Prostatome: A combined anatomical and disease based MRI atlas of the prostate

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Purpose: In this work, the authors introduce a novel framework, the anatomically constrained registration (AnCoR) scheme and apply it to create a fused anatomic-disease atlas of the prostate which the authors refer to as the prostatome. The prostatome combines a MRI based anatomic and a histology based disease atlas. Statistical imaging atlases allow for the integration of information across multiple scales and imaging modalities into a single canonical representation, in turn enabling a fused anatomical-disease representation which may facilitate the characterization of disease appearance relative to anatomic structures. While statistical atlases have been extensively developed and studied for the brain, approaches that have attempted to combine pathology and imaging data for study of prostate pathology are not extant. This work seeks to address this gap.

Methods: The AnCoR framework optimizes a scoring function composed of two surface (prostate and central gland) misalignment measures and one intensity-based similarity term. This ensures the correct mapping of anatomic regions into the atlas, even when regional MRI intensities are inconsistent or highly variable between subjects. The framework allows for creation of an anatomic imaging and a disease atlas, while enabling their fusion into the anatomic imaging-disease atlas. The atlas presented here was constructed using 83 subjects with biopsy confirmed cancer who had pre-operative MRI (collected at two institutions) followed by radical prostatectomy. The imaging atlas results from mapping the *in vivo* MRI into the canonical space, while the anatomic regions serve as domain constraints. Elastic co-registration MRI and corresponding *ex vivo* histology provides “ground truth” mapping of cancer extent on *in vivo* imaging for 23 subjects.

Results: AnCoR was evaluated relative to alternative construction strategies that use either MRI intensities or the prostate surface alone for registration. The AnCoR framework yielded a central gland Dice similarity coefficient (DSC) of 90%, and prostate DSC of 88%, while the misalignment of the urethra and verumontanum was found to be 3.45 mm, and 4.73 mm, respectively, which were measured to be significantly smaller compared to the alternative strategies. As might have been anticipated from our limited cohort of biopsy confirmed cancers, the disease atlas showed that most of the tumor extent was limited to the peripheral zone. Moreover, central gland tumors were typically larger in size, possibly because they are only discernible at a much later stage.

Conclusions: The authors presented the AnCoR framework to explicitly model anatomic constraints for the construction of a fused anatomic imaging-disease atlas. The framework was applied to constructing a preliminary version of an anatomic-disease atlas of the prostate, the prostatome. The prostatome could facilitate the quantitative characterization of gland morphology and imaging features of prostate cancer. These techniques, may be applied on a large sample size data set to create a fully developed prostatome that could serve as a spatial prior for targeted biopsies by urologists. Additionally, the AnCoR framework could allow for incorporation of complementary imaging and molecular data, thereby enabling their careful correlation for population based radio-omics studies. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4881515>]

Key words: anatomic imaging atlas, prostate cancer, guided biopsy, *in vivo* imaging, image processing

1. INTRODUCTION

Statistical biomedical atlases allow for the succinct encapsulation of structural, functional, and anatomical variability of organs across a population within a single reference or canonical representation. For example, imaging data from multiple patients may be projected into the canonical space to create a statistical imaging atlas.^{1,2} This could help facilitate the characterization of the variation in appearance and shape of organ anatomy and morphology across a population. Similarly, disease atlases from imaging data have been constructed to characterize the 3D spatial distribution of diseases, such as prostate cancer.^{3,4} These atlases could help improve interventional procedures, such as image guided biopsies^{4,5} to sample the organ in those regions where the atlas indicates the higher likelihood of disease. Thus these disease atlases may serve as *a priori* cancer probability maps to facilitate the computer assisted diagnosis of disease.^{6,7}

However, these disease atlases require explicit delineation of disease presence and extent on the imaging data. Typically this is only possible to do definitively on histopathology and not on *in vivo* imaging which does not have the resolution or sensitivity to confirm disease extent. This suggests that the region of disease delineated on histology needs to be mapped onto the corresponding *in vivo* imaging. This mapping of disease extent from histology onto the corresponding *in vivo* imaging and then subsequently onto the canonical space representation could allow for creation of a fused anatomic imaging-disease atlas. Such fused imaging-disease atlases may further the discovery of quantitative *in vivo* imaging biomarkers for distinguishing benign, indolent, and aggressive variations of the same disease.

In vivo imaging atlases have been previously constructed for various organs, such as brain,^{1,2} heart,^{8,9} and prostate.¹⁰ Where available, histology can be fused with imaging to define targets *in vivo* for which variations in morphology can be quantified across a population. However for the brain, availability of corresponding histopathology is only possible post-mortem in healthy human subjects¹¹ or animal models.^{12,13}

In the context of the prostate, relatively little work has been done in creating imaging atlases or disease atlases.^{3-5,10,14,15} Additionally there has been no work, that we are aware of, that has attempted to marry the MRI and disease atlases into a single canonical representation. In this work, we attempt to combine an MRI based prostate atlas with a disease based atlas constructed from histology to create a fused anatomic-disease atlas for the prostate, one that we refer to as the prostatome. MRI has been increasingly used over the past decade for staging of prostate cancer.¹⁶⁻¹⁸ However, definitive validation of the ability of MRI to identify prostate cancer requires corresponding histopathology. Cancer delineations on histology can be accurately mapped onto corresponding *in vivo* MRI via deformable co-registration methods.¹⁹ Histopathology is usually available in settings where men who have been diagnosed with prostate cancer subsequently undergo a staging MRI prior to radical prostatectomy. Constructing a histology based disease atlas based off the radical prostatectomy specimens and then subsequently mapping the disease onto

in vivo MRI allows for precise study of variation of structural, functional, and morphologic parameters within the diseased region. While a disease atlas (without the fusion of corresponding imaging) can only provide the spatial location and distribution of the disease, an imaging atlas alone without the corresponding disease mapping from histopathology will be unable to capture the population based imaging variations within the diseased regions.

