A Bayesian nonrigid registration method to enhance intraoperative target definition in image-guided prostate procedures through uncertainty characterization

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Purpose: This study introduces a probabilistic nonrigid registration method for use in image-guided prostate brachytherapy. Intraoperative imaging for prostate procedures, usually transrectal ultrasound (TRUS), is typically inferior to diagnostic-quality imaging of the pelvis such as endorectal magnetic resonance imaging (MRI). MR images contain superior detail of the prostate boundaries and provide substructure features not otherwise visible. Previous efforts to register diagnostic prostate images with the intraoperative coordinate system have been deterministic and did not offer a measure of the registration uncertainty. The authors developed a Bayesian registration method to estimate the posterior distribution on deformations and provide a case-specific measure of the associated registration uncertainty.

Methods: The authors adapted a biomechanical-based probabilistic nonrigid method to register diagnostic to intraoperative images by aligning a physician's segmentations of the prostate in the two images. The posterior distribution was characterized with a Markov Chain Monte Carlo method; the maximum *a posteriori* deformation and the associated uncertainty were estimated from the collection of deformation samples drawn from the posterior distribution. The authors validated the registration method using a dataset created from ten patients with MRI-guided prostate biopsies who had both diagnostic and intraprocedural 3 Tesla MRI scans. The accuracy and precision of the estimated posterior distribution on deformations were evaluated from two predictive distance distributions: between the deformed central zone-peripheral zone (CZ-PZ) interface and the physician-labeled interface, and based on physician-defined landmarks. Geometric margins on the registration of the prostate's peripheral zone were determined from the posterior predictive distance to the CZ-PZ interface separately for the base, mid-gland, and apical regions of the prostate.

Results: The authors observed variation in the shape and volume of the segmented prostate in diagnostic and intraprocedural images. The probabilistic method allowed us to convey registration results in terms of posterior distributions, with the dispersion providing a patient-specific estimate of the registration uncertainty. The median of the predictive distance distribution between the deformed prostate boundary and the segmented boundary was ≤ 3 mm (95th percentiles within ± 4 mm) for all ten patients. The accuracy and precision of the internal deformation was evaluated by comparing the posterior predictive distance distribution for the CZ-PZ interface for each patient, with the median distance ranging from -0.6 to 2.4 mm. Posterior predictive distances between naturally occurring landmarks showed registration errors of ≤ 5 mm in any direction. The uncertainty was not a global measure, but instead was local and varied throughout the registration region. Registration uncertainties were largest in the apical region of the prostate.

Conclusions: Using a Bayesian nonrigid registration method, the authors determined the posterior distribution on deformations between diagnostic and intraprocedural MR images and quantified the uncertainty in the registration results. The feasibility of this approach was tested and results were positive. The probabilistic framework allows us to evaluate both patient-specific and location-specific estimates of the uncertainty in the registration result. Although the framework was tested on MR-guided procedures, the preliminary results suggest that it may be applied to TRUS-guided procedures

as well, where the addition of diagnostic MR information may have a larger impact on target definition and clinical guidance. © 2012 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4760992>]

Key words: deformable probabilistic registration, prostate, brachytherapy

I. INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men in the U.S. and the second leading cause of death from cancer in American men.¹ Three major modalities are used to treat clinically localized prostate cancer: surgery, external beam radiation therapy, and interstitial radiation therapy (brachytherapy). It has been shown that all three may have significant side effects, including urinary, rectal, and sexual dysfunction.² With 10-year survival rates of 95% in low-risk patients,³ these complications represent significant issues, requiring a balance between definitive cancer control, preservation of physiologic function, and maintenance of quality of life as the goals of treatment. These issues make highly accurate treatment techniques an important part of prostate cancer therapy.

In prostate brachytherapy, low dose-rate radioactive seeds may be permanently implanted throughout the prostate gland. Conventionally this is performed under intraoperative image guidance that is inferior to diagnostic-quality imaging. Magnetic resonance imaging (MRI) with an endorectal coil (ERC) is widely accepted as the modality of choice for prostate imaging due to its superior soft-tissue contrast. While some institutions have reported on the use of intraoperative MRI, transrectal ultrasound (TRUS) imaging is almost universally used for image guided prostate procedures. TRUS identifies the prostate boundaries well at mid-gland but not so well at the base and apex. Furthermore, with TRUS it is difficult to visualize the prostate substructure, namely the central zone (CZ) and peripheral zone (PZ). Due to the limited visualization of the gland, less than ideal placement of the radioactive seeds can occur, potentially leading to increased complications and decreased local control. Partial gland implants using MRI-guided seed placements have demonstrated the ability to reduce acute toxicities by targeting prostate substructures visible on MRI.⁴ As the majority of prostate cancers are confined to the PZ,⁵ partial-gland implants targeting the PZ may be desirable to treat localized disease while potentially reducing treatment complications.

