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Effect of Material Property Heterogeneity on Biomechanical Modeling of Prostate under Deformation

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Abstract

Biomechanical model based deformable image registration has been widely used to account for prostate deformation in various medical imaging procedures. Biomechanical material properties are important components of a biomechanical model. In this study, the effect of incorporating tumor-specific material properties in the prostate biomechanical model was investigated to provide insight into the potential impact of material heterogeneity on the prostate deformation calculations. First, a simple spherical prostate and tumor model was used to analytically describe the deformations and demonstrate the fundamental effect of changes in the tumor volume and stiffness in the modeled deformation. Next, using clinical prostate model, a parametric approach was used to describe the variations in the heterogeneous prostate model by changing tumor volume, stiffness, and location, to show the differences in the modeled deformation between heterogeneous and homogeneous prostate models. Finally, five clinical prostatectomy examples were used in separately performed homogeneous and heterogeneous biomechanical model based registrations to describe the deformations between 3D reconstructed histopathology images and *ex vivo* Magnetic Resonance Imaging (MRI), and examine the potential clinical impact of modeling biomechanical heterogeneity of the prostate. The analytical formulation showed that increasing the tumor volume and stiffness could significantly increase the impact of heterogeneous prostate model in the calculated displacement differences compared to homogeneous model. The parametric approach using a single prostate model indicated up to 4.8 mm of displacement difference at the tumor boundary compared to a homogeneous model. Such differences in the deformation of prostate could be potentially clinically significant given the voxel size of the *ex vivo* MR images.

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(0.3×0.3×0.3 mm). However, no significant changes in the registration accuracy were observed using heterogeneous models for the limited number of clinical prostatectomy patients modeled and evaluated in this study.

Keywords

Biomechanical Modeling; Prostate Cancer; Heterogeneous Material Property; Deformable Image Registration; Pathology Correlation; Tumor Boundary; Magnetic Resonance Elastography

1. Introduction

Deformable Image Registration (DIR) has become an essential tool in a variety of medical applications (1-3). Several algorithms have been developed during the past two decades to achieve the clinical needs in image-guided interventions (4). Biomechanical modeling has been shown to provide accurate and reliable clinical results (5-7). Its usefulness has been shown in a variety of applications in different anatomical sites (7-9). A biomechanical model is typically characterized by its geometry discretization method, material properties, boundary conditions, and solution technique. Numerous techniques have been proposed to optimize each of these components for specific anatomical sites (7, 10). One of these important components is the material property. Material properties differ between and within soft tissue organs such as the prostate, lungs, and liver. To accurately model the tissue deformations different elastic properties have been implemented for DIR applications. A simple homogeneous (within each organ) linear elastic model has been shown to achieve promising average registration accuracies (2.0 ~ 4.0 mm) for a number of anatomical sites (11). This model can be explained by two parameters: Young's modulus (E) and Poisson's ratio (ν), which are measures of stiffness and compressibility, respectively. However, for certain applications even sub-millimeter improvements resulting from more sophisticated material models (e.g., heterogeneous, nonisotropic or hyper-elastic) could have a potential clinical impact. For instance, image-guided surgical intervention requires such a registration accuracy to precisely localize incisions in order to identify the disease boundary while avoiding the neighboring critical structures (12). Biomechanical models can provide a sufficiently accurate description of the deformation of the organs and tissue under intervention by balancing the required precision and the complexity of the model (13). Another example is correlative pathology, which is used to validate tumor visualization on medical images in organs such as the prostate (14, 15). The goal in correlative pathology is to map the tumor definition and boundary defined by histopathology, the 'gold-standard', to *in vivo* imaging. This mapping provides insight into the different image signals representing the tumor with the ultimate goal of validating imaging techniques and providing confidence for the clinicians in their identification of the tumor for therapeutic interventions and assessment of treatment response. Therefore, uncertainties resulting from the residual errors of the DIR methods used to resolve the geometric differences between the *in vivo* and histopathology images must be well understood and minimized.

