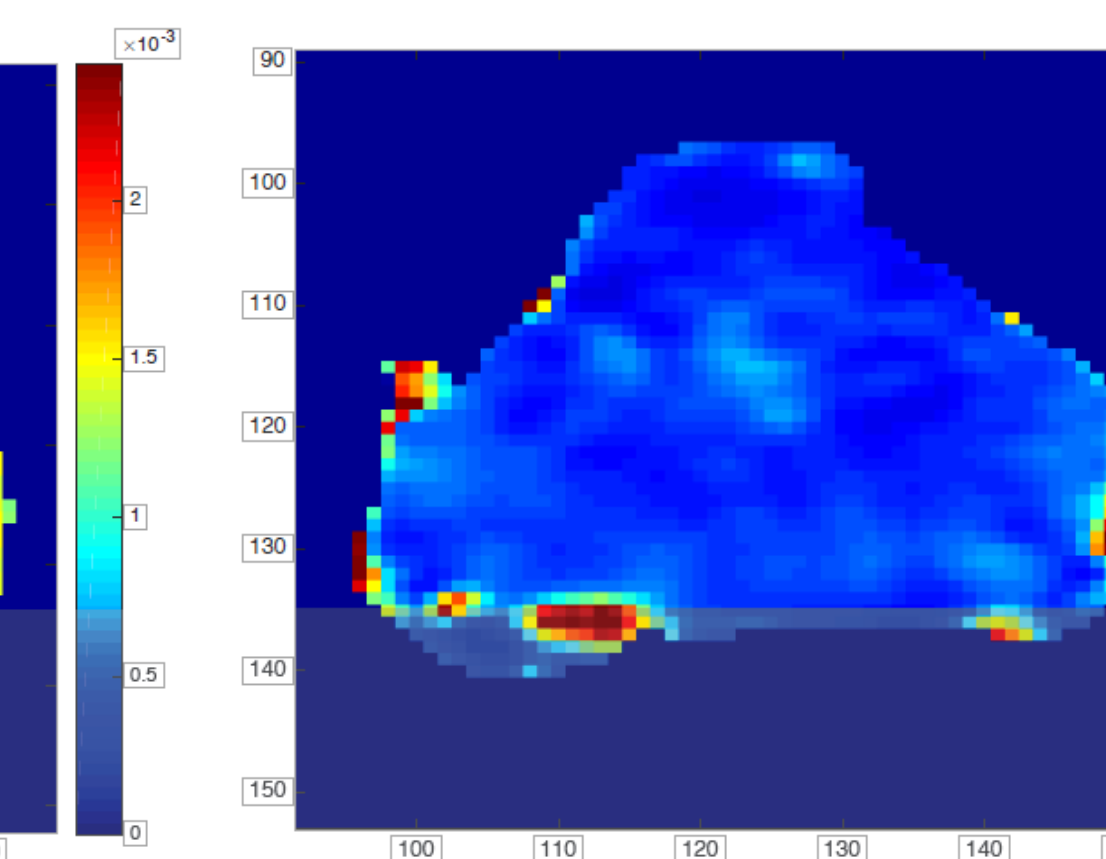


Figure 7a: The DDC map for the prostate from stretched-exponential model.