If brought into the intraoperative coordinate system, the additional details available in diagnostic-quality images may improve the target definition for brachytherapy, making it possible to target the PZ or a localized tumor during an implant. However, large changes in prostate shape have been observed between diagnostic images taken with the patient supine and using an ERC and intraoperative images taken with the patient in the lithotomy position and using a rectal obturator (to attach a perineal template).⁶ These changes are likely caused by differences in patient positioning and bladder and rectal filling. Due to the difference in quality between diagnostic and intraoperative imaging and the potentially large shape changes

in the prostate, it is difficult to manually align diagnostic and intraoperative images.

To date, several works have been published with the objective of applying nonrigid registration methods to prostate images. Intensity-based methods, such as the demon's algorithm,^{7,8} maximize a similarity criterion by comparing image intensities, which is not possible between different modalities such as MRI and TRUS. Mutual information is a popular similarity criterion and has been reported to be effective for registering prostate images.⁹ Other methods employed include free-form deformation,¹⁰ narrow band registration,¹¹ viscous-fluid models,¹² thin-plate splines,¹³ B-splines,¹⁴ and elastic finite element (FE) model-based methods.^{15–17} Several authors reported the registration accuracy using the residual error in implanted fiducials as a metric, either with clinical data or phantoms. Brock *et al.* calculated residual error between the surface points of the FE model and the segmented intratreatment prostate following deformable registration.¹⁸ None of the available methods can estimate the registration uncertainty on the exterior prostate surface or the internally deformed prostate substructure.

The objective of this study was to introduce a Bayesian biomechanical-based nonrigid method of registering diagnostic MR to intraprocedural MR prostate images. This registration method, previously presented elsewhere,¹⁹ is uniquely suited for modeling prostate substructure because it jointly estimates both the surface and volumetric deformations under an elastic constraint. In Bayesian registration, a posterior probability distribution is defined over the space of possible deformations and conditioned on the data, which in this case was the physician-segmented prostates in the diagnostic and intraprocedural images. In the proposed framework, a Monte Carlo sampler was used to characterize the posterior distribution over deformations that align the two segmentations. The maximum *a posteriori* (MAP) deformation that aligns the two images was given by the mode of the posterior distribution, whereas the spread of the posterior distribution around the mode, described by distribution quantiles or percentiles, gives information about the registration uncertainty or the probability of the deformation to move away from the most likely result. With this information, the prostate substructure may be viewed in the intraoperative coordinate system along with the position uncertainty of the boundaries and transformed substructures or landmarks. Knowing the most likely position and the estimated uncertainty on the location of the target may allow a clinician to make better informed decisions about adjusting a treatment plan to improve target coverage or spare critical structures.

Because it requires only manual segmentations of the prostate gland in both the diagnostic and the intraoperative

images, the Bayesian registration approach is not restricted to a specific imaging modality or to using common modalities. To check the feasibility of the method, we used it to register diagnostic MR to intraprocedural MR images instead of TRUS. By starting with intraprocedural MR images, we were able to evaluate the accuracy of the registration by comparing the internal gland substructure between the deformed diagnostic and intraoperative target images. With intraoperative TRUS images, it would be difficult to evaluate the accuracy of internal deformations because the substructure is not well visualized in TRUS. Using the same modality to check the registration method also minimizes additional sources of uncertainty, such as uncertainty in segmentation of the prostate, and allows us to characterize the uncertainty due primarily to the method.

This study presents a Bayesian registration approach with the ability to provide both patient-specific and region-specific estimates of the uncertainty in the registration results. This approach was applied to MRI datasets and used MRI imaging features for evaluation.

II. MATERIALS AND METHODS

The feasibility of the probabilistic registration method was checked on a dataset of images obtained from ten MRI-guided prostate biopsy cases.^{20,21} The registration was performed between the physician-segmented prostates in diagnostic 3 Tesla (T) MR images and intraprocedural 3 T MR-guided images. Registration accuracy was evaluated using both the physician-segmented prostate substructure and physician-defined prostate landmarks. The distribution of registrations was then used to estimate a geometric margin around the most probable deformation.

II.A. Patient data

This study was performed as part of a clinical research protocol for MRI-guided prostate biopsy which is HIPAA compliant and approved by the appropriate Institutional Review Board. MR images were collected from ten consecutive patients with clinical indications of prostate cancer (palpable abnormality under digital rectal examination and/or rising levels of prostate specific antigen).^{20,21} Patients accepted into the protocol had at least two previous negative TRUS-guided biopsies or an inability to access the rectum by TRUS, for example due to a prior colostomy. The imaging studies consisted of a preprocedural multiparametric MRI and an intraprocedural MRI used for biopsy guidance.