Previous studies have investigated the use of biomechanical modeling for prostate deformable registration. Linear elastic Finite Element Modeling (FEM) has been applied to

predict prostate deformations by several investigators (7, 10, 16). In most cases, the peripheral and central zones of the prostate have been assigned different E values to account for differential stiffness within the organ (7, 16). The effect of peripheral to central zone E ratio on the prostate under deformation was studied by McAnearney *et al.* (17). It was reported that the predicted deformations are weakly dependent on the E ratio even for the extreme case of 1:40 (peripheral to central zone E ratio). However, their results showed significant non-uniformity in the deformations near the interface of the two zones, which could be critical for image-guided procedures. In a phantom sensitivity study, Jahya *et al.* (18) showed that the accuracy of FEM deformation of the prostate can be increased by maximizing the fidelity of the model by including selected structures such as the puboprostatic ligament. Lee *et al.* (3) developed a platform for simultaneous estimation of E value of the prostate and the internal deformations. They obtained a positive correlation between the homogeneous material property (a single E value) for the entire prostate and the cancer staging in 10 prostate cancer patients. Alternatively, Chi *et al.* (19) used orthotropic materials to account for tissue anisotropy due to muscle fibers of the prostate. They showed that 30% uncertainty in orthotropic material parameters could lead to up to 4.5 mm error in registration of prostate images. However, such a large error was only observed in a small part of the volume, far from the prostate boundary. Kim *et al.* (20) incorporated the volume and the location of tumors to develop a modified tumor-containing prostate (TCP) model, and validated it using pathological samples. They found Young's modulus is approximately 3 times larger in the tumor versus the normal prostate tissue ($E_{tumor} = 41.6$, $E_{prostate} = 14.7$ KPa). Overall, these studies have shown the importance of modeling material property heterogeneity of the normal prostate anatomy when computing the prostate deformation. However, there is still a need to investigate how including heterogeneities in the tumor, which can vary between patients in size, stiffness, and position in the prostate, will affect the deformation.

The goal of this work is to investigate biomechanical modeling of prostate deformation using material property heterogeneity due to the presence of cancer by specifically studying tumor parameters including volume, stiffness, and location. The investigation was organized as follows, first, the theoretical background and the analytical solution to a simplified spherical tumor-prostate geometry was evaluated. Next, a parametric study of tumor properties including E values, volume, and location and their effect on the deformation was performed. This is related to clinical results where the registration of five clinical cases using patient-specific material property measurements was investigated. Finally, the clinical implications and impacts of the current study were explored in a pilot patient study.

2. Materials and methods

To investigate the effect of tumor inclusion, first a simplified geometry (i.e., spherical) was used to model both the prostate and the tumor (see figure 1(a)). The deformation equation for this geometry was derived by solving the differential equations obtained by the generalized Hooke's law. Next, a realistic prostate model with spherical geometry tumor inclusion was utilized to further analyze the effect of various tumor parameters (see figure 2(b)). In the last section (2.3), clinical experiments using prostatectomy patient datasets were performed.

2.1. Analytical solution of a composite sphere

In this section the analytical solution to the fundamental deformation equations of a composite sphere is presented. For the purpose of finding the analytical solution, the prostate can be approximately modeled as a sphere. The tumor was also modeled as another sphere centered in the spherical prostate. As a general material model, Roy (21) used

$$C_{ij} = \lambda_{ij} \exp(-\kappa r^2) \quad (i, j=1, 2, 3, 4) \quad (1)$$

where λ_{ij} and κ are material parameters to express heterogeneity. Various scenarios using this material model were previously studied (21). These include a general solution for a composite sphere with an inner region of homogenous and an outer shell of heterogeneous (according to equation 1) spherically isotropic linear elastic materials.

For a spherically isotropic material, generalized Hooke's law can be written as:

$$\begin{aligned} \bar{\sigma}_r &= C_{11}e_{rr} + C_{12}e_{\theta\theta} + C_{12}e_{\phi\phi} \\ \bar{\sigma}_\theta &= C_{12}e_{rr} + C_{22}e_{\theta\theta} + C_{23}e_{\phi\phi} \\ \bar{\sigma}_\phi &= C_{12}e_{rr} + C_{23}e_{\theta\theta} + C_{22}e_{\phi\phi} \\ \bar{\sigma}_{\theta\phi} &= \frac{1}{2}(C_{22} - C_{23})e_{\theta\phi} \\ \bar{\sigma}_{r\phi} &= C_{44}e_{r\phi} \\ \bar{\sigma}_{r\theta} &= C_{44}e_{\theta} \end{aligned} \quad (2)$$