Creating a fused anatomic-disease atlas is replete with challenges in the construction of the imaging atlas and disease atlases, and their subsequent fusion. In the context of the prostate, the anatomic substructures of the prostate, the central gland (CG), and peripheral zone, vary greatly in shape, dimension, and imaging appearance between subjects. Such natural variability hinders the process of intersubject registration, potentially reducing the accuracy of the imaging atlas. Moreover, the disease atlas relies on tumor ground truth delineated on *ex vivo* histology which is only available for those patients that choose radical prostatectomy as treatment. Furthermore, the MRI appearance of disease not only varies between subjects but is also function of spatial location of disease.⁶

To address these challenges we introduce an anatomically constrained registration (AnCoR) framework to construct a fused imaging-disease atlas of the prostate and its anatomic substructures. We refer to this fused atlas as the “prostatome.” AnCoR allows for explicit constraint based modeling of both the central gland and prostate boundaries. The AnCoR framework allows for simultaneous construction of both the imaging and disease atlases, while ensuring the proper accurate alignment of prostatic anatomic substructures. The imaging atlas was constructed by integrating the pre-operative T2-w MRI for men with biopsy confirmed prostate cancer. The disease atlas used the cancer ground truth mapped from histology onto corresponding *in vivo* MRI.¹⁹ The prostatome thus allows for the characterization of the tumor extent relative to the anatomic structures of the prostate in 3D, while providing a statistical model that accurately captures the variation in imaging and shape of these substructures across a population.

In this work, the AnCoR framework was applied on data collected from 83 subjects at two different institutions. The first cohort (S_1) includes 43 subjects with 3.0 Tesla (T) T2-w MRI from one institution, while the second cohort, S_2 , is composed of 40 subjects with 1.5 T T2-w MRI from a second institution. Moreover, 23 subjects from the cohort S_1 had whole mount histology with annotated tumor that was mapped onto corresponding *in vivo* T2-w MRI using the elastic registration approach developed by Chappelow *et al.*¹⁹ The cancer annotations from the 23 patients were used to create the disease atlas.

The AnCoR framework was compared against two state of the art methods. One scheme employed a prostate surface³ and the second method was based off using MRI intensities alone.¹ Region overlap and anatomic landmark deviation were estimated to determine the registration accuracy.

The remainder of this paper is organized as follows. Previous work in atlas construction is presented in Sec. 2. In Sec. 3,

we introduce the AnCoR framework and the methodological details for constructing the imaging and the disease atlases. The atlas fusion scheme is presented in Sec. 4. Section 5 presents results of evaluation for the prostatome obtained via our AnCoR framework and also results of comparative evaluation against other extant schemes. Concluding remarks and future directions are laid out in Sec. 6.

2. PREVIOUS WORK

Many atlas based approaches have been employed in the context of segmentation of anatomic structures.^{20–25} Atlases represent an aggregation of heavily annotated images from multiple subjects. New unsegmented images can be aligned with the deeply annotated atlas in order to map the segmented structures onto the new unseen images. These atlas based segmentation methods have been previously used^{22,23,25} to segment the substructures of the prostate.

Our atlas framework seeks to provide a statistical characterization of organ anatomy and disease extent. We endeavor to create such an atlas by first projecting images from multiple patient studies into the same canonical space representation,^{1,2,26} by co-registering each new study with a predefined template. Previous attempts at atlas construction tend to choose one or more subjects²⁶ as templates. However, in these approaches the registration outcome was biased by the template choice. To address this issue, Evans *et al.*¹ created the template by averaging the registered images. More sophisticated methods²⁷ consider the template as a term in the objective function. Other methods^{28,29} have focused on iteratively averaging the invertible elastic transformation of the template to better fit a target population. Additionally, template-free techniques^{30,31} register all images simultaneously in a groupwise fashion; however, this is known to be computationally challenging due the size of the search space.

Attempts to construct statistical atlases of the prostate have focused on building either an imaging atlas¹⁰ or disease atlas.^{3,14} Very rarely have any of these approaches considered the anatomic substructures in the atlas construction and no study has thus far attempted to include both anatomical substructures and disease distribution within the same atlas. Betrouni *et al.*¹⁰ presented a simulation of a digital imaging atlas of prostatic substructures, but ignored image intensities and spatial distribution of cancer in the digital phantom. Other researchers^{3,14} have looked to develop an *ex vivo* disease atlas from histology with the goal of optimizing prostate biopsy procedures. The lack of (a) *in vivo* imaging data and (b) anatomic constraints to drive the model construction, tends to limit the utility of such atlases for *in vivo* characterization of cancer appearance. More recent studies^{4,5} have looked to coregister histopathology image atlases³ with *in vivo* transrectal ultrasound, but have tended to ignore the anatomic regions within the prostate. Unlike the approach in Ref. 15 that defined the 2D distribution of cancer relative to the prostate boundary, our approach attempts to build a model that captures the 3D spatial distribution of disease extent *in vivo*, relative to an atlas representation of the other anatomic substructures. The prostatome, to the best of our knowledge

represents the first attempt to create a fused *in vivo* imaging-disease atlas in the context of prostate or any other disease.

3. OVERVIEW OF AnCoR AND PROSTATOME

The AnCoR framework (Fig. 1) builds upon our previous work³² by (1) incorporating additional refinements to the original scheme,³² (2) extending the atlas to include data from multiple institutions, and (3) comparing the AnCoR approach against multiple different strategies.

The AnCoR framework allows for the construction of the imaging [Fig. 1(a)] and disease atlases [Fig. 1(b)] and their fusion into the prostatome [Fig. 1(c)], while simultaneously constraining and ensuring the alignment of different anatomic regions. Such anatomic constraints are incorporated directly into the similarity measure, which evaluates both MRI intensity as well as the surface misalignment of the central gland and the prostate boundaries. The central gland is assumed to encompass both the central and transitional zones since their boundaries cannot be readily discerned on T2-w MRI. Surrounding the central gland, the peripheral zone occupies the rest of the prostate and is implicitly modeled by our framework. The central gland and the peripheral zone are anatomically different,³³ as can be seen on T2-w MRI,³⁴ where typically peripheral zone appears hyperintense, while the central gland and tumor reveal a hypointense appearance.