The same multiparametric MR imaging protocol was applied for all patients, and included T1-weighted, T2-weighted (T2W), diffusion-weighted, and dynamic contrast-enhanced series. Imaging was performed with the patient supine on a 3 T GE SignaHdx scanner (GE Medical Systems, Milwaukee, WI). In eight out of ten patients, an ERC (MEDRAD, Warrendale, PA) with a combination of body and surface coils was used. For two patients the ERC could not be used due to the patient's medical condition. This study utilized only the axial T2W series that was acquired using a 2D fast-recovery fast-

FIG. 1. MR image transverse slice through the prostate mid-gland for one patient. (a) shows a diagnostic image with endorectal coil (ERC) and the corresponding prostate gland segmentation with the central zone depicted in gray and the peripheral zone in white. (b) shows an intraprocedural image without an ERC and the corresponding prostate gland segmentation.

spin-echo (FRFSE) sequence with the following parameters: repetition time (TR), 3083 ms; echo time (TE), 106 ms; field of view (FOV), 160 mm; matrix, 384×224 ; slice thickness, 3 mm; and pixel spacing, 0.3 mm. The number of slices in the diagnostic image ranged from 22 to 30.

The MRI-guided biopsy procedure was performed in a 70-cm bore 3 T Siemens Magnetom Verio scanner (Siemens Medical Systems, Erlangen, Germany). The patient was placed in the lithotomy position with custom MR-compatible stirrups, and a T2W axial image of the prostate gland was obtained using a combination of Body Matrix and Spine surface coil elements (Siemens Medical Systems, Erlangen, Germany). The ERC was not used in intraprocedural imaging to simplify procedural logistics. The imaging was done using a turbo spin echo (TSE) sequence with: TR/TE, 5250/100 ms; FOV, 140 mm; matrix, 320×224 ; slice thickness, 3 mm; and pixel spacing, 0.4 mm. The number of slices in the intrabiopsy image ranged from 22 to 40.

The prostate gland (PG), central zone (CZ), and peripheral zone (PZ) were segmented for each patient on both the diagnostic and intraprocedural MR images. Segmentation was performed manually by an abdominal radiologist with over 10 years experience in prostate imaging using the 3D Slicer,²² and the segmentations were stored as binary masks. An example of an image slice through the prostate mid-gland and the corresponding segmentation are shown in Fig. 1 for one patient.

II.B. Image registration

We designed a Bayesian nonrigid registration method that uses an elastic biomechanical model to align the physician's segmentation of the prostate gland Ω_r in the diagnostic MRI

$$I_r(\mathbf{x}) = \begin{cases} 1 & \text{if } \mathbf{x} \in \Omega_r \\ 0 & \text{otherwise} \end{cases},$$

with the prostate gland Ω_t in the intraoperative image

$$I_t(\mathbf{x}) = \begin{cases} 1 & \text{if } \mathbf{x} \in \Omega_t \\ 0 & \text{otherwise} \end{cases}.$$

In this section we first present the underlying biomechanical prostate model, followed by a description of the Bayesian registration framework that aligns the segmented prostates under the constraint of the biomechanical model. The characterization of the posterior distribution is then explained. Finally, we discuss preprocessing of the segmentations before registration.

II.B.1. Biomechanical prostate model

We assume that a prostate Ω_r is well modeled with an isotropic elastic biomechanical model. In the FE-setting,^{23,24} Ω_r is discretized with a FE-mesh $\mathcal{M} = \{\mathcal{E}, \mathcal{V}\}$; the disjoint finite tetrahedral elements $\mathcal{E} = \{\mathbf{e}_1, \dots, \mathbf{e}_E\}$ are connected at the set of mesh vertices $\mathcal{V} = \{\mathbf{v}_1, \dots, \mathbf{v}_N\}$, where $\mathbf{v}_i$ has coordinates $(x_i, y_i, z_i)^\top$ in Ω_r . Associated with each vertex $\mathbf{v}_i$ is a displacement vector $\mathbf{u}_i = (\delta x_i, \delta y_i, \delta z_i)^\top$. The displacement vector at any voxel $\mathbf{x} \in \Omega_r$ can be determined using linear interpolation of the displacements at the vertices of its enclosing tetrahedral element. The elastic energy of the displacement $\mathbf{u}$ of the mesh takes the form

$$E_{\text{el}}(\mathbf{u}) = \frac{1}{2} \int_{\mathbf{x} \in \Omega_r} \mathbf{u}(\mathbf{x})^\top \mathbf{K}_\mathbf{x} \mathbf{u}(\mathbf{x}) d\mathbf{x}. \quad (1)$$

The stiffness matrix $\mathbf{K}_\mathbf{x}$ is a constant in a linear elastic material model, but spatially varying if using inhomogenous tissue parameters. The elastic energy is characterized by two material parameters: Young's elastic modulus E and Poisson's ratio ν . Young's modulus is a measure of the stiffness of an elastic material, and is defined as the ratio of stress (force per unit area) to strain (fractional increase in length) in the direction of the load. Poisson's ratio is the ratio of the strain perpendicular to the applied load (contraction or transverse strain) to the strain in the direction of the load. Together, these parameters determine the elastic properties of the material being modeled.

