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A Survey of Prostate Modelling for Image Analysis

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Abstract

Computer technology is widely used for the multimodal image analysis of the prostate gland. Several techniques have been developed, most of which incorporate the *a priori* knowledge extracted from organ features. Knowledge extraction and modelling are multi-step tasks. Here, we review these steps and classify the modelling according to the data analysis methods employed and the features used. We conclude with a survey of some clinical applications where these techniques are employed.

Keywords

Prostate, modelling, statistical analysis, biomechanical analysis, atlas.

1. Introduction

In the past few years, much research has been undertaken and many procedures have been developed to assist clinicians in managing prostate cancer. Diagnostic techniques have significantly improved through the combination of prostate-specific antigen (PSA), digital rectal examination (DRE), and biopsies guided by trans-rectal ultrasound (TRUS) or magnetic resonance imaging (MRI).

Currently, the entire prostate gland can be assessed by multiparametric imaging protocols, particularly those using MRI (Puechet *et al.*, 2009). Multiparametric MRI, a combination of multiple complementary morphological (T2W) and functional imaging sequences (such as dynamic contrast-enhanced (DCE-MRI), and diffusion-weighted (DWI) and MR spectroscopic imaging (MRSI)), generates a large amount of data. These data require an integrated interpretation to increase the reproducibility, and some authors have also suggested that new standardized reporting tools are needed (Kozlowski *et al.*, 2006; Haider *et al.*, 2007).

Semi-automatic or automatic image analysis is essential for managing and treating the large amount of generated data. Currently, one of the important diagnostic challenges for the optimal detection and staging of cancer is developing computer-aided diagnosis (CAD) software based on multimodal and multiparametric images (Chan *et al.*, 2003; Voset *et al.*, 2008). For treatment, the challenges involve developing tools that enable efficient treatment planning, guidance, and monitoring.

In all these procedures, one of the most important tasks is prostate gland detection and segmentation, which have been the subject of many studies and for which related surveys have been published. Shao *et al.* (2003) presented a survey on the prostate segmentation methodologies developed for TRUS images. In addition, Noble *et al.* (2006) offered a survey on US segmentation methods for different organs (prostate, heart, and breast) and for detecting vascular diseases. Zhu *et al.* (2006) conducted a survey on the computerized techniques developed for prostate cancer detection and staging, including prostate segmentation, prostate staging, computerized visualization and simulation of prostate biopsy, volume estimation and registration between the US and MR modalities. More recently, Ghose *et al.* (2012a) classified, reviewed and compared different segmentation methods to provide an overall qualitative estimation of their performance.

However, the prostate is a movable and deformable organ; thus, automatic analysis of prostate images has quickly concentrated on integrating all available information about its

properties to guide the algorithms. The accurate integration of these data requires a standardized representation through a modelling process. Atypical modelling process consists of the following steps:

- Extraction of characteristics and knowledge
- Analysis of characteristics
- Generation of a model and an atlas.

The previous steps involve knowledge from different specialties, such as medicine, physics and mathematics. The aim of this paper is to summarize all the techniques used for prostate modelling in a unique document, which will be helpful for this large scientific community. Thus, we review the different types of extracted knowledge (section 2) and the modelling techniques (section 3) employed in developing computer technology for prostate image analysis. Section 3 provides a synthetic mathematical description of each technique and the application of these techniques to generate a model. Each part concludes with a brief analysis summary. Section 4 describes the most representative clinical applications where these techniques and models were employed.

2. Extraction of characteristics and knowledge

Accurate modelling of the prostate depends first on the definition of the characteristics that will be analyzed and the database that will be used to extract these characteristics. The anatomy must be defined correctly for any of the considered characteristics. As described by Mac Neal (McNeal, 1981), the prostate gland is divided into four zones: the peripheral zone (PZ), the central zone (CZ), the transition zone (TZ), and the anterior fibromuscular stroma (AFMS). This anatomy could be affected by different parameters, such as the prostate volume, the presence of a tumor, the PSA level, the tumor stage, the tumor location and the Gleason score. All these variables must thus be considered when constructing a statistically representative sample of the population. In addition, the development and growth of benign prostatic hyperplasia (BPH) can lead to a variety of deformation models within the same volume range, thus illustrating the complexity of the organ.