Assuming a purely radial deformation of the sphere, components of the displacement (u, v, w) will be $u = u(r)$, $v = 0$, and $w = 0$. Applying the displacement components in the general equations of strains in the spherical coordinate system yields:

$$\begin{aligned} \bar{e}_{rr} &= \frac{du}{dr}, \quad \bar{e}_{\theta\theta} = \frac{u}{r} = \bar{e}_{\phi\phi}, \\ \bar{e}_{\theta\phi} &= 0 \\ \bar{e}_{r\theta} &= \bar{e}_{r\phi} = 0. \end{aligned} \quad (3)$$

Given the strain components in (2), the non-zero equations in (1) may be written as

$$\begin{aligned} \bar{\sigma}_r &= \exp(-\kappa r^2) \left[\lambda_{11} \frac{du}{dr} + 2\lambda_{12} \frac{u}{r} \right], \\ \bar{\sigma}_\theta &= \exp(-\kappa r^2) \left[\lambda_{12} \frac{du}{dr} + (\lambda_{22} + \lambda_{23}) \frac{u}{r} \right], \end{aligned} \quad (4)$$

The equilibrium equations for a linear elastic model in spherical coordinates are

$$\begin{aligned}
& \frac{d\bar{\sigma}_{rr}}{dr} + \frac{1}{r} \frac{d\bar{\sigma}_{r\theta}}{d\theta} + \frac{1}{r \sin \theta} \frac{d\bar{\sigma}_{r\phi}}{d\phi} + \frac{1}{r} (2\bar{\sigma}_{rr} - \bar{\sigma}_{\theta\theta} - \bar{\sigma}_{\phi\phi} + \bar{\sigma}_{r\phi} \cot \theta) + F_r = 0 \\
& \frac{d\bar{\sigma}_{r\theta}}{dr} + \frac{1}{r} \frac{d\bar{\sigma}_{\theta\theta}}{d\theta} + \frac{1}{r \sin \theta} \frac{d\bar{\sigma}_{\theta\phi}}{d\phi} + \frac{1}{r} [(\bar{\sigma}_{\theta\theta} - \bar{\sigma}_{\phi\phi}) \cot \theta + 3\bar{\sigma}_{r\theta}] + F_\theta = 0 \\
& \frac{d\bar{\sigma}_{r\phi}}{dr} + \frac{1}{r} \frac{d\bar{\sigma}_{\theta\phi}}{d\theta} + \frac{1}{r \sin \theta} \frac{d\bar{\sigma}_{\phi\phi}}{d\phi} + \frac{1}{r} [2\bar{\sigma}_{\theta\phi} \cot \theta + 3\bar{\sigma}_{r\phi}] + F_\phi = 0
\end{aligned} \quad (5)$$

Replacing (3) in (5) under no external loading, the equilibrium equation becomes:

$$\frac{d}{dr}(\bar{\sigma}_r) + \frac{2}{r}(\bar{\sigma}_r - \bar{\sigma}_\theta) = 0, \quad (6)$$

With the aid of (4), this equation will be in the form of

$$r^2 \frac{d^2 \bar{u}}{dr^2} + 2(1 - \kappa r^2) r \frac{d\bar{u}}{dr} - 2 \left\{ \frac{\lambda_{22} + \lambda_{23} + (2\kappa r^2 - 1)\lambda_{12}}{\lambda_{11}} \right\} \bar{u} = 0. \quad (7)$$