Both imaging and disease atlases are constructed using anatomical constraints placed on the central gland and prostate surface. The AnCoR framework uses an iterative approach that progressively increases the optimized degrees of freedom, from simple translation and scaling to deformable transformations. At each step, the framework maintains the alignment of the MRI, the subregions, and tumor. This ensures that only one transformation is needed to project all information pertinent to a subject onto the canonical space.

4. METHODOLOGICAL DESCRIPTION

4.A. Notations

The notations used in this paper are summarized in Table I. A study $\mathcal{X}$ is defined by (1) an MRI scene $\mathcal{X}^M = (C^M, f^M)$, where C^M is the 3D grid and $f^M(c)$ represents the MRI intensity at each voxel $c \in C^M$ and (2) a histology scene $\mathcal{X}^H = (C^H, f^H)$, with $f^H(d)$ the hematoxylin and eosin (H and E) information at each pixel $d \in C^H$. Several anatomic regions are defined relative to the MRI scene: (1) the prostate (pr), $\mathcal{X}^{pr} = (C^M, f^{pr})$ with $f^{pr}(c) = 1$ within the prostate and zero elsewhere; (2) the central gland (cg), $\mathcal{X}^{cg} = (C^M, f^{cg})$, where $f^{cg}(c) = 1$ within the central gland, and (3) the peripheral zone (pz), $\mathcal{X}^{pz} = (C^M, f^{pz})$, with $f^{pz}(c) = 1$ within the peripheral zone. The tumor is delineated by an expert pathologist relative to the histology scene, $\mathcal{X}^H$, and defined by $\mathcal{X}^{ca} = (C^H, f^{ca})$ where $f^{ca}(d) = 1$ where the cancer is present.

The prostatome $\mathcal{A}$ results from the fusion of the disease atlas $\mathcal{A}^{ca}$, the MRI intensity atlas, $\mathcal{A}^M = (C^M, g^M)$, the central gland shape atlas $\mathcal{A}^{cg} = (C^M, g^{cg})$, and the prostate shape

FIG. 1. Overview of the AnCoR framework for the construction of the prostatome. (a) The anatomic atlas is constructed by simultaneously optimizing MR image intensities and anatomic region alignment; the central gland is depicted in red, while the prostate is shown in yellow. (b) The disease atlas results from the fusion of histology and MRI into the canonical space; the cancer outlined on histology is shown in blue. (c) The prostatome results from merging the anatomic and disease atlases to define the spatial likelihood of cancer relative to the anatomic regions.

atlas $\mathcal{A}^{pr} = (C^M, g^{pr})$. We define $g^\sigma(c)$, $\sigma \in \{M, cg, pr, ca\}$, as the outcome of an aggregation operator that combines the information from the N subject scenes into one value. This aggregated value represents either an MRI intensity, denoted g^M , or a frequency, $g^\sigma(c) \in [0, 1]$, for region $\sigma \in \{cg, pr, ca\}$ and $c \in C^M$.

4.B. Construction of the statistical imaging atlas

The statistical anatomic atlas $\mathcal{A}$ results from the fusion of the subject scenes $\mathcal{X}^\sigma$, $\sigma \in \{M, cg, pr\}$, following their alignment to the registration template and projection into the canonical space of $\mathcal{A}$.¹

To construct the prostatome $\mathcal{A}$, AnCoR optimizes

$$\psi(\mathcal{A}, \mathcal{X}) = I(\mathcal{A}^M, \mathcal{X}^M) + \sum_{\sigma \in \{cg, pr\}} w^\sigma \cdot \psi^\sigma(\mathcal{A}^\sigma, \mathcal{X}^\sigma), \quad (1)$$

where $\mathcal{X}^\sigma$, $\sigma \in \{M, cg, pr\}$ are the different scenes of the subject $\mathcal{X}$ and $\mathcal{A}$ is the anatomic atlas assumed to be available from a previous optimization step. The mutual information,³⁵ I , assesses the similarity of $\mathcal{A}^M$ and $\mathcal{X}^M$, $\psi^\sigma(\mathcal{A}^\sigma, \mathcal{X}^\sigma)$ quantifies the alignment of the anatomic structures $\sigma \in \{cg, pr\}$, and w^σ is an empirically determined weight. In this work, we choose the normalized squared error to evaluate the σ region alignment via

$$\psi^\sigma(\mathcal{A}^\sigma, \mathcal{X}^\sigma) = -\frac{\sum_{c \in C^M} [g^\sigma(c) - f^\sigma(c)]^2}{\sum_{c \in C^M} f^\sigma(c)^2}, \quad (2)$$

where $c \in C^M$, f^σ represents the outline of the region $\sigma \in \{cg, pr\}$ in subject $\mathcal{X}$, while g^σ is the binary representation of region σ in the atlas $\mathcal{A}$. We set $w^{cg} = w^{pr} = w$ to ensure an equal influence of both surface boundary terms on the optimized similarity measure ψ .

TABLE I. Symbols and notations employed in this paper. The following abbreviations are used: *pr*-prostate; *cg*-central gland; *pz*-peripheral zone; *ur*-urethra; *vm*-verumontanum; *ca*-prostate cancer; *Pp*-preprocessing; *Su*-prostate surface registration; and *Mi*-MRI based registration.

Symbol	Description	Symbol	Description
$\mathcal{X}^M = (C^M, f^M)$	MRI scene	$\mathcal{A}^M = (C^M, g^M)$	MRI atlas
$\mathcal{X}^\sigma = (C^M, f^\sigma)$	Region outline $\sigma \in \{pr, cg, pz\}$	$\mathcal{A}^\sigma = (C^M, g^\sigma)$	Shape atlas, $\sigma \in \{pr, cg, pz\}$
$\mathcal{X}^H = (C^H, f^H)$	Histology scene	$\mathcal{A}^{ca} = (C^M, g^{ca})$	Disease atlas
$\mathcal{X}^{ca} = (C^H, f^{ca})$	Cancer outline	$\mathcal{A}$	AnCoR-based prostatome
τ^H	Transformation of $\mathcal{X}^H$ on $\mathcal{X}^M$	$\mathcal{A}_\theta$	Prostatome obtained via method $\theta \in \{Pp, Su, Mi\}$
τ^M	Transformation of $\mathcal{X}^M$ on $\mathcal{A}^M$	I	Mutual information
ψ	Scoring function	ψ^r	Surface similarity measure

TABLE II. Summary of scene parameters for the datasets in S_1 and S_2 . A total of 83 subjects are included in the anatomic atlas, $\mathcal{A}$, which 11 studies were used for parameter optimization. A total of $N_H = 23$ studies have corresponding histology that was mapped onto the corresponding MRIs enabling the construction of $\mathcal{A}^{ca}$.