Of the various methods used to image the prostate, TRUS and MRI are the most effective for measuring volume and describing zonal anatomy. In addition, TRUS is widely used for needle biopsies and for guiding manipulations in subsequent treatments, such as brachytherapy and HIFU and laser therapies. TRUS helps to ensure that specific parts of the

prostate are sampled or targeted, but its role in identifying tumor foci is very limited (Beerlage *et al.*, 2001). Currently, MRI is the gold standard for the morphometric evaluation of the prostate because it provides the best depiction of both the gland contours and the internal zonal anatomy. In addition, performing multiparametric MRI of the prostate prior to biopsy in patients with suspected prostate cancer is effective in detecting significant tumor foci in both anterior and posterior locations (Ouzzane and Villers, 2011).

Due to the variability in prostate morphology and appearance, many works have focused on the combination of different image characteristics to define the prostate boundaries. These characteristics include variations in volume and shape, appearance on images, and tissue properties, such as elasticity and rigidity.

Moreover, prostate location is also an important feature that contributes to prostate shape characterization. Liao and Shen (Liao and Shen, 2011) used online learning to integrate both inter- and inpatient variations in information to localize the prostate using a sigmoid function. Contextual information was considered and is defined as "*any information that can be used to characterize the situation of an entity*". Makniet *et al.* (2011) used the spatial neighborhood as the contextual information. Li *et al.* (2011) obtained context features from the classification maps from the previous iterations, as in a previous study (Tu and Bai, 2010).

Internal structures are another information source. Zhan *et al.* (2007b) and Ouet *et al.* (2009) used internal salient blob-like structures from histologic and MR images. The interconnection of the internal structures was used by Shen *et al.* (2001, 2004).

2.1 Shape

Shape is the most used feature when extracting characteristics and knowledge because it allows the organ limits to be defined. However, voxel intensities, which exploit the neighborhood, can also be used to define the geometry. Following image registration terminology, we can call the use of shape an '*iconic description*', in contrast to a '*geometric description*'. Indeed, the iconic representation describes the shape of the prostate by exploiting the differences between its appearance and that of other organs.

A *geometric description* of the prostate can be obtained using various formalisms. The simplest and most generic method mostly involves a set of distributed points across the surface (Cootes *et al.*, 1992). This modelling is also known as an explicit representation. The coordinates for n points are concatenated into one vector, S , that describes the shape:

$$(x_1, y_1, z_1, \dots, x_n, y_n, z_n)^T \quad (1)$$

This description is called a point distribution model (PDM)(Fig. 1).

An implicit representation is based on the use of level set functions that can represent arbitrary shapes and intrinsically support topology changes during deformation (Tsai *et al.*, 2003). In the level set formalism, the shape is not parameterized but is implicitly defined through a function of a higher dimension defined by Φ . The method involves characterizing the shape as one of the level curves (e.g., isovalue 0) of a regular function $\Phi, R^3 \times R \rightarrow R$. In other words, at time t :

$$S(t) = \{(x, y, z) \in \mathbb{R}^3 | \Phi(x, y, z, t) = 0\} \quad (2)$$

Different representations can be considered by different level set functions. The signed distance function (Lu *et al.*, 2011) is the most commonly used function due to its simplicity and the good results obtained. Other functions have also been used, and their efficiency has been proven, particularly for the hyperbolic tangent of the signed distance (Gao *et al.*, 2010).

Starting from the two previous representations and adding additional connectivity information between the points, a new, more complete representation is obtained, called the *mesh model*. This modelling is obtained by the division of an initial shape, which is represented by points, into tetrahedral or triangular facets (Fig. 2) or by a reconstruction based on three-dimensional (3D) geometric figures (i.e., sphere, ellipsoid or cube) that closely resemble the organ. This modelling also forms the basis for two different variations: the 3D standard deviation surface meshes (SDSM) (Wu *et al.*, 2010) and the shape-constrained deformable mesh (SCDM) (Ghanei *et al.*, 2001). Gokse *et al.* (2005) used *Nuages*, which was developed by Geiger (Geiger, 1993), to obtain a surface definition of the prostate. Hu *et al.* (Hu *et al.*, 2011) reconstructed smooth triangular spherical harmonic (SH) surface from manually drawn prostate contours.