Let us separate the nodes in $\mathcal{V}$ into boundary nodes $\mathcal{B} = \{\mathbf{n}_{b,1}, \dots, \mathbf{n}_{b,B}\}$, where $\mathbf{n}_{b,i} \in \partial\Omega_r$, and internal nodes $\mathcal{I} = \{\mathbf{n}_{i,1}, \dots, \mathbf{n}_{i,I}\}$, where $\mathbf{n}_{i,i} \in \Omega_r \setminus \partial\Omega_r$; then $\mathcal{V} = \mathcal{B} \cup \mathcal{I}$. Given the displacements $\mathbf{u}_b$ for the nodes in $\mathcal{B}$, the displacements $\mathbf{u}_i$ of the internal nodes are found by solving the linear system $\frac{\partial E_{\text{el}}}{\partial \mathbf{u}} = 0$ under the boundary conditions.

II.B.2. Bayesian nonrigid prostate registration

We formulate the registration in a Bayesian framework where we treat the boundary displacements $\mathbf{u}_b$ as random variables and estimate the posterior distribution over $\mathbf{u}_b$ under an elastic prior model,

$$\Pr(\mathbf{u}_b \mid \mathcal{D}, \mathcal{M}) \propto \Pr(\mathcal{D} \mid \mathbf{u}_b, \mathcal{M}) \Pr(\mathbf{u}_b \mid \mathcal{M}), \quad (2)$$

where $\mathcal{D}(\mathbf{x}) = \text{dist}(\mathbf{x}, I_t)$ is a signed distance map which measures the distance of a point $\mathbf{x}$ to the boundary of the segmented intraoperative prostate gland $\partial\Omega_t$. We compute the distance map using the signed Danielsson's distance map method.²⁵

Because of the lack of tissue contrast between the PG and other structures, there is an uncertainty in the prostate seg-

mentation in most imaging modalities.^{26,27} Even in MR images, where the soft-tissue resolution is excellent, there are limitations due primarily to the 3 mm slice thickness. In contrast to previously published methods on segmentation-based alignment of the prostate, the Bayesian framework allows us to include a model of the uncertainty of the prostate segmentation in the registration. In the likelihood, the distance of each boundary node from $\partial\Omega_t$ is modeled with independent identically distributed univariate zero-mean normal distributions,

$$\Pr(\mathcal{D} \mid \mathbf{u}_b, \mathcal{M}) = \prod_{j=1}^B \mathcal{N}(\mathcal{D}(\mathbf{n}_{b,j}) + \mathbf{u}_{b,j}, 0, \sigma^2). \quad (3)$$

The variance σ^2 of the normal distributions models the uncertainty in the prostate segmentation, and its value should be determined by the observed or predicted uncertainty of the segmentations. Now, the segmentation uncertainty is one factor that affects the posterior uncertainty.

The prior restricts the deformation of the mesh to conform to an elastic material:

$$\Pr(\mathbf{u}_b \mid \mathcal{M}) \propto \exp\left(-\frac{E_{\text{el}}(\mathbf{u}_b)}{T}\right), \quad (4)$$

where $E_{\text{el}}(\mathbf{u}_b)$ solves for the internal elastic displacement $\mathbf{u}_i$ given the boundary conditions $\mathbf{u}_b$ and returns the elastic energy. The energy is then converted to a probability by way of the Boltzmann distribution modeled with temperature T .