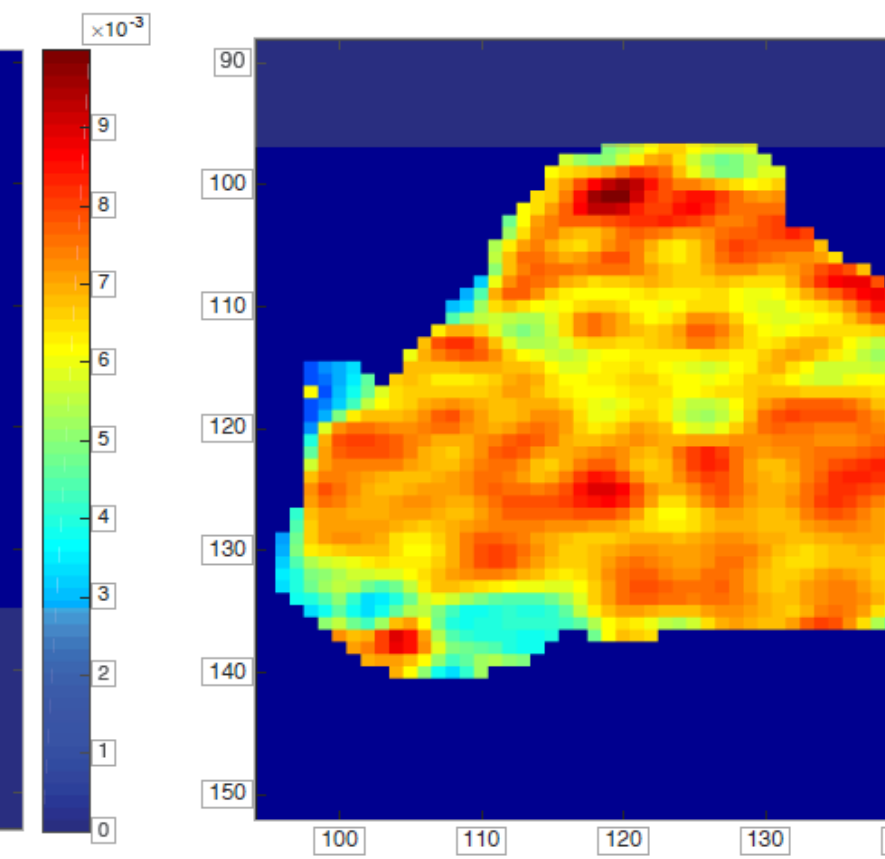


Figure 7b: The deviation of attenuation ( $\alpha$ ) map from mono-exponential model.

# Conclusions & Impact

- Matching in-vivo mpMRI to whole embedded RP sections is a challenging technical hurdle due to image resolution and scale.
- This process is critical for evaluating new imaging modalities.
- Our initial findings illustrate the potential of the stretched exponential model for high grade prostate cancer.
- Additional work is underway to establish the correspondence between the DDC and the entire prostate gland.
- Development of a non-invasive quantitative imaging biomarker for high grade prostate cancer will increase biopsy yield and grade accuracy, accurately identifying men appropriate for surveillance biopsies needed on surveillance of indolent disease.

# Selected References

[1] Epstein, J. I. et al. Euro. Urol. 61 (2012): 1019-1024.  
 [2] Bennett, K. M., et al. Magn. Reson. Med. 50 (2003): 727-734.  
 [3] Berbian-Santos, M.N. et al. Chemical Physics 315 (2005): 171-182.

# Prostate Cancer Classification Using a Stretched Exponential Model of Diffusion

THE UNIVERSITY OF ILLINOIS AT CHICAGO

Meltem Uyanik<sup>1</sup>, Michael Abern<sup>2</sup>, Brandon Caldwell<sup>2</sup>, Jin Gao<sup>1</sup>, Muge Karaman<sup>3</sup>, Winnie Mar<sup>3</sup>, Xiaohong Joe Zhou<sup>3</sup>, and Richard L. Magin<sup>1</sup>

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## INTRODUCTION

Prostate cancer is one of the most prevalent diseases among men. Early detection and classification are essential for effective treatment. Diffusion-weighted MRI (DWI) uses a single exponential signal decay model,

$$S = S_0 \exp[-b \times \text{ADC}], \quad (1)$$

to generate a spatial map of the apparent diffusion coefficient (ADC,  $\text{mm}^2/\text{s}$ ). While ADC maps are sensitive to regional changes in prostate tissue, their diagnostic specificity remains inadequate for distinguishing between benign prostate inflammation and hyperplasia [1]. In addition, high-grade prostate cancer, which has a large degree of tissue heterogeneity, may not be adequately classified by a single ADC value.

In order to quantify the degree of tissue heterogeneity in the brain, Bennett et al. [2] proposed a stretched-exponential model,

$$S = S_0 \exp[-(b \times \text{DDC})^\alpha], \quad (2)$$

where DDC is the distributed diffusion coefficient, and  $\alpha$  ( $0 < \alpha < 1$ ) is a heterogeneity index that characterizes the multi-exponential nature of diffusion-related signal decay [3]. In this study, we apply the stretched exponential model to characterize aggressive prostate cancer.

## METHODS

A cohort of patients was identified that underwent *in-vivo* 3 T multi-parametric MRI (GE Healthcare, Discovery 750 MRI) prior to radical prostatectomy (RP). Whole embedded RP sections were digitized at 20X magnification using a digital scanner (Scanscope CS, Aperio Technologies), and all tumor foci were annotated (Aperio ImageScope 11.2.0.780, Leica Biosystems) by Gleason pattern by a board certified genitourinary pathologist.

DWI images (TR 2500 ms, TE 68 ms, FOV 28x28  $\text{cm}^2$ , matrix 256x256, resolution 1.09 mm, slice thickness 3 mm) were acquired at multiple b-values (50, 500, 1000, 1500, and 2000  $\text{s}/\text{mm}^2$ ) with the corresponding averages (2, 4, 8, 12, and 16). On each image, the prostatic capsule and regions of interest (ROI) were identified.