Nonlinear representations have also been used. M-reps (medial representation) models (Pizer *et al.*, 2003) have been used to represent the 3D shape of the prostate (Crouch *et al.*, 2007). They are composed of a set of medial atoms, which are linked together to describe an object (Fletcher *et al.*, 2002). Another nonlinear representation is the conditional shape probability distribution (CSPD) presented by Jeon *et al.* (2008).

Other representations, including ellipse (Badie *et al.*, 2006; Kachouie *et al.*, 2006; Liu *et al.*, 2009; Mahdavi *et al.*, 2011), catenary curve (Makni *et al.*, 2011), super ellipse (Gong *et al.*, 2004), tapered super ellipse (Saroulet *et al.*, 2008), superquadrics (Tutare *et al.*, 2004), and

spherical harmonics (Tutaret *et al.*, 2006), have been used and tested. They primarily involve parametric curves.

An *iconic description* of the prostate uses all the image content. The Markov model used for the description of ‘*pixel being prostate*’ allows a shape model to be built (Firjaniet *al.*, 2010, 2011). Yin *et al.* (Yin *et al.*, 2012) presented the layered optimal graph image segmentation of multiple objects and surfaces (LOGISMOS) model. The LOGISMOS model contains both the shape and topology information during deformation (Yin *et al.*, 2012).

2.2 Appearance

Appearance features can be based on individual pixels (e.g., pixel intensities), areas (regions having specific shapes), transformations of the original data (e.g., wavelets), or time (changes in the images compared to the previous examination). Typically, appearance features include all textural characteristics, which are usually categorized as statistical, structural, model-based and transformation-based (Materka and Strzelecki, 1998).

Statistical approaches represent the texture indirectly using the non-deterministic properties that govern the distributions and relationships between the grey levels of an image (Materka and Strzelecki, 1998). *First-order statistics* measure the likelihood of observing a grey value at a randomly chosen location in the image (Tuceryan and Jain, 1998). These statistics are computed from the histogram of the grey levels of the image and depend only on the individual pixels and not on their neighborhood. In the prostate, first-order statistics have been used in the following models: the intensity profile model (Cosio, 2008; Kirschner *et al.*, 2012), gradient models (Zwiggelaar *et al.*, 2003; Feng *et al.*, 2010), models using the grey level threshold of the regions extracted from a neural network (Rafiee *et al.*, 2009), a radial basis relief model (Liu *et al.*, 1997), an instantaneous variation coefficient (ICOV) model (Yu *et al.*, 2004), a model using the local standard deviation in a multi-resolution framework (Aarnink *et al.*, 1998), posterior probability models (Ghose *et al.*, 2011a, 2011b), mixture probability distribution models (Allen *et al.*, 2006; Makni *et al.*, 2009; Firjaniet *al.*, 2010, 2011), or models that are combined in many other ways (Diaz and Castaneda, 2008; Liao and Shen, 2011; Li *et al.*, 2011; Akabri and Fei, 2012). Feng *et al.* (2010) proposed a weighted combination of gradient and probability distribution functions. *Second-order statistics* are defined as the likelihood of observing a pair of gray values at the endpoints of a dipole (or needle) of random length that is placed in the image at a random location and orientation (Tuceryan and Jain, 1998). They are calculated from the grey-level co-occurrence matrix (GLCM), which is used to extract the texture features of the image (Tahiret *et al.*, 2005). Lastly,

Richard *et al.* (1996) defined the microtexture created from the input picture using Laws' 5x5 feature masks.

Structural models of texture are based on well-defined primitives (microtexture) and the near-regular repetitive spatial arrangement (macrotexture) of those primitives (Haralick, 1979). They model the spatial relationships between the primitive elements that constitute the image.