Cohort	Size	Modality	Data size	Voxel/pixel size	Pr volume (cm ³) median (range)	Annotation cohort size	Annotated region
S_1	43	3.0T T2-w MRI	$512 \times 512 \times N$ ($32 \leq N \leq 56$)	$M \times M \times M'$ $0.27 \text{ mm} \leq M \leq 0.32 \text{ mm}$ $2.2 \text{ mm} \leq M' \leq 3 \text{ mm}$	32.6 (17.4, 139.1)	39 4	Pr, CG Pr, CG, Ur, Vm
	23	Histology	2048×1536	$M \times M \times 5 \mu\text{m}$ $6 \text{ mm} \leq M \leq 8 \mu\text{m}$		23	PCa
S_2	40	1.5T T2-w MRI	$400 \times 400 \times N$ ($19 \leq N \leq 40$)	$0.4 \text{ mm} \times 0.4 \text{ mm} \times M$ $3 \text{ mm} \leq M \leq 5 \text{ mm}$	33.4 (13.0, 138.3)	33 7	Pr, CG Pr, CG, Ur, Vm

The number of degrees of freedom in this model is progressively increased, such that the optimized transformation initially encodes a simple translation and scaling while at the last iteration it represents a deformable transformation. The deformable transform in AnCoR is based on the free form deformation (FFD) (Ref. 36) which optimizes the location of control points initially uniformly distributed on a 3D grid with B-spline interpolation between the points.

The AnCoR framework comprises the following steps:

Step A.1. Ground truth delineation of anatomic structures, prostate, central gland, peripheral zone, urethra (ur), and verumontanum (vm) on MRI, denoted by $\mathcal{X}^\sigma$, $\sigma \in \{pr, cg, pz, ur, vm\}$. These anatomic delineations are obtained via interactive segmentation by an expert radiologist. Note that the regions $\sigma \in \{pr, cg\}$ are used to construct the shape atlases, $\mathcal{A}^\sigma$, while the landmarks $\sigma \in \{pz, ur, vm\}$ are employed for the evaluation of the atlas.

Step A.2. The image intensity, $\mathcal{X}^M$, is preprocessed to remove bias field artifacts via the approach described in Ref. 37, in which low frequency artifacts are moved by normalizing the MRI intensities to the Gaussian filtered MRI intensities.

Step A.3. The simple transformation τ^M to map $\mathcal{X}^M$ to $\mathcal{A}^M$ is determined such that it centers and scales $\mathcal{X}^M$. The centering ensures that the prostate regions $\mathcal{X}^{pr}$ are anchored to a common point, while the scaling corrects for large variations in gland size by restraining the prostate volume to the median within the cohort (approximately 33cm³, see Table II) while maintaining isotropic scaling in the X , Y , and Z axes.

This translation + scaling transformation brings $\mathcal{X}^\sigma$, $\sigma \in \{M, pr, cg, pz, ur, vm\}$ into the canonical space without having to perform an actual affine registration to a selected subject as done by Xing *et al.*²⁶ Previous work²⁷ has indicated that the use of a specific subject as template can inherently introduce bias as the atlas will resemble the chosen template.

Step A.4. Create the MRI intensity atlas $\mathcal{A}^M$, the statistical shape atlases $\mathcal{A}^\sigma$, $\sigma \in \{cg, pz, pr\}$ and fuse them to generate the initial anatomic atlas $\mathcal{A}_{pp}$. The MRI intensity atlas $\mathcal{A}^M = (C^M, g^M)$ results from aggregation of $\mathcal{X}_i^M$, with $g^M = \Phi_{i=1..N}(f_i^M)$ where Φ is a median filter operation and f_i represent the MRI intensity of the subject i . Similarly, the statistical shape atlas $\mathcal{A}^\sigma = (C^M, g^\sigma)$ is created by computing the frequency g^σ as a function of the transformed $\mathcal{X}^\sigma$, and $\sigma \in \{cg, pr\}$. Specifically, the frequency $g^\sigma(c)$ is estimated as

the ratio between the number of occurrences of region σ at location $c \in C^M$, across the total number of considered studies. This initial anatomic atlas, $\mathcal{A}_{pp}$, results from a template free alignment procedure and is used as baseline strategy for comparing against other alternative strategies. The following **Steps A.5-A.6** are expected to produce more accurate results compared to $\mathcal{A}_{pp}$ as the number of degrees of freedom to be optimized increase.

Step A.5. Perform affine registration using anatomic constraints to project the subject scene $\mathcal{X}$ onto $\mathcal{A}_{pp}$. Update τ^M using the optimal affine transformation and update $\mathcal{A}^\sigma$, $\sigma \in \{M, cg, pr\}$ as done in **Step A.4**.

Step A.6. Perform deformable registration using FFD (Ref. 36) with $11 \times 11 \times 11$ grid points to align the subject scenes $\mathcal{X}$ onto the anatomic atlas obtained in **Step A.5**. Update τ^M to include the optimal deformation transform. Update $\mathcal{A}^M$ and $\mathcal{A}^\sigma$, $\sigma \in \{cg, pr\}$, into $\mathcal{A}$ using the aggregation scheme described in **Step A.4**.