The solution of equation 6 under $\bar{\sigma}_r = -p_1$, on the surface $r = b$ and on the $u = 0$, $\sigma_r = \bar{\sigma}_r$, on the surface $r = a$, to ensure the continuity of radial displacements and stress, will be

$$u = \frac{p_1 \exp \left[\frac{\kappa}{2} (a^2 + b^2) \right] \cdot b^{3/2}}{N a^{m+1}} \left[a_p(a) M_{k^*, -p}(\kappa a^2) - a_{-p}(a) M_{k^*, p}(\kappa a^2) \right] r^{m-1/2}, \quad 0 \leq r \leq a$$

and

$$u = \frac{p_1 \exp \left[\frac{\kappa}{2} (b^2 + r^2) \right] \cdot \left(\frac{b}{r} \right)^{3/2}}{N} \left[\left\{ \frac{a_m}{a} \exp(\kappa a^2) M_{k^*, -p}(\kappa a^2) - a_{-p}(a) \right\} M_{k^*, p}(\kappa r^2) - \left\{ \frac{a_m}{a} \exp(\kappa a^2) M_{k^*, p}(\kappa a^2) - a_p(a) \right\} M_{k^*, -p}(\kappa r^2) \right], \quad a \leq r \leq b \quad (8)$$

where $M_{k^*, \mp p}(x)$ are Whittaker functions in which

$$k^* = \frac{3}{4} - \frac{\lambda_{12}}{\lambda_{11}}, \quad 2p = \left\{ \frac{\lambda_{11} + 8(\lambda_{22} + \lambda_{23} - \lambda_{12})}{4\lambda_{11}} \right\}^{1/2} > 0 \quad (\text{and non-integer}),$$

and

$$N = a_{-p}(b) \left\{ \frac{a_m}{a} \exp(\kappa a^2) M_{k^*, p}(\kappa a^2) - a_p(a) \right\} - a_p(b) \left\{ \frac{a_m}{a} \exp(\kappa a^2) M_{k^*, -p}(\kappa a^2) - a_{-p}(a) \right\},$$

where

$$a_{\pm p}(r) = \left[\left(kr - \frac{3}{2r} \right) \lambda_{11} + \frac{2\lambda_{12}}{r} \right] M_{k^*, \pm p}(\kappa r^2) + 2\lambda_{11} \kappa r \times M'_{k^*, \pm p}(\kappa r^2),$$

$$a_m = 2C_{12} + C_{11} \left(m - \frac{1}{2} \right),$$

$$2p = \left\{ \frac{\lambda_{11} + 8(\lambda_{22} + \lambda_{23} - \lambda_{12})}{4\lambda_{11}} \right\}^{1/2} > 0,$$

in which

$$m = \left\{ \frac{1}{4} + \frac{2(C_{22} + C_{23} - C_{12})}{C_{11}} \right\}^{1/2}.$$

Equation (8) describes a homogenous spherically isotropic sphere ($0 < r < a$) surrounded by a non-homogeneous spherically isotropic shell ($a < r < b$). The general solution can be used to calculate the displacement of a spherical prostate model including a spherical tumor in the center in which both the prostate and the tumor are homogenous isotropic linear elastic materials with different or identical E and ν . Figure 1(a) shows a schematic view of the spherical model with two layers representing the tumor and the rest of the prostate. The effect of changing the tumor volume (V) and E on the deformation of the spheres under a uniform pressure is shown in figures 1(c) and 1(d) using $|U_{ht} - U_{hm}|$ in which U_{hm} and U_{ht} represent the displacement of points in the homogenous and heterogeneous spheres. The parameters used to generate figure 1(c) include $V_{prostate} = 40 \text{ cc}$, $E_{prostate} = 15 \text{ KPa}$, $\nu_{prostate} = 0.4$, $V_{tumor} = 5 \text{ cc}$, $\nu_{tumor} = 0.4$ with varying tumor E_{tumor} and those of figure 1(d) include the same prostate parameters, $E_{tumor} = 45 \text{ KPa}$ and $\nu_{tumor} = 0.4$ with varying V_{tumor} . The pressure on the surface of the outer sphere in all experiments was such that the inward radial displacement is always 4 mm.

According to the relationship between the spherically isotropic and fully isotropic materials (expressed by Lamé coefficients λ_0 and μ_0)

$$\lambda_{11} = \lambda_{22} = \lambda_0 + 2\mu_0, \lambda_{12} = \lambda_{23} = \lambda_0, \lambda_{44} = \mu_0$$

where

$$\mu_0 = \frac{E}{2(1+\nu)}, \lambda_0 = \frac{E\nu}{(1+\nu)(1-2\nu)}.$$

By replacing the parameter set of the experiments in (8), analytical ground truth displacement for any location in the composite spherical prostate model was determined.