II.B.3. Characterizing the posterior distribution

The posterior distribution cannot be assumed to take on a parametric form and is therefore difficult to characterize directly. Our approach is to characterize the posterior distribution over deformations by generating samples from the posterior with a Markov Chain Monte Carlo (MCMC) (Metropolis-Hastings) method.²⁸ The MCMC method constructs a Markov chain that asymptotically has the posterior distribution as its equilibrium distribution. In practice, we start with an initial estimate of the deformation, $\mathbf{u}_b^0$, and generate candidate samples from a Gaussian proposal distribution with variance ζ centered on the previous sample, $\hat{\mathbf{u}}_b \sim \mathcal{N}(\mathbf{u}_b^t, \zeta)$. Candidate samples are accepted with probability $A(\hat{\mathbf{u}}_b, \mathbf{u}_b^t) = \min(1, \frac{\Pr(\hat{\mathbf{u}}_b \mid \mathcal{D}, \mathcal{M})}{\Pr(\mathbf{u}_b^t \mid \mathcal{D}, \mathcal{M})})$. If a sample is accepted we set $\mathbf{u}_b^{t+1} = \hat{\mathbf{u}}_b$, otherwise $\mathbf{u}_b^{t+1} = \mathbf{u}_b^t$. After running the MCMC simulation with a suitable thinning factor τ and number of burn-in samples η , the resulting set of deformation samples $\mathbf{u}^0, \dots, \mathbf{u}^T$ define the posterior distribution over deformations. The mode of the set of deformation samples is also the sample with the maximum posterior probability and characterizes the MAP deformation, while the dispersion of the set can be used as a measure of the registration uncertainty.

II.B.4. Segmentation preprocessing

Before beginning the deformable registration, the diagnostic and intraoperative images were rigidly registered by minimizing the sum of squared differences between the two

segmentations. Rotational corrections were not considered in the rigid registration. We assumed that the prostate has a smooth surface. To correct for the jagged edges of the manually contoured segmentations caused by the slice thickness, the segmentations were first subsampled by a factor of 4 to create a high-resolution segmentation. This was followed by an antialiasing²⁹ and binary Gaussian smoothing ($\sigma = 1$) step. We used the Computational Geometry Algorithms Library (CGAL) (Ref. 30) to create the tetrahedral meshes conforming to Ω_r .

II.C. Registration accuracy and precision

Because the likelihood of the posterior distribution was based on matching the boundary surfaces of the prostate segmentations, any measure of volume overlap of the prostate segmentations would be a biased metric of registration quality. Instead, segmentations of the internal prostate substructure were used to evaluate the accuracy and precision of the deformable registration. Specifically, the internal interface surface between the CZ and PZ segmentations was compared between the deformed diagnostic images and the intraprocedural segmentation, which was taken as ground truth. Voxels along the interface were identified in the undeformed diagnostic image and transformed for each sampled deformation to build a predictive marginal distribution of the position of the transformed surface. The shortest distance in three dimensions was calculated from each transformed point to the intraprocedural surface. The distribution of distances gives a measure of the accuracy and precision of the registration on the prostate's internal substructure. This distribution was used to evaluate geometric margins on the peripheral zone registration in the three regions of the prostate gland: base, mid-gland, and apex. The regions were defined by dividing the number of segmented slices by 3 and classifying the superior slices of the segmented prostate as base, middle slices as mid-gland, and inferior slices as apex.

As an additional measure of the deformable registration accuracy and precision, the landmark registration error (LRE) was estimated for image features which can be identified in

both the diagnostic and intraprocedural images. Landmarks were defined as naturally occurring patient-specific features of the prostate gland, such as cysts, calcifications, or benign prostatic hyperplasia (BPH) nodules. Each image feature was required to be local (spanning 2-3 slices) and identified in both diagnostic and intraprocedural images. Small features such as calcifications were marked as points, while larger features such as BPH nodules were contoured manually in each of the slices, with the landmark defined as the center of mass of the 3D volume defined by the segmentations. Most of the landmarks were located in the central zone (25/30). Of the five landmarks in the peripheral zone, two were located in the apex, one in the mid-gland, and two in the base region. Most of the landmarks were also located in the mid-gland (21/30), with only 2/30 in the apex (both in the PZ) and 7/30 in the base region. These landmarks have been used in another study to validate an automated registration method on the same patient dataset.²¹

The LRE was defined as the distance between a corresponding point in the deformed diagnostic image and the intra-procedural image. For each landmark, we have a distribution of LRE from the predictive distance distribution between the deformed and contoured landmark. Summary statistics of this predictive LRE distribution were then used to evaluate the registration accuracy and precision.

III. RESULTS

III.A. Prostate volume variations

As expected, the shape of the prostate gland and its segmented substructures was observed to change between the diagnostic and intraprocedural images. The segmented prostate gland volumes were measured for each patient, with the results summarized in Table I. For this cohort, five patients had a decreased total prostate (PG) volume in the intraprocedural image compared to the diagnostic image, while five patients had an increased prostate volume. For smaller prostate volumes, less than 50 cm³, the difference was up to $\pm 17\%$. Frequently, the majority of the change occurred in the segmented PZ volume, as shown in the table. Exact causes of the volume

TABLE I. Measurement of the segmented prostate gland volume in both diagnostic and intraprocedural images for ten patients (P1–P10). The volume change between images may be caused by many factors, and was greatest for smaller prostate volumes (<50 cm³). The DSC between the procedural PG segmentation and the registered diagnostic PG segmentation were calculated after the rigid registration and from the MAP deformation.