Following **Steps A.1-A.6**, the AnCoR based anatomic atlas $\mathcal{A}$ will be created when $w > 0$. We also endeavor to compare $\mathcal{A}$ with other strategies to construct the atlas either (1) by using MRI intensity based registration alone, denoted by $\mathcal{A}_{Mi}$ by setting $w = 0$ when optimizing ψ , or (2) by optimizing $\psi = \psi^{pr}$ in a prostate surface based scheme that generates $\mathcal{A}_{Su}$.

4.C. Constructing disease atlas, $\mathcal{A}^{ca}$, and fusing with the anatomic imaging atlas

Tumor extent is assessed using up to 40 $\times$ magnification on H and E stained *ex vivo* radical prostatectomy specimens obtained from the cohort S_1 for 23 subjects (Table II). The construction of $\mathcal{A}^{ca}$, and its fusion with the anatomic atlas into the prostatome $\mathcal{A}$, is achieved via the following steps.

Step D.1. The cancer extent $\mathcal{X}^{ca}$ is delineated by an expert pathologist relative to the H and E stained histology, $\mathcal{X}^H$. After fixation, the excised prostate was embedded in a paraffin block. The block was cut in thin 3-4 mm sections perpendicular to the urethra, which allowed a rough alignment of histology slices and T2-w MRI in the axial plane.^{19,38} A microtome was used to further cut the sections into 5 μm thick slices. The slices were then stained and digitized using a digital camera following annotation of the disease extent by the expert pathologist.

Step D.2. Correspondences between the slices in the histology $\mathcal{X}^H$ and MRI Scenes $\mathcal{X}^M$ are identified by an expert radiologist and an expert pathologist working in unison. This strategy previously described in details in Refs. 15 and 19 involves identifying corresponding anatomic landmarks, e.g., urethra, verumontanum, or benign prostatic hyperplasia on both the MRI and histology sections to determine the best match. This correspondence determination is facilitated by the fact that the histology slices are cut perpendicular to the urethra, in roughly the same orientation as the MR images.

Step D.3. The mapping of tumor extent $\mathcal{X}^{ca}$ onto $\mathcal{X}^M$ was achieved using the deformable transform τ^H that warps $\mathcal{X}^H$ onto $\mathcal{X}^M$ obtained via the approach presented by Chapelow *et al.*¹⁹ The approach uses a multiattribute combined mutual information (MACMI) scheme to automatically align $\mathcal{X}^H$ onto $\mathcal{X}^M$, and subsequently map $\mathcal{X}^{ca}$ onto $\mathcal{X}^M$.

Step D.4. $\mathcal{X}^{ca}$ is projected onto $\mathcal{A}$ by applying τ^M , obtained and update iteratively in Steps A.3, A.5.-A.6.

Step D.5. Update $\mathcal{A}^{ca}$ by estimating the frequency of cancer occurrence, $g^{ca}(c)$ for $\forall c \in C^M$, as a function of the cancer extent $f_i^{ca}(c)$ of each subject $\mathcal{X}_i$, $i \in \{1, \dots, 23\}$ for which the cancer was mapped from histology onto MRI. The frequency $g^{ca}(c)$ is obtained as the ratio between the number of occurrences of cancer at location $c \in C^M$ aggregated for all subjects $\mathcal{X}_i$, $i \in \{1, \dots, 23\}$ and the total number of subjects (23) with a histologic annotation of cancer presence. $\mathcal{A}^{ca}$ is assessed in 3D relative to $\mathcal{A}^M$, and when merged with the intensity atlas $\mathcal{A}^M$ and shape atlases $\mathcal{A}^{pr}$ and $\mathcal{A}^{cg}$, results in the prostatome $\mathcal{A}$.

5. EXPERIMENTAL RESULTS AND DISCUSSION

5.A. Data description

Table II describes the data used in our study. The imaging anatomic atlas was built based on endorectal T2-w MRI acquired from 83 subjects with biopsy confirmed cancer from two institutions. The disease atlas, $\mathcal{A}^{ca}$ was constructed from the 23 subject subpopulation in cohort S_1 for which *ex vivo* histopathology of the radical prostatectomy was available. S_1 was used for mapping extent of cancer onto the corresponding *in vivo* MRI. Figure 1 shows corresponding MRI for two different subjects from S_1 , for which the central gland, prostate, and tumor are highlighted in red, yellow, and blue, respectively.

The 23 patient studies used to construct the disease atlas $\mathcal{A}^{ca}$ were chosen from a larger cohort of 124 cases, all of which included an MRI exam prior to radical prostatectomy. Of the 124 cases, only 65 studies had usable T2-w MRI with corresponding digitized whole mount histological sections. Of those, 43 randomly chosen cases had the central gland and peripheral zone annotated by an expert radiologist and were included in the cohort S_1 . Twenty three patient studies in S_1 were identified with histological sections on which CaP was visible and could be annotated by the expert pathologist. Forty studies were chosen randomly from a cohort of 83 consecutive cases available from a second institution. These were annotated by the expert radiologist and included in S_2 .

5.B. Evaluation of the imaging atlas

The imaging atlas is evaluated through two performance measures, the deviation between the anatomic landmarks $\sigma \in \{ur, vm\}$ and overlap of anatomic regions, $\sigma \in \{pr, cg, pz\}$. The measures are estimated based off landmarks and regions that are consistently discernible across different subjects in S_1 and S_2 .

5.B.1. Landmark based measures

The anatomic landmarks considered for evaluation are the urethra (ur) and verumontanum (vm). Anatomically, the urethra is a tubular curved structure located centrally within the prostate from base to apex while the verumontanum has a v-like shape visible in the midgland region on just a few axial slices. Other landmarks such as benign prostatic hyperplasia nodules or calcifications are not consistent discernible across subjects and hence were not considered. The successful registration of the subject scene $\mathcal{X}^M$ with the prostatome $\mathcal{A}$ is expected to result in the intersubject alignment of the landmarks that are consistently distinguishable between patients.