The stretched exponential parameters  $S_0$ , DDC, and  $\alpha$  were calculated on a voxel basis. A zonal scheme was devised for matching the MRI to the RP sections based on the orientation to the urethra (anterior/posterior, left/right, level from base to apex).

The data was fit pixel by pixel for selected slices to the mono-exponential and to the stretched-exponential models using a nonlinear least squares fitting algorithm in Matlab (MathWorks).

## RESULTS

Figure 1 shows a whole prostate ADC map from a patient in this study that was calculated on a pixel-by-pixel basis by fitting the DWI signal intensities to the mono-exponential model.

Figures 2a and 2b show the corresponding DDC and  $\alpha$  parameter maps for the same prostate determined by fitting the stretched exponential diffusion model.

The  $\alpha$ -map highlights different regions of the gland. Figure 3 shows a comparison of the signal decay curves for the two models for a region (5x5 pixels) near the periphery of the gland. For this patient, the ADC and DDC maps are similar, but the  $\alpha$ -map exhibits a different contrast pattern, and the stretched exponential model more closely fits the observed decay curve.

## ACKNOWLEDGMENTS

We would like to express my special appreciation and thanks to our participants for taking part in the study.

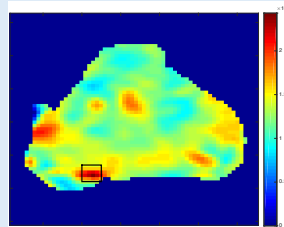


Figure 1: The apparent diffusion coefficient (ADC) map ( $\text{mm}^2/\text{s} \times 10^{-3}$ ) for a human prostate fit using the mono-exponential model. FOV: 7x7  $\text{cm}^2$ .

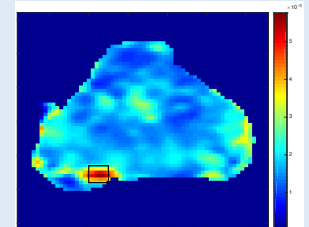


Figure 2a: The distributed diffusion coefficient (DDC) map ( $\text{mm}^2/\text{s} \times 10^{-3}$ ) for the same human prostate as in Fig. 1 fit using the stretched-exponential model.

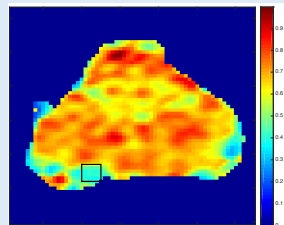


Figure 2b: The heterogeneity parameter ( $\alpha$ ) map for the human prostate shown in Fig. 1 fit using the stretched-exponential model.

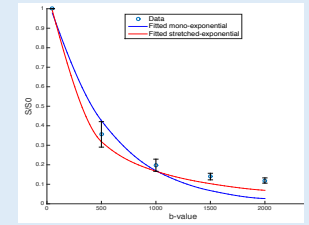


Figure 3: The signal attenuation decay for the selected ROI as a function of b-values. The error bars are displayed as plus and minus one SD about the mean.

## DISCUSSION AND CONCLUSION

The stretched-exponential decay model initially used by Bennet et al. [2] for diffusion imaging of the brain was applied here to examine heterogeneity of high-grade prostate cancer. The  $\alpha$  parameter was shown by Berbian-Santos et al. [3] to capture a distribution of decay rates (in this case, local tissue diffusion coefficients), and as  $\alpha$  values decrease, the width of the distribution increases.

Our initial findings illustrate the potential of the stretched exponential model parameters to better characterize high-grade prostate cancer.

Additional work is underway to establish the correspondence between the DDC and  $\alpha$ -maps with histological sections of the entire prostate gland. Also, we will examine multi-parameter fractional order models [4] to investigate their ability to identify new features in high-grade prostate cancer.

Development of a non-invasive quantitative imaging biomarker for high grade prostate cancer will be useful for improving biopsy yield and grade accuracy, accurately identifying men appropriate for surveillance versus curative therapy, and reduce biopsies needed on surveillance of indolent disease.

## REFERENCES

- [1] Epstein, J. I., et al. Euro. Urol. 61 (2012): 1019-1024.
- [2] Bennett, K. M., et al. Magn1019-1024. Reson. Med. 50 (2003): 727-734.
- [3] Berbian-Santos, M.N. et al. Chem. Phys. 315 (2005): 171-182.
- [4] Ingo, C., et al. Magn. Reson. Med. 71 (2014): 617-627.