In the **model-based approach**, some parameters (such as the fractal dimension (Huang and Lee, 2009), the medical texture local binary pattern (MTLBP) feature (Kechouie and Fieguth, 2007), and wavelet and spectral features extracted from the radiofrequency time series (Mohammad *et al.*, 2009)) are used to characterize the local texture of a region. Zaim (2005) conquered neural networks using a feature-based self-organizing map (SOM) formed from the spatial information, grey-level and texture information.

Transformation-based approaches, such as the Gabor filter response (Shenet *et al.*, 2003; Zhan and Shen, 2003; Mohamed *et al.*, 2009; Yang and Fei, 2012) and wavelet (Khouzani and Soltanian-Zadeh, 2001, 2003; Zaimet *et al.*, 2007; Mohamed *et al.*, 2009) methods, represent an image in a space in which the coordinate system can be interpreted in a manner that is related to the characteristics of the texture, such as the frequency (Prater and Richard, 1992).

Finally, note that shape and appearance features can be combined, as in the studies by Zouqi and Samarabandu (2008), Song *et al.* (2010), Yuan *et al.* (2013) and Qiu *et al.* (2013).

2.3 Tissue properties

Prostate tissue mobility and deformability may result from many physical and physiological phenomena. Deformability may result from long-term physiological processes and organ growth, simple bladder filling or the outcome of clinician actions. Biomechanics provides a suitable modelling framework, which can consider these interactions and numerically simulate the prostate movement. However, biomechanics must consider the laws governing the mechanical parameters of the tissue (e.g., stiffness, elasticity, and compressibility), and *in vivo* or *ex vivo* experimental procedures are required to estimate these parameters. In most studies, these parameters are determined from one or more experiments (Krouskopet *et al.*, 1998) or from numerical simulations where the parameters are the variables to be adjusted (Hu *et al.*, 2010, 2011; Risholmet *et al.*, 2011).

Ex vivo measurements, which are performed on non-living tissues, are easy to set up but often lead to an under-estimation of the real parameters, whereas *in vivo* measurements remain invasive with a complex set up. Elastography could provide an intermediate solution.

It is a non-invasive imaging modality (Ophiret *et al.*, 2002) that permits measurements of tissue properties using ultrasound or magnetic resonance images. The aim is to obtain an image of the physical distribution of mechanical parameters, such as the Young's modulus, Poisson's ratio, and similar factors.

Last but not least, for any of the considered features, pre-processing is applied before the extraction and the analysis. This pre-processing consists of two essential steps, spatial registration and normalization, with the aim of having the same spatial reference for the data. These two issues are not discussed in this review because they are related to the registration issue for multimodality images, which is widely discussed elsewhere (Maintz and Viergever, 1998).

3. Analysis and modelling

The analysis methods can be grouped into two classes: statistical and biomechanical.

3.1 Statistical analysis

A. Techniques

Statistical analysis of the extracted features is mainly performed using methods inspired from data analysis and reduction techniques:

- *Principal component analysis (PCA)*

PCA is a statistical technique for dimensionality reduction (Jolliffe, 2002). The aim is to reduce the dimensionality of multivariate data while preserving the relevant information. In practice, this is achieved by computing the covariance matrix for the full data set. The eigenvectors and eigenvalues of this matrix are computed and sorted according to decreasing eigenvalues (Pasquieret *et al.*, 2007). The most significant eigenvalues and their associated eigenvectors are then kept.

- *Principal geodesic analysis (PGA)*

PGA is a variant of PCA using geodesic distances on symmetric spaces (Fletcher *et al.*, 2004). PCA has been proven to be effective both in characterizing anatomical shape variability using mean point positions and their modes of variation and in easing the considerable problem of low sample size in shape analysis. However, PCA cannot be directly applied to m-reps due to their nonlinearity. In this case, principal geodesic analysis could be applied (Fletcher *et al.*, 2004; Jeonget *et al.*, 2008). Given a data distribution, the aim of PGA is to find a set of geodesic directions, called 'principal

geodesic directions’ or ‘principal geodesics’, that best represent the variability of the data and that allow the precise reconstruction of the data (Said *et al.*, 2007). Unlike the linear case of PCA, the number of principal geodesics is not, in general, limited by the dimension of the space where the data are taken (Smith and Hancock, 2008).