In order to compute the deviation between the anatomic landmarks $\sigma \in \{ur, vm\}$, their 3D medial axis³⁹ was first computed and then the deviation between the points on the medial axis was estimated. The medial axis is defined in 3D as the points at the interior of the region σ that are furthest away from the annotated surface. For two subjects $\mathcal{X}_i$ and $\mathcal{X}_j$ we estimated the medial axis deviation denoted by $\|\mathcal{X}_i^\sigma, \mathcal{X}_j^\sigma\|_m$ as to the average Euclidean distance between proximal points on their respective medial axes.

The point c_{ip} on the medial axis of subject $\mathcal{X}_i$ is considered proximal to c_{jq} on the medial axis of subject $\mathcal{X}_j$ if $\|c_{ip}, c_{jq}\|_2 \leq \|c_{ip}, c_{jr}\|_2$, where c_{jr} is any point on the medial axis of subject $\mathcal{X}_j$, such that $r \neq q$. Note that if c_{ip} is proximal to c_{jq} this does not imply that c_{jq} is proximal to c_{ip} . Thus, we estimate the average deviation between anatomic landmarks of subject $\mathcal{X}_i^\sigma$ and $\mathcal{X}_j^\sigma$ as

$$\|\mathcal{X}_{i,j}^\sigma\|_m = \frac{1}{2} \cdot (\|\mathcal{X}_i^\sigma, \mathcal{X}_j^\sigma\|_m + \|\mathcal{X}_j^\sigma, \mathcal{X}_i^\sigma\|_m), \quad (3)$$

where $\sigma \in \{ur, vm\}$.

The average deviation of the landmarks within the evaluation cohort ($N_{ev} = 11$ studies from cohorts S_1 and S_2) is determined as the averaged intersubject deviations for any possible pair-wise combination of subjects. For N_{ev} subject scenes $\mathcal{X}_i^\sigma$, $\forall i \in \{1, \dots, N_{ev}\}$, $\|\mathcal{X}_{1,\dots,N_{ev}}^\sigma\|_m$ is defined for $\sigma \in \{ur, vm\}$ as

$$\|\mathcal{X}_{1,\dots,N_{ev}}^\sigma\|_m = \frac{2}{N_{ev}(N_{ev} - 1)} \cdot \sum_{i=1}^{N_{ev}-1} \sum_{j=i+1}^{N_{ev}} \|\mathcal{X}_{i,j}^\sigma\|_m. \quad (4)$$

5.B.2. Region based measures

The Dice similarity coefficient (DSC) represents the overlap between two regions $\mathcal{X}_i^\sigma$ and $\mathcal{X}_j^\sigma$:

$$DSC(\mathcal{X}_i^\sigma, \mathcal{X}_j^\sigma) = \frac{2 \times |\mathcal{X}_i^\sigma \cap \mathcal{X}_j^\sigma|}{|\mathcal{X}_i^\sigma| + |\mathcal{X}_j^\sigma|}, \quad (5)$$

FIG. 2. Trend of performance evaluation measures and errors estimated for $\mathcal{A}$ as a function of w (a) prostate DSC, (b) central gland DSC, misalignment error of the (c) urethra, and (d) verumontanum. Higher DSC and lower misalignment errors are desirable. Error bars are used to indicate the standard deviation of the measure.

where $|\mathcal{X}^\sigma|$ represents the number of voxels in region $\sigma \in \{cg, pr\}$.

To estimate the population overlap of anatomic regions $\sigma \in \{cg, pr\}$, we compute the averaged DSC as

$$DSC(\mathcal{X}_{1,...,N}^\sigma) = \frac{1}{N} \sum_{i=1}^N DSC(\mathcal{X}_i^\sigma, \mathcal{A}^\sigma), \quad (6)$$

where $\mathcal{A}^\sigma$ represents the binary form of the shape atlas with $\sigma \in \{pr, cg, pz\}$.

The atlas construction framework was implemented using the ITK framework.⁴⁰

5.C. Parameter optimization

In order to identify the optimal contribution of the anatomic constraints, defined by the weight w , the prostateome $\mathcal{A}$ was constructed using $N_{ev} = 11$ studies selected from the two cohorts S_1 and S_2 (Table II). For $w \in [0, 1]$, with a step size of 0.05-0.1, we evaluate the landmark deviation, $\|\mathcal{X}_{1,...,N_{ev}}^\sigma\|_m$, $\sigma \in \{ur, vm\}$, and region overlap, $DSC(\mathcal{X}_{1,...,N_{ev}}^\sigma)$, $\sigma \in \{cg, pr, pz\}$, obtained when constructing the anatomic atlas $\mathcal{A}$ in the affine (Step A.5.) and deformable (Step A.6.) registration steps, respectively.

Our results suggest that $w > 1.0$ did not yield significant changes in landmark misalignment or region overlap. This is probably because increasing w transforms the registration into a surface based alignment scheme with essentially no contribution from the intensity term, I .

In the affine registration step (Fig. 2), both $\|\mathcal{X}_{1,...,N_{ev}}^\sigma\|_m$, $\sigma \in \{ur, vm\}$ and $DSC(\mathcal{X}_{1,...,N_{ev}}^\sigma)$, $\sigma \in \{cg, pr, pz\}$ improved for $w > 0$ when compared to the baseline $w = 0$, which is equivalent to $\mathcal{A}_{Mi}$. These results indicate the need of surface constraints as defined in the AnCoR framework for accurate prostatome construction. However, for $w > 0.5$, the central gland or prostate DSC and landmark misalignment error remain relatively constant, indicating that the influences of the surface terms significantly outweigh the influence of the intensity term. Therefore since $w = 0.5$ yielded the highest $DSC(\mathcal{X}_{1,...,N_{ev}}^\sigma)$ with minimal $\|\mathcal{X}_{1,...,N_{ev}}^\sigma\|_m$, we choose this value for constructing $\mathcal{A}$.

When evaluating $\mathcal{A}$ after deformable registration, trends in DSC were observed to be similar to the affine registration step (Fig. 2). $DSC(\mathcal{X}_{1,...,N_{ev}}^\sigma)$ increases progressively up to $w = 0.2$, beyond which, it converges to a region overlap value of 93%. This value is higher than observed in the affine registration step which suggests the need of the deformable registration step when constructing $\mathcal{A}$. The landmark misalignment is roughly constant for values of $w < 0.1$, but fluctuates as w increases. The value of w was set equal to 0.05 in the deformable registration step based on an optimal trade-off between $\|\mathcal{X}_{1,...,N_{ev}}^\sigma\|_m$ and $DSC(\mathcal{X}_{1,...,N_{ev}}^\sigma)$.