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Diagnostic PG volume (cm ³)	41	24	48	69	64	82	27	59	44	41
Procedural PG volume (cm ³)	34	28	51	71	71	81	29	56	41	39
PG volume change (%)	–17	16	5	3	11	–2	7	–6	–7	–5
Diagnostic CZ volume (cm ³)	21	14	29	51	44	66	15	33	22	18
Procedural CZ volume (cm ³)	15	14	31	54	48	61	16	33	23	19
CZ volume change (%)	–30	1	6	4	8	–8	7	2	5	10
Diagnostic PZ volume (cm ³)	20	10	19	18	20	16	11	27	22	23
Procedural PZ volume (cm ³)	19	14	20	18	23	20	12	22	18	20
PZ volume change (%)	–3	36	35	0	20	26	8	–16	–19	–16
Rigid registration DSC	0.83	0.80	0.85	0.90	0.87	0.92	0.87	0.89	0.86	0.89
MAP deformation DSC	0.92	0.86	0.91	0.94	0.94	0.95	0.91	0.94	0.91	0.94

FIG. 2. MR image transverse slice demonstrating the deformable registration results for one patient. The prostate gland segmentation for this intra-procedural image is shown in white. The deformed diagnostic prostate gland segmentation is shown for three lines of iso-probability: 90%, 50%, and 10%. This is only one two-dimensional representation of the full three-dimensional deformation.

differences are unknown but could be due to a combination of factors—patient positioning, bladder and rectal filling, inconsistencies in the physician segmentations, or the time elapsed between images (varying from 1 week to over a month).

The Dice similarity coefficient (DSC) between the intra-procedural prostate segmentation and the registered diagnostic prostate segmentation were calculated after the rigid registration and from the MAP deformation for each patient, and included in Table I. Comparison of the rigid and MAP deformation DSC is an indication of the potential improvement of using a deformable algorithm over a rigid registration. After the rigid registration, the median DSC was 0.87 (0.80, 0.92). For all patients, the DSC improved after nonrigid registration compared to rigid registration, by 6.4% on average. The median DSC calculated from the MAP deformation was 0.93 (0.86, 0.95).

III.B. Registration experiments

To our knowledge, exact values for the elastic parameters of prostate tissue have not been established. In this study, we used values similar to those used by Bharatha *et al.*¹⁵ for the peripheral zone: Young's modulus $E = 3$ kPa and Poisson's ratio $\nu = 0.4$. These values were used for the entire prostate gland; separate values were not assigned to the CZ and PZ as there is no empirical knowledge of what the change in elasticity might be for different parts of the gland. The lower-bound uncertainty on the accuracy of the prostate segmentations was taken to be the slice thickness of 3 mm, as it is difficult for any physician to do sub-voxel delineation of the prostate boundaries. Thus the variance of the likelihood, which models the uncertainty in the segmentations, was set to $\sigma^2 = 3 \text{ mm}^2$. The temperature of the Boltzmann equation was determined experimentally by running the optimization for two cases several times, and set to $T = 6000$. Determining the optimal value would require multiple runs over all datasets with different temperatures, and is not the main focus of this study. The sampling kernel variance was tuned to $\sigma_{\text{kernel}}^2 = 0.09 \text{ cm}^2$ to achieve a Metropolis-Hastings acceptance rate of approximately 24%.

We generated 2×10^5 samples from the posterior. Our sampler generated about five samples per second, thus the total computation time was approximately 12 h for each patient. We used the Geweke criteria³¹ to test whether the posterior distribution was adequately characterized when the sampling was stopped; as a result, there should be limited variability in the posterior estimates on repeat registration. Qualitative results for one patient can be seen in Fig. 2. Quantitative results from the registration are given in Table II.

III.C. Registration accuracy and precision

The distance from points on the deformed CZ-PZ interface to the ground truth CZ-PZ interface were calculated, and the predictive distribution of these distances is shown in Fig. 3 for the ten patients. The median, $\pm 75\text{th}$, and $\pm 95\text{th}$ percentiles for each distribution are shown in Table III. For all ten cases, the median distance between the deformed and segmented interfaces was less than the slice thickness of 3 mm.

Quantitative evaluation of the registration accuracy used a total of 30 landmarks identified for the registered image pairs (three landmarks per patient). The landmark registration error (LRE) distribution was given by the predictive distance

TABLE II. Registration results in terms of the posterior predictive distribution of distance between the MAP position of the deformed boundary nodes ($\mathbf{n}_b + \mathbf{u}_b$) and $\partial\Omega_t$ for ten patients. Negative numbers indicate nodes are inside Ω_t , whereas positive numbers indicate nodes fall outside $\partial\Omega_t$. Shown are the median, 95th, and 75th percentiles. All distances are in mm.