- *Multiple linear regression (MLR)*

In regression analysis, the aim is to identify a predictive relationship (the ‘regression function’) between a set of p predictor variables $x = [x_1, x_2, \dots, x_p]^T$ (the ‘independent variables’) and a set of q response variables $y = [y_1, y_2, \dots, y_q]^T$ (the ‘dependent variables’), given a set of N training observations ($p=q=k$ number of pixels/voxels in the images). In linear regression, data are modelled using linear predictor functions, and unknown model parameters are estimated from the data (Castelanet *et al.*, 2009). Every single observation y_i is defined as:

$$y_i = x_i^T B + \varepsilon_i \quad (3)$$

where B is a $(k + 1)$ -dimensional column vector of parameters, x_i^T is a $(k + 1)$ -dimensional row vector, and ε_i is a scalar (the ‘error term’). The entire sample of N observations can be expressed in matrix notation:

$$Y = XB + \varepsilon \quad (4)$$

where Y is an N -dimensional column vector, X is an $N \times (k + 1)$ matrix, and ε is an N -dimensional column vector of error terms. B is estimated by minimizing the following expression (Castelan *et al.*, 2009):

$$\text{trace}((XB - Y)(XB - Y)^T) \quad (5)$$

The most well-known estimation techniques for linear regression are ordinary least squares (OLS) (Lai *et al.*, 1978), generalized least squares (GLS) (Del Pino, 1989), percentage least squares (PLS) (Tofallis, 2009), optimal linear estimation (OLE), total least squares (TLS) (Nievergelt, 1994), maximum-likelihood estimation (Stone, 1975), ridge regression (RR) (Hoerlet *et al.*, 1985), least absolute deviation (LAD), principal component regression (PCR) (Jolliffe, 1982), and least-angle regression (LAR) (Efronet *et al.*, 2004). Shi *et al.* (2011) were inspired by the particular applications of multiple linear regression (MLR). Using and comparing three different MLR methods (ridge regression (RR), canonical correlation analysis (CCA) and principal component

regression (PCR)), the authors elucidated the statistical deformation correlation between the prostate boundary and non-boundary regions.

Brief summary: Most prostate statistical modelling techniques are based on the principal component analysis method. PCA is used not only because it is straightforward and intuitive but also because prostate characteristics are often represented in a linear space (as in the point distribution model). For the characteristics represented in a non-linear space as a conditional shape probability distribution, the most suitable technique is certainly principal geodesic analysis, which is a generalization of the principal component analysis method.

Statistical modelling is not only focused on the variations of a characteristic but may also include the relationship between two or more features and the influences of one feature over another. Regression analysis can be used to address this issue.

B. Model generation

Once the data have been analyzed, models can be generated. The most popular ones are the following:

- *Active Shape Model*

Applying PCA to the corresponding PDM (equation (1)) allows the main variation modes to be determined, as in Cootes *et al.* (1992, 1994):

$$\tilde{S} = \bar{S} + E_s d_s \quad (6)$$

with \tilde{S} as the estimated shape, \bar{S} as the average shape, and E_s and d_s as the n eigenvectors corresponding to the largest eigenvalues and all the shape deformation parameters, respectively.

Tsai *et al.* (2001) proposed a representation of the estimated shape as the zero level curve of a function Φ , which is defined as the weighted sum of the k linear principal modes (eigenshapes $\{\Phi_1, \Phi_2, \dots, \Phi_k\}$) plus their average shape:

$$\Phi(w) = \bar{\Phi} + \sum_{i=1}^k w_i \Phi_i \quad (7)$$

where $w = \{w_1, w_2, \dots, w_k\}$ are the weights of the k principal modes.

These two models were called the active shape model (ASM) (Betrouni *et al.*, 2005; Pasquier *et al.*, 2007; Cosio, 2008; Zhu *et al.*, 2008; Fenget *et al.*, 2009).

To determine the patient-specific local prostate shape, the incremental subspace learning algorithm (Ross *et al.*, 2008) was modified using the incremental shape

statistics learning (ISSL) model to incrementally elucidate the shape statistics of the deformable contours of the prostate (Yan and Kruecker, 2010). As a result, the shape statistics could be updated by incorporating the new observations without having to perform another computation using all the training shapes.