5.D. The anatomic imaging atlas

The anatomic imaging atlas is constructed using $N = 83$ from S_1 and S_2 . Figure 3 illustrates the MRI atlas $\mathcal{A}^M$,

FIG. 3. Visualizing resulting image intensities within the AnCoR-based atlas in the (a) base, (b) midgland, and (c) apex of $\mathcal{A}^M$. The optimal alignment of the anatomic regions (central gland and prostate capsule) is suggested by the presence of a consistent hypointense boundary [see arrows in (b)]. Additionally one can observe that the urethra for all the patient studies are well aligned as suggested by the distinct capsule boundary [see arrow in (c)].

FIG. 4. Cancer spatial distribution atlas $\mathcal{A}^{ca}$ coupled with the statistical shape atlas of the prostate anatomic substructures: (a)–(c) $\mathcal{A}^{cg}$, $\mathcal{A}^{pz}$, $\mathcal{A}^{pr}$; (d)–(f) $\mathcal{A}^{ca}$ relative to statistical shape of the prostate, $\mathcal{A}^{pr}$; (g)–(i) $\mathcal{A}^{ca}$ relative to statistical shape of the central gland, $\mathcal{A}^{cg}$, and, peripheral zone, $\mathcal{A}^{pz}$. (d)–(i) Cancer frequency are assessed relative to $\mathcal{A}^{ca}$ as: low (green) for $0.05 \leq g^{ca} \leq 0.11$, medium (blue) when $0.11 < g^{ca} \leq 0.16$, and high (red) for $g^{ca} > 0.16$.

showing hypointense regions within the central gland and hyperintense values in peripheral zone. The clarity of the urethra and the boundary between central gland and peripheral zone within $\mathcal{A}^M$, suggests a very good registration. The statistical shape atlases, $\mathcal{A}^\sigma$, $\sigma \in \{pr, cg, pz\}$, illustrated in

Figs. 4(a)–4(c), shows the average shape of these regions as well as their relative spatial arrangement in the prostate. The volume of $\mathcal{A}^\sigma = (C^M, g^\sigma)$, $\sigma \in \{pr, cg, pz\}$, was found to be 25.2 cm^3 , 11.4 cm^3 , and 9.2 cm^3 , respectively. The volume of the prostate is slightly smaller than the median population

FIG. 5. Comparing the prostate statistical shape between $\mathcal{A}^{pr}$ and (a)–(c) $\mathcal{A}^{pr}(S_1)$, (d)–(e) $\mathcal{A}^{pr}(S_2)$; colors indicate minimal surface distances (in mm) between $\mathcal{A}^{pr}$ and $\mathcal{A}^{pr}(S_\beta)$, where $\beta \in \{1, 2\}$: (a),(d) base; (b),(e) midgland region; and (c)-(f) apex.

TABLE III. Prostate, central gland DSC, and landmark misalignment evaluated when computing the anatomic atlas across sites $\mathcal{A}$ or within sites, $\mathcal{A}(S_1)$ and $\mathcal{A}(S_2)$. Cohort S_1 seems to have a more homogeneous population compared to cohort S_2 , as reflected via the DSC and minimal landmark misalignment measures.

Atlas	Cohort	Pr DSC (%)	CG DSC (%)	Ur Dev (mm)	Vm Dev (mm)
$\mathcal{A}$	$S_1; S_2$	88	90	3.45	4.73
$\mathcal{A}(S_1)$	S_1	92	90	2.57	2.82
$\mathcal{A}(S_2)$	S_2	89	89	3.76	4.51

volume, on account of shrinkage caused by preprocessing step and the affine registration.

5.E. The disease atlas, $\mathcal{A}^{ca}$

Figure 4 illustrates the spatial distribution of cancer within $\mathcal{A}^{pr}$ [Figs. 4(d)–4(f)] as well as within $\mathcal{A}^{cg}$ and $\mathcal{A}^{pz}$ [Figs. 4(g)–4(i)]. As previously suggested,⁴¹ the highest frequency of cancer is present in the peripheral zone proximal to the neurovascular bundles. However, preponderance of cancer is also observed in the central gland toward the prostate apex. Central gland tumors were observed to be larger in volume

which renders them more likely to spatially overlap within the atlas, thus resulting in a visibly higher spatial frequency within the central gland. Although atypical, such findings are consistent with the fact that central gland tumors are often detected at later stages of disease, and thus are considerably larger in volume than the peripheral zone tumors. Additionally, the spatial distribution of tumor was not symmetric as indicated previously.⁴²

5.F. Comparing atlas appearance across sites

To evaluate the precise variability in the appearance of the imaging atlases constructed using data from the two sites, we constructed $\mathcal{A}$ using data from (1) cohort S_1 alone (43 subjects) and referred to as $\mathcal{A}(S_1)$, (2) cohort S_2 alone (40 subjects) and referred to as $\mathcal{A}(S_2)$ and (3) cohorts S_1 and S_2 together (83 subjects) referred to as $\mathcal{A}$ (Fig. 5). Although the prostate median volume was consistent across the two sites (Table II), the statistical shape of the anatomic regions differs, particularly in the base and apex regions. Figure 5 shows the surface distances between the $\mathcal{A}^{pr}$ compared to the prostate shape in $\mathcal{A}^{pr}(S_1)$ and $\mathcal{A}^{pr}(S_2)$. Near perfect alignment is observable in the midgland [Figs. 5(b) and 5(e)], while up to 5 mm misalignment error is observable in the base and apex.

FIG. 6. Heatmap showing the error in alignment of the urethra across patient studies, (left column) $\mathcal{A}_{Mi}^M$, (middle column) $\mathcal{A}_{Su}^M$, and (right column) $\mathcal{A}^M$. Representative sections are illustrated from (a)–(c) the base, (d)–(f) the midgland, and (g)–(i) the apex; the blue color indicates substantial overlap (low error) for the urethra across studies, while red reflects the converse (high error).