Percentiles	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
−95th	−0.99	0.46	−2.27	−3.57	1.55	−1.29	−1.46	0.25	−0.89	−1.19
−75th	−0.57	0.92	−1.69	−3.03	2.10	−0.13	−0.86	1.03	−0.18	−0.84
50th (median)	−0.11	1.16	−1.40	−2.72	2.31	0.49	−0.52	1.43	0.46	−0.58
+75th	0.71	1.66	−1.09	−2.28	2.55	0.82	0.16	1.82	0.87	0.14
+95th	2.39	2.60	−0.60	−1.54	3.30	1.76	1.02	2.46	1.54	1.27

FIG. 3. Posterior predictive distribution of distances from the CZ-PZ interface in the deformed diagnostic image to the CZ-PZ interface in the intraoperative segmentation, shown separately for each of the ten patients. Included are all points on the CZ-PZ surface as well as all samples in the posterior distribution of deformations. Histograms are normalized to an area of one.

between the deformed landmark position and the contoured position in the intraprocedural image. A distribution was formed for each direction (x, y, and z in a right-handed coordinate system with z pointing superiorly in the patient) separately, and the mode calculated for each landmark. The mean LRE $\pm$ the standard deviation, with the maximum given in parentheses, over all the landmarks in the ten patients was $1.6 \pm 0.8(4.6)$ mm, $1.4 \pm 0.7(2.9)$ mm, and $1.3 \pm 0.5(2.3)$ mm in the x, y, and z directions, respectively.

III.D. Geometric uncertainties on the PZ

The distribution of distances from the CZ-PZ interface was then used to determine a geometric margin on the deformed peripheral zone. The results were evaluated separately for the base, mid-gland, and apex regions. In each region we calculated the percentage of interface voxels in all sampled deformations found within a given distance of the true interface. The resulting histograms for all patients combined are shown

in Fig. 4. The 1σ margin is defined as the distance within which 68% of voxels fall, while the 2σ margin is the distance in which 95% of voxels fall. For both the base and mid-gland, the 1σ margin was 1.75 mm and the 2σ margin was 3.25 mm. For the apex, the 1σ margin was 2.75 mm and the 2σ margin was 6.50 mm. For the total gland (all three regions combined), the 1σ margin was 2 mm and the 2σ margin was 4 mm. These are the geometric margins which should be added to the boundary of the deformed PZ to ensure that a given percentage of the peripheral zone tissue falls within the margin for all ten patients considered here. Margins may also be determined for one specific patient based on the posterior distribution from the registration for that patient.

IV. DISCUSSION

We analyzed a dataset of segmented prostate glands from ten patients with both multiparametric diagnostic MR and

TABLE III. Shown are the median, 95th, and 75th percentiles of the distributions in Fig. 3. These statistics describe the predictive distribution of distances from the CZ-PZ interface in the deformed diagnostic image to the CZ-PZ interface in the intraoperative segmentation. Included are all points on the CZ-PZ surface as well as all samples in the posterior distribution of deformations. All distances are in mm.

Percentiles	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
−95th	−2.13	−0.38	−2.63	−3.13	−1.88	−1.13	−2.63	−2.88	−4.38	−2.88
−75th	1.38	0.63	−1.63	−1.63	−0.13	0.38	−0.63	−1.38	−1.88	−1.88
50th (median)	2.38	1.63	−0.63	−0.38	0.63	1.38	0.88	−0.13	0.13	−0.63
+75th	3.38	2.38	1.63	1.63	1.63	2.13	2.13	1.38	2.63	0.88
+95th	4.38	4.13	3.63	3.63	2.63	3.88	6.13	3.38	9.38	3.13

FIG. 4. Distribution of distances from the CZ-PZ interface in the deformed diagnostic image to the CZ-PZ interface in the intraoperative segmentation, shown as the percentage of all points falling within a given distance. Results are for all ten patients combined, with the (a) base, (b) mid-gland, and (c) apex regions of the prostate shown separately. The apex requires a larger margin to fully include all of the PZ. Values for the 1σ and 2σ margins are given in the text.

intrabioopsy MR images. The two data series were registered with a biomechanical-based Bayesian nonrigid registration method. By using intraoperative MR images, we were able to compare the deformed prostate substructure with the true substructure as contoured by a physician. As judged by the location of the deformed central zone-peripheral zone interface and physician-identified landmarks, this registration method was successfully applied to all ten cases, with results similar to those of previous methods.¹⁸ With the diagnostic information and an associated uncertainty available in the intraoperative coordinate system, clinical judgments may be made about target location and coverage versus sparing critical structures.