2.2 Parametric study of prostate deformation based on tumor inclusion

To analyze the impact of heterogeneous materials, a spherical tumor was modeled inside a prostate model constructed from a clinical prostate image (with the volume of 65 cc) using a different E value from that of the normal healthy tissue (see figure 1(b)). The deformation was applied by a plate moving in the Anterior-Posterior (AP) direction to simulate the effect

of inserting an endorectal MR coil into a patient's rectum. This is a common clinical scenario in prostate MR acquisitions that leads to significant deformations in the AP direction (22). The moving plate exerts force in contact with the posterior side of the prostate, mimicking the endorectal coil. The anterior side of the prostate is being pushed against a fixed parallel plate, mimicking the restriction of prostate motion due to the pubic symphysis, while being initially in contact with it. Several studies have shown that tumors in the prostate have higher E values than the surrounding healthy tissues (20, 23). In order to study the effect of modeling the tumor with stiffer material properties several stiffness values were evaluated while other parameters were kept constant. For every specific plate displacement, simulations with different E values for the tumor were performed. In addition, prostate tumors can be located in various regions within the organ. Previous statistical studies have reported that the majority of the prostate tumors occur in the peripheral zone (24, 25). To investigate the effect of tumor location on the deformation, three sets of simulations including Left-Right (X_{LR}), Anterior-Posterior (X_{AP}), and Superior-Inferior (X_{SI}) were performed. In each set, the location of the tumor was changed in one anatomical direction while the prostate underwent a certain plate displacement in the AP direction. Besides the stiffness and location, tumor volume (V) within the prostate can vary depending on the extent of the disease. In a study by Nakanishi *et al.* prostate and tumor volume ranges of 16.0 – 74.1 cc and 0.0003 – 8.64 cc were reported amongst 96 patients (26). Furthermore, a percent tumor volume of 15.7 ± 18.9 was measured for 1567 patients indicating a possibility of having tumors as large as approximately half of the entire gland's volume (27). Thus, spherical tumors with a volume of as low as 0.3 cc (0.5% of total prostate volume) up to 25 cc (38% of the total prostate volume) were simulated in order to account for mechanically relevant possibilities (avoiding extremely small lesion volumes). To evaluate the interplay effect between the applied displacement magnitude and these parameters, the prescribed displacement of the moving plate (D) was also varied. Table 1 summarizes an overview of the parameters investigated in each set of experiments (denoted as Exp).

2.3 Clinical experiment using deformable image registration

In this experiment, the 3D reconstruction of the whole-mount histological sections (voxel size: $5.0 \text{ um} \times 5.0 \text{ um} \times 3 \text{ mm}$) of five salvage prostatectomy patients were registered to *ex vivo* MR images (voxel size: $0.3 \text{ mm} \times 0.3 \text{ mm} \times 0.3 \text{ mm}$) of the prostate using Morfeus, an in-house developed biomechanical modeling algorithm (14). The contours of the prostate were manually created in MIPAV (NIH, Bethesda, MD), and were then converted into triangular surface meshes. Volumetric meshes were subsequently generated using the histology and the *ex vivo* surface meshes of the prostate (HyperMesh, Altair Engineering, Troy, MI). These normal prostate and tumor meshes were assigned different E values (table 2) measured using an *ex vivo* quasi-static Magnetic Resonance Elastography (MRE) technique. To acquire the MRE maps, the prostate specimens were scanned using an in-house developed MR pulse sequence and external excitation equipment prior to the fixation process (23). Both normal prostate tissue and the tumors were assigned the same Poisson's ratios ($\nu = 0.4$). Boundary conditions were determined using a surface matching algorithm between the histology and the *ex vivo* MR (HyperMorph, Altair Engineering, Troy, MI). The deformations were then obtained by solving the displacement equation in the form of $KU = F$ using Finite Element Analysis (FEA) software (ABAQUS, ABAQUS Inc, Pawtucket, RI).

where K is global stiffness matrix constructed using material parameters, U is the nodal displacement vector, and F is the force applied to the nodes. The accuracy of registration was measured by Target Registration Error (TRE) (28). TRE is calculated based on the Euclidean distance of common anatomical points on both image volumes that are being registered.