To cope with shadow artifacts, the partial active shape model (ParASM) is used (Yan *et al.*, 2009). The statistical model is established using probabilistic PCA (PPCA) (Tipping and Bishop, 1999), which allows the optimal shape to be reconstructed and the remaining variance in the statistical model to be computed from partial information. The idea is to use only the contour points with salient features to estimate the shape. To obtain these points, an algorithm incorporating the normal vector profile (NVP) is used (Yan *et al.*, 2009). The partial contour can be represented as:

$$S_p = \overline{S}_p + E_{sp}d_{sp} + \varepsilon \quad (8)$$

with S_p , \overline{S}_p , E_{sp} , d_{sp} and ε being the subset of salient contour points, the average item shape, the corresponding sub-matrix of the eigenvalues of shape, the parameter vector, and the approximation error, respectively.

The estimated shape resulting from ParASM is the same as in equation (6) with just the replacement of d_s by d_{sp} (Yan *et al.*, 2010).

Another variant of ASM has been introduced (Zhou *et al.*, 2010). The model, called the anatomy-constrained robust ASM (ACRASM), is a global-to-local deformable mesh model (Zhou *et al.*, 2012).

The 3D standard deviation surface mesh (SDSM) (Wu *et al.*, 2010) model is calculated using the perpendicular distances between the individual boundary surface meshes and the average surface mesh. This average structure surface mesh is generated from the structure contours drawn by different observers. An average structure surface mesh is then constructed to be the reference mesh for the population-based model using ACP. In the same manner, Ghane *et al.* (2001) used a shape-constrained deformable mesh. This model has a discrete structure that is created from a set of vertices that form triangular facets in the 3D space.

Kirschner *et al.* (2012) determined the bounding box for the prostate and then segmented the gland with the probabilistic active shape model (ProASM). The key contribution of this work is a new term for the shape energy, thus allowing shapes to be constrained in the original data space; the authors simultaneously use PCA to reduce the dimensionality of the model (Kirschner and Wesarg, 2011).

A probabilistic shape model was used by Akabri and Fei(2012). It is based on registration using a principle axis transformation (Alpert *et al.*, 1990). After registration, the prostate models overlie each other, and the shape probability model is created based on the number of overlying prostates in each voxel.

- *Active Appearance Model*

This appearance model can be described in the same manner as the active shape model. However, before applying PCA, the average shape is aligned and normalized (Cootes *et al.*, 2001). Let A be a vector representing the appearance of m pixels/voxels:

$$A = [a_1, a_2, \dots, a_m]^T \quad (9)$$

PCA allows one to obtain:

$$\tilde{A} = \bar{A} + E_a d_a \quad (10)$$

with \tilde{A} as the estimated grayscale appearance, \bar{A} as the average grayscale appearance, E_a containing the first n principal components, and d_a as all appearance deformation parameters.

Shape and appearance are often correlated; thus, the application of PCA to the two models produces a combined model known as the active appearance model (AAM). It has parameters, c , that control the shape and texture (in the model frame) as described by Cootes *et al.* (2001):

$$\begin{cases} \tilde{S} = \bar{S} + Q_s c \\ \tilde{A} = \bar{A} + Q_a c \end{cases} \quad (11)$$

where Q_s , and Q_a are matrices describing the variation modes derived from the training set.

Yang and Duncan (2004) built a shape-intensity model over the distribution of the level set function and intensity pair. An estimate of the shape-intensity pair $[\Phi^T, I^T]^T$ can be represented by k principal components and a k -dimensional vector of coefficients (where $k < n$), α :

$$\begin{bmatrix} \tilde{\Phi} \\ \tilde{I} \end{bmatrix} = \begin{bmatrix} \bar{\Phi} \\ \bar{I} \end{bmatrix} + U_k \alpha \quad (12)$$

where U_k is a $2N^d \times k$ matrix consisting of the first k columns of matrix U , whose column vectors represent the set of orthogonal modes of the shape-intensity variation.