FIG. 7. Quantitative evaluation of region overlap (% DSC) and landmark misalignment (mm) in A_{Pp} , A_{Mi} , A_{Su} , and A ; The symbol * indicates statistical significance based on Wilcoxon tests with multiple comparison correction.

Table III shows the evaluation measures (DSC and landmark misalignment) for $A(S_1)$, $A(S_2)$, and A . The DSC measures were consistent across S_1 and S_2 ; however, the landmark deviation errors are smaller when using S_1 alone. While a certain amount of variability in the atlases constructed using S_1 and S_2 is to be expected, given the variability in imaging performed across different sites and populations being scanned, vendors and platform, the results in Table III suggest that the atlas construction framework is relatively resilient to the intersite imaging differences. For the remainder of the paper, we will use the data from both sites (S_1 and S_2) to construct the imaging atlas, disease atlas, and the prostatome.

5.G. Comparative strategies for prostatome construction

We compared A built via AnCoR with the atlases resulting from the alternative strategies using surface, A_{Su} , and intensity, A_{Mi} , terms alone. A_{Mi} employs MRI intensity alone without invoking any anatomic constraints, and achieved by setting $w = 0$ in Eq. (1). Moreover, similar to Ref. 3, A_{Su} is constructed through the prostate surface registration.

Figure 6 illustrates the accuracy of urethra alignment in the apex, midgland, and base regions within A_{Su} , A_{Mi} , and A . A achieves the best alignment of urethrae, particularly between the midgland and apex where the curvature of the urethra is minimal.

Figure 7 summarizes the quantitative comparison of A_{Mi} , A_{Su} , and A , as well as the baseline atlas A_{Pp} . A yields statistically better landmark alignment as well as large region overlap. Not surprisingly, A_{Su} yielded the highest $DSC(\mathcal{X}_{1,...,N}^{pr})$ value (Fig. 7) given that the atlas construction is solely driven by prostate surface alignment. However, it can be noted that A resulted in better $DSC(\mathcal{X}_{1,...,N}^{cg})$ a statistically significantly

improvement compared to A_{Mi} and A_{Su} . By contrast, A_{Mi} yielded the lowest DSC, independent of the region, as well as the largest misalignment error for the verumontanum. The fact that this error was even worse than A_{Pp} suggests that a registration purely based in MRI intensity is insufficient to accurately construct the prostatome.

6. CONCLUDING REMARKS

In this work, we presented the anatomically constrained registration (AnCoR) framework for the construction of an imaging and a disease atlas, and subsequent fusion of these two atlases. The AnCoR framework was applied here to construct the prostatome, a fused anatomic-disease atlas of the prostate by constraining the prostate and the central gland surfaces, while using an MRI intensity similarity term to drive patient-atlas registration. The AnCoR framework benefits from uniquely leveraging the complementary nature of surface based and MRI intensity based registration techniques, ensuring accurate alignment of anatomic regions as well as internal structures. In comparison, neither of the alternative approaches considered (surface or MRI intensity based)^{3,10} was able to accurately align the anatomic substructures. The registration based solely on MRI intensities introduced errors due to the subtle image intensities between anatomic substructures. By contrast, the registration based solely on prostate surface boundaries introduced large deformations and smearing effects. The AnCoR framework provides good alignment at the apex and base of the prostate, where expert annotations errors are known to be the largest. Such a result is likely the outcome of optimizing the influence of the surface terms by the weight w .

The anatomic atlas was built based on data collected at two sites. The heterogeneity in the image scanning parameters and

population is reflected most prominently in the base and apex of the prostatome. Future work will attempt to capture the variability in MRI intensity between sites.

Through the fusion of *in vivo* MRI and histology with prostate cancer delineation, we were able to create a disease atlas which allowed us to estimate the 3D spatial distribution of cancer relative to the anatomic substructures of the prostate. While our studies comprised a larger number of peripheral zone tumors, the central gland tumors tended to be larger in size. To our knowledge this is the first study attempting to estimate the prostate cancer distribution in 3D relative to the anatomic structures of the prostate via *in vivo* MRI. The small cohort of 23 patient for which cancer ground truth was available in this study, allowed us to create a preliminary version of the prostatome. With inclusion of additional studies in the future, we seek to increase the statistical power of the prostatome. We anticipate that the atlas could serve as a guide for directed biopsies and targeted treatment. Of potential clinical impact as well, is the use of this approach for surgical or radiotherapy planning intended to spare the anatomically closely adjacent neurovascular bundles so as to reduce the incidence of unintended impotence.

We acknowledge that our study had a few limitations. Our approach used manual delineation of the anatomic regions, the central gland, peripheral zone, and prostate. As we look to increase the number of studies to be incorporated into prostatome, clearly manual delineation will be unfeasible and also subject to inter- and intraobserver variability. Toward this end our group has already developed automated schemes for segmentation of substructures within the prostate.^{43,44} The AnCoR framework is designed to allow the simultaneous optimization of MR image intensity similarity and anatomic region overlap without explicitly reinforcing the preservation of region volume. The choice of template and the simultaneous consideration of both central gland and prostate region in the optimization will affect the volume of the prostate following registration. The possible changes in prostate volume after registration does not however influence the ability of the framework to create a unified canonical representation of the patient cohort to study the spatial distribution of cancer. Finally, our elastic registration step uses free form deformation (FFD).³⁶ We will look to integrate smoothness and additional regularization within FFD as part of future work.

Despite these limitations, our AnCoR framework provides a platform for the fusion of multimodal data into a single canonical representation. The prostatome could ultimately pave the way for the study of *in vivo* imaging markers associated with aggressive disease. Moreover, this framework could serve as a model for the integration of multimodal, multiscale imaging and molecular data which could pave the way for creation of a fused imaging-pathology-omics atlas for cross-scale interrogation of disease. This could enable correlative studies of imaging and omics features associated with the disease.

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