3. Results

3.1. Analytical solution of simplified geometry

In figure 1(c), the nodal displacement difference between the heterogeneous and the homogeneous prostate models are displayed in form of boxplots. $E_{tumor} / E_{prostate}$ varies between 1.5 and 10 where the maximum vector displacement difference ranges from 0.5 up to 1.6 mm, respectively. Figure 1(d) shows that maximum nodal displacement differences of 0.4 to 1.3 mm result when $V_{tumor} / V_{prostate}$ is increased from 0.62% to 62.5 %. Moreover, as the tumor volume exceeds half of the total prostate volume, the displacement difference starts to decline as more internal prostate tissue becomes homogenous in all directions making a reverse effect.

3.2. Parametric study

Parametric experiments were performed to examine the effect of tumor stiffness, volume, and location on the prostate deformation. As illustrated in figures 2(a) and 2(b), as the tumor becomes stiffer the difference in the deformation field increases compared to a homogeneous model with the same plate displacement. The maximum difference in the nodal displacement compared to homogeneous model (denoted by $\max |U_{het} - U_{hom}|$) ranged from 0.8 to 2.6 mm for 8.0 to 20.0 mm plate displacements, respectively. The mean nodal displacement (denoted by $\text{mean} |U_{het} - U_{hom}|$) was substantially smaller, ranging from 0.2 to 0.9 mm.

Figures 2(c) and 2(d) indicate the difference in the nodal displacement compared to a homogeneous model increases as the volume of the tumor increases. However, when the tumor volume exceeds 25% of the prostate volume, the difference in the deformation gradually decreases since in these cases the majority of the prostate tissue in the direction of the plate displacement will be the tumor. In the current experiments, when the spherical tumor is nearly 30 cc (46% of the prostate volume), it intersects the prostate boundary causing it to be partially outside of the prostate gland. Therefore simulations were only considered for tumor volumes of up to 25 cc. When the tumor volume increased from 2 to 5 percent of the total prostate volume, the difference in mean and maximum nodal displacement compared to the homogeneous model increase from 0.1 and 0.4 mm to 0.2 and 0.6 mm, respectively, with the smallest plate displacement (8 mm). Furthermore, the same amount of increase in the tumor volume produces a greater increase in the mean and max nodal displacement differences with larger plate displacements (notice the slope of the curves in figures 2(c) and 2(d)).

As illustrated in figures 2(e) and 2(f), there is a slight increase in the mean nodal displacement difference as the tumor gets closer to the moving plate due to X_{AP} changes.

However, the overall change in the maximum and mean nodal displacement differences caused by X_{AP} changes by less than 0.2 mm even for larger plate displacements. The results of the simulations evaluating the impact of changing X_{LR} and X_{SI} indicate that there is no apparent variation in the nodal displacement differences compared to the homogeneous model. Thus, $\max |U_{het} - U_{hom}|$ and $\text{mean} |U_{het} - U_{hom}|$ plots were not shown in figure 2 for changing X_{LR} and X_{SI} .

3.3. Clinical experiment

Table 2 shows that heterogeneous modeling of the prostate did not result in a significant difference in TRE compared to the homogeneous model. To better understand these results, one must consider the various parameters involved: the maximum deformation applied to the prostate models, the tumor volume, and the tumor stiffness. Based on table 2, the maximum deformation (denoted as max motion) is limited to the range of 2.5 - 5.3 mm indicating very small deformation applied to the prostates during the registration compared to what was previously examined in the experiments in section 2.3. Comparing the clinical patients' specifications given in table 2 against table 1, and the corresponding results in figure 2 it is reasonable that lower nodal displacement differences are obtained using clinical cases. In fact, by looking at the maximum nodal differences in the range of (0.0 - 0.5 mm) and the average distance between the anatomical points used to calculate TRE and the node with maximum displacement difference for each patient (denoted by mean distance and ranging between 11.1 to 23.6 mm) in table 2, it becomes more apparent why TRE does not show any marked difference.