Heimann and Meinzer (2009) present a review of the methods and procedures for generating, training and employing statistical models of shape and appearance for 3D medical image segmentation.

Starting from the AAM model, other models have been proposed, such as the parametric model, which combines shape and texture (Feng *et al.*, 2010), and the multifeature active shape model (MFAM) (Toth *et al.*, 2011), which uses an explicit representation of the difference of the multifeature landmark-free active appearance model (MFLAAM) (Toth and Madabhushi, 2012) (which itself uses the implicit representation). MFLAAM was extended for the simultaneous segmentation of multiple objects. The extended technique was called multiple-levelset AAM (MLA) (Toth *et al.*, 2013) and was used for zonal segmentation of the prostate.

Another combination was also tested: the shape and *a posteriori* probability distribution (Ghose *et al.*, 2011a, 2011b, 2012b, 2013). Three types of features were employed by Li *et al.* (2011) to obtain information about the movement of the prostate in the pelvis: appearance, the histogram of the oriented gradient, and the coordinates of each pixel.

- *Atlas*

An atlas can be constructed in different ways. It can be considered the mean of a given feature as a shape (\bar{S} and \bar{S}_p terms in equations 6 and 8, respectively) or appearance (\bar{A} term in equation 10). It can also be more generic by considering the most representative cases in a population: the mean value of a feature and the deviations around this mean. For instance, ASM and AAM allow the generation of shape and appearance atlases, respectively.

A labelled image, typically a mean image, where all the structures of interest are defined by an expert is also considered an atlas. In this case, it is called a topological atlas.

Topological atlases are mainly used for segmentation purposes through a registration process where the image to be segmented (target image) is non-rigidly registered to the atlas image.

Two strategies are considered (Fig. 3). The first involves a single atlas (Hwee *et al.*, 2011), while in the second, multiple atlases are considered. This multi-atlas approach (Klein *et al.*, 2008; Langerak *et al.*, 2010; Acosta *et al.*, 2011; Gao *et al.*, 2012; Ouet *et al.*, 2012; Litjeans *et al.*, 2012) implies successive registrations of the target image with

the images atlases. A score based on a similarity measure is associated with each registration, and the atlas image with the best score serves as a reference to segment the target image.

Another atlas class exists; these atlases are probabilistic. A probabilistic atlas is an image containing the *a priori* probabilities of the distributions of the different structures distributions. Figure 4 depicts an example of this type of atlas.

Brief summary: Starting from the fact that prostate shape variations are limited and known, active shape modelling and its derivatives seem to be the most suitable models for generating a prostate model. However, adding the appearance makes the model richer. This is possible through the active appearance model and its derivatives. Indeed, these techniques allow the building of a statistical model that includes both the shape and the texture. Understandably, a finer model requires a more complex database that is representative of the real clinical data. In this case, atlases (topological or probabilistic) provide a fairly inspired solution.

Despite their intuitive aspects, statistical models do not consider the behavior of internal prostate tissues. Biomechanical modelling provides a solution to this issue.

3.2 Biomechanical analysis

A. Techniques

Biomechanics modelling unquestionably provides answers when medical applications strive to account for tissue deformations (Carter *et al.*, 2005). Biomechanics has been defined as the study of the movement of living things using the science of mechanics, which is a branch of physics that is concerned with the description of motion and how forces create motion (Knudson, 2007). Three steps are usually required to develop a biomechanical model: geometric reconstruction; meshing; and the integration of material properties (often Young's modulus and Poisson's ratio) and boundary conditions, such as any rigid constraint imposed by the pelvic bone and displacement of the rectal wall (Hu *et al.*, 2010). The first step concerns the segmentation (manual, semi-automatic or automatic) of the anatomical structure in the images (usually CT, MRI or ultrasound). In the second step, the volumes are discretized, and the meshes are created.

Usually, two broad classes of biomechanical models are defined: discrete and continuous models. Discrete models represent the material by a set of discrete elements, such as a system of particles (Jaillet *et al.*, 1998; Marchalet *et al.*, 2007). In continuous modelling, the materials are described directly by continuum mechanics equations, which are solved by finite element

methods (FEMs) (Mohamed A. *et al.*, 2001; Bharathaet *al.*, 2001; Alterovitzet *al.*, 2006; Crouch *et al.*, 2007; Boubakeret *al.*, 2009; Hu *et al.*, 2010; Risholmet *al.*, 2011).