Conventional optimization methods are not capable of quantifying the registration uncertainty, and conventional registration methods are not capable of modeling the uncertainty of the physician segmentations. The Bayesian registration method presented here is capable of handling both tasks. In this probabilistic framework, the registration uncertainty was quantified from the dispersion of the posterior distribution. The uncertainty on the physician segmentation was modeled in the likelihood function by allowing the position of each boundary node to vary according to a zero-mean normal distribution, with the variance σ^2 corresponding to the assumed segmentation uncertainty. In the current validation, the segmentation uncertainty was spatially homogeneous, with the same uncertainty applied to the entire segmentation. A more sophisticated approach may be to allow the uncertainty to vary along the segmentation boundary; particularly for TRUS, the segmentation uncertainty is expected to be larger in the apical region and smaller at mid-gland.

The registration results in Table II show that the median distance between boundary nodes in the deformed and contoured images was less than ± 3 mm for all ten patients. This agreement could be improved by reducing the thickness of the image slices, currently 3 mm, thereby reducing the uncertainty on the segmentations. This study used segmentations by only one physician, and there was no evaluation of interob-

server variability in contouring. Before clinical use, the inter-observer variability, which is likely both site-dependent and modality-dependent, would have to be characterized to properly estimate the segmentation uncertainty. In this study we also used the same estimated elastic parameters for the whole prostate gland; previous studies have used different values for the CZ and PZ,¹⁵ which may have an effect on the registration results with this method.

This method estimates the boundary conditions of an elastic biomechanical model of the prostate by matching the surfaces of the diagnostic and intraoperative prostate segmentations, and the internal deformations are assumed to adhere to the space of elastic deformations. However, some cases may not be well modeled by the assumption that all changes in shape are elastic deformations. From the dataset used for this evaluation, one case (P9) showed large variation in the distance from the CZ-PZ interface, as shown in Fig. 3(i). Distances of up to 15 mm were observed from the deformed interface to the segmented interface. Upon visual inspection of the images, we found a considerable change in the shape and location of the CZ between the diagnostic and intraoperative images, as shown in Fig. 5. In the diagnostic segmentation, the CZ was surrounded by the PZ, whereas in the intraoperative segmentation, the CZ was superior to the PZ. This method cannot accurately track the substructure location with this type of deformation.

Because this registration framework relies only on segmentations of the prostate gland, the method may be applied to MRI-to-TRUS registration or MRI-to-CT registration. However, the parameters of the model must be evaluated for each new modality. This includes external parameters, such as the physician segmentation uncertainty, and model parameters, such as the appropriate Boltzmann distribution temperature. A MRI-to-TRUS registration was not attempted in this study because TRUS data were not available for the patients in this clinical research protocol. Due to the long computation time, this method is not yet suitable for intraoperative use. With further automation, better

FIG. 5. MR image slices through the prostate for one patient with a poor registration of the internal substructure. (a) shows a diagnostic image and the corresponding prostate gland segmentation, with the CZ depicted in gray and the PZ in white. (b) shows a three-dimensional representation of the entire prostate gland, with the CZ in dark gray and the PZ in light gray. In the diagnostic image, the CZ is surrounded by the PZ. (c) shows an intraprocedural image and segmentation, while (d) shows the three-dimensional representation. In the intraprocedural image, the CZ is superior to the PZ.

modeling, faster computers, and parallelization, it should be possible to approach intraoperative running times in the future.

Future development of the model for MRI-to-TRUS registration is also being considered.³² On TRUS, it is difficult to identify the superior and inferior borders of the prostate gland. The registration model described here relies on surface matching; however, it is possible to modify the model to use an incomplete surface match and extrapolate the location of the apex from the optimization of the remaining surface. The result would be the most probable location of the apex and an estimate of the registration uncertainty on this location. Because the apex is not well-visualized on CT or TRUS, a probable location of the apex from MRI registration would be valuable information for a clinician when deciding on the target volume. Further study is needed to quantify the optimal registration model parameters and accuracy achievable when a given percentage of the surface is missing. These studies may be performed on the same dataset used in this analysis.

V. CONCLUSION

The probabilistic nonrigid registration framework presented in this paper was capable of registering physician-segmented diagnostic and intraprocedural prostate MR images. The registration results achieved were comparable to those from other finite-element registration models. The advantages of the probabilistic framework are that it conveys the registration results in terms of distributions, provides a means of evaluating registration uncertainty, and includes the segmentation uncertainty in the likelihood model. This method also allows for local variations in the uncertainty. The registration framework may be applicable to MRI-to-TRUS registration, but further development is required before it could be clinically useful.

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