4. Discussion

The clinical prostate specimens used in this work were from the patients who were previously treated using external beam radiation, which has been shown to lead to inflammation, atrophy, and fibrosis of the prostate tissue (29). The presence of fibrosis was confirmed in all clinical specimens in this study by an experienced pathologist (TVK). The presence of fibrosis explains the increase in the average stiffness of the prostate tissue compared to the average value reported in the literature (30). In addition, a subset of the tumor to normal prostate stiffness ratios in these irradiated specimens (table 2) were lower than the average expected ratio in previous investigations (31). This could be due to the differences in the degree of fibrosis and other pathologic changes in the normal and cancerous tissue which could lead to a higher increase in the stiffness of the post-radiation prostate tissue versus the cancerous regions.

The results of the clinical experiment were in agreement with the findings of the sensitivity study in section 3.2 in terms of the magnitude of the deformation changes. The results of all studies (3.1 – 3.3), supports the conclusion that the order of magnitude of deformation variations due to inclusion of heterogeneity is less correlated with the prostate or tumor geometry. The agreement of the clinical results with the parametric study implies that the results of the current study can be used as a general guideline to plan, assess, and predict outcome of macroscopic analysis of biomechanical modeling of the prostate in terms of using heterogeneous versus homogeneous materials. For instance, using figures 2(b) and

2(d), tumor volume percent of 8 and tumor stiffness ratio of 3 with displacement magnitudes of less than 8 mm will not result in maximum nodal difference of more than 0.5 mm, which is consistent with the results in table 2.

The simulation experiments were conducted using two rigid plates to model the boundary conditions. In an *in vivo* MR scan of the prostate, the main source of deformation is primarily due to the insertion of the endorectal coil (if used). Considering the geometry of the coil (an inflated cylinder) in the rectum, one can notice that the majority of deformation occurs in the Anterior-Posterior (AP) direction; the coil forces the posterior surface of the prostate against the anterior side, which is supported by the pubic symphysis and the bladder. Therefore, to simplify the modeling process while simulating a scenario close to real clinical application, the prostate is deformed by means of the rigid plates. In the registration section, the prostate is under surface boundary conditions that are derived based on matching the surface of the *ex vivo* MRI model with the reconstructed whole-mount histology model. Although the boundary conditions used in the registration are inherently different from those used in the sensitivity simulations, the results were still in agreement.

Inclusion of tumor as a stiffer material in the prostate has a relatively limited effect on the mean nodal displacement difference compared to the homogeneous material model (see figure 2). However, the maximum nodal displacement difference could be as large as 4.8 mm (see figure 2(b)) which is larger than the voxel size of the *ex vivo* MR images ($0.3 \text{ mm} \times 0.3 \text{ mm} \times 0.3 \text{ mm}$) used to create the prostate model of the parametric study in section 2.2. Such differences were consistent to the findings of Chi's *et al.* (19) where they investigated anisotropy parameter variations. It should be noted that here 4.8 mm difference were obtained when there was an 8 cc (12% of total prostate volume) tumor with ten times larger E value than the normal prostate tissue, and 20 mm displacement applied using the plates. Such parameter specifications may only occur in smaller population of patients. However, the impact of 4.8 mm difference between heterogeneous and homogeneous models for these patients could drastically alter the tumor location leading to inaccurate treatments. In fact, the location of the node with maximum displacement difference due to tumor inclusion is exactly at the border of the tumor and the prostate in all the cases in the tumor parametric study. Also, the top five percent of the nodes with largest nodal displacement differences are within approximately 1 mm of the border between the tumor and the normal prostate tissue. Together, these findings suggest that there is a potential clinical impact by modeling heterogeneous material properties for a small subset of patients who could exhibit such tumor specifications. The aim of the current investigation was to systematically study the effect of modeling prostate tumor on the deformation and to show under what conditions the impact of the modeling could be clinically important. Those conditions (i.e., a combination of tumor volume, E value, and deformation magnitude which could result in differences of more than 1.0 mm) did not occur for the small cohort of patients in this study. However, for a larger cohort of patients such tumor parameter combinations are likely to be found.

Prostate cancer is a heterogeneous disease; meaning that for the majority of cases the cancer is multifocal rather than unifocal (32). Four out of the five clinical cases reported in section 3.3 had multiple foci which were modeled as separate tumor volumes. These patients are marked with an asterisk sign (*) in table 2. The overall effect of modeling tumor as multiple

regions in terms of maximum nodal displacement difference compared to homogeneous material seems to be correlated with the total volume of the regions as well as the stiffness (E) as reported for these patients (table 2). Furthermore, for a multifocal tumor model, the majority of large displacement differences are still present in the proximity of individual tumor regions.

5. Conclusion

In this study, the potential impact of material heterogeneity on modeling prostate deformation was presented by examining the effect of incorporating tumor-specific materials in the prostate biomechanical model. The parametric study showed that a relative tumor volume of more than 5% (out of the total prostate volume), and a minimum of 3 times more tumor stiffness (compared to the rest of the prostate) when combined with at least 14 mm magnitude of applied deformations, would result in over 1 mm uncertainty in the calculated deformations if homogeneous material properties are assumed. Therefore, in more stringent applications where sub-millimeter accuracy is needed, heterogeneous material characteristics should be considered. In patients with less relative tumor volume and stiffness (compared to the rest of the prostate) and less deformation magnitude the inclusion of heterogeneity in the assigned material properties has less impact (sub-millimeter differences in the modeled deformation compared to assigning homogeneous material properties).

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Figure 1.

(a) and (b) display schematic views used for analytical and parametric experiments, respectively. (c) and (d) are the results of analytical formulation of a spherical composite model with respect to changes in stiffness and volume of the inclusion. LR, AP, and SI are Left-Right, Anterior-Posterior, and Superior-Inferior directions, respectively. U , E , and V are nodal displacement, Young's modulus, and volume, respectively.

Figure 2.

The average and maximum nodal displacement differences between the heterogeneous and homogeneous models with respect to changes in (a,b) tumor stiffness, (c,d) tumor volume, and (e,f) tumor location in AP direction.

Table 1

Parameter selection for tumor inclusion.

	V (cc)	E (KPa)	X_{LR} (cm)	X_{AP} (cm)	X_{SI} (cm)	D (cm)
Exp. 1: V	(1.0, 25)	45	0.0	0.0	0.0	(0.8, 2.0)
Exp. 2: E	8	(22.5, 150)	0.0	0.0	0.0	(0.8, 2.0)
Exp. 3: X_{LR}	8	45	(-0.5, 0.5)	0.0	0.0	(0.8, 2.0)
Exp. 4: X_{AP}	8	45	0.0	(-0.5, 0.5)	0.0	(0.8, 2.0)
Exp. 5: X_{SI}	8	45	0.0	0.0	(-0.5, 0.5)	(0.8, 2.0)

Each row indicates experiment number (Exp. #) and shows the fixed value of constant parameters, and range of the parameter under investigation.

Table 2

The result of the clinical experiments of prostatectomy patients.

Patient ID	A*	B*	C*	D	E*
TRE with U_{hom} mean $\pm$ SD (max) [mm]	1.9 $\pm$ 0.6 (3.0)	1.4 $\pm$ 0.7 (3.1)	1.6 $\pm$ 0.9 (3.1)	2.3 $\pm$ 1.4 (4.3)	1.8 $\pm$ 0.8 (3.9)
TRE with U_{het} mean $\pm$ SD (max) [mm]	1.9 $\pm$ 0.6 (3.0)	1.4 $\pm$ 0.7 (3.1)	1.6 $\pm$ 0.9 (3.1)	2.4 $\pm$ 1.3 (4.3)	1.8 $\pm$ 0.8 (3.8)
Points # for TRE	12	16	13	7	27
$Max(U_{het} - U_{hom})$ [mm]	0.2	0.0	0.1	0.2	0.5
Mean dist [mm]	13.9	23.6	14.8	11.1	19.7
Max motion [mm]	2.5	4.3	2.6	5.2	2.7
$100 \times \frac{V_{tumor}}{V_{prostate}}$	5.0	1.1	8.0	3.9	2.9
$\frac{E_{tumor}(KPa)}{E_{prostate}(KPa)}$	$\frac{81.0}{34.0}$	$\frac{56.0}{58.0}$	$\frac{160.0}{110.0}$	$\frac{42.0}{62.0}$	$\frac{182.0}{56.0}$