Because the prostate deformation caused by the probe pressure in TRUS imaging is mostly elastic (Krouskopet *al.*, 1998), some authors (Baumann *et al.*, 2012; Niret *al.*, 2013) have introduced a linearized elastic potential for TRUS imaging.

Brief summary:The basis of continuous models in continuum mechanics leads to a direct link between the model parameters and the physical properties of the materials. By assuming that the physical properties are known, continuous methods have the advantage of allowing an accurate representation of the organs and their deformations. In contrast, in discrete models, the parameters are not directly related to the physical properties. However, discrete models have the advantage of being easier to implement.

B. Model generation

Jailletet *al.* (1998) determined the volume of the pelvic organs (rectum, bladder and prostate) from cross-sectional CT images and subsequently filled the volume with spherically shaped particles. Large particles were reserved for the internal organs. Because of the stiffness/elasticity of biological tissue, interactions were often described by the Lennard-Jones potential (particle interaction), which simulates the interaction between two atoms. The stiffness and viscosity were modelled by springs and dampers, respectively.

Marchalet *al.* (2007) developed a model to simulate soft tissue behavior. This discrete model is composed of particles connected by physical laws and simulates the behavior of rigid, elastic or muscular regions.

Bharathaet *al.* (2001) considered the gland to be a heterogeneous linear elastic medium, and its deformation was calculated by varying the Young's modulus and Poisson's ratio. The authors estimated the boundary condition flow by basing their estimation of the internal deformation on an elastic model. However, Risholmet *al.* (Risholmet *al.*, 2011) estimated the boundary conditions and the internal deformation jointly under an elastic constraint.

Crouch *et al.* (2007) modelled prostate deformation using a finite element model with an m-rep shape representation.

Alterovitz *et al.* (2006) developed a 2D finite element model of the pelvic area from a sagittal section, with optimization of stiffness parameters. Following the previous authors but using 3D, Henselet *al.* (2007) built a finite element model using linear elastic properties based on the results of Bharatha *et al.* (Bharathaet *al.*, 2001).

An ‘initial’ biomechanical model that simulates the mobility of the pelvic organs was created by Boubaker *et al.* (2009). The initial model is enhanced by experimental data, i.e., the properties of the materials, the internal pressures, and the thickness and geometry of the pelvic organs. The finite element method is adopted in the initial model as a mechanical tool to calculate the movement of the pelvic organs in real time. Mohammad *et al.* (2011) optimized the “initial” model to create a model that can predict prostate movement in the anatomical environment following rectal, bladder and lung distension.

Mohamed A. *et al.* (2001) developed a biomechanical model that simulates the movement and deformation of the prostate that results from the insertion of a transrectal probe. They have also presented an approach combining biomechanical and statistical modelling to estimate the deformed prostate shape created during TRUS probe insertion. Hu *et al.* (Hu *et al.*, 2010) combined the two approaches. The authors built a statistical motion model (SMM) in the same manner as ASM, but the training data reflect the variability in the position, orientation and shape of an organ that results from intra-subject tissue motion and deformation rather than inter-subject variability in organ shape alone. To counteract the disadvantages of this approach, Crouch *et al.* (2007) linked medial geometry and biomechanics to generate a deformation.

Brief summary: The biomechanical properties of prostate tissue were modelled and measured recently for incorporation into modelling methods for accurate tissue behavior simulations under constraints and for movement prediction. For precise and effective values, these properties must be measured *in vivo*. However, due to the complexity of this task, they are measured *ex vivo* on tissue samples. Moreover, an important inter-patient variability exists that makes the complete description of these parameters complex and therefore limits their real impact in the modelling process.

Table 1 summarizes the different modelling techniques and their application to the features extracted from the images.

4. Clinical Applications

Many clinical applications utilize prostate imaging with different imaging modalities. The obtained images are used in various manners based on the final purpose. In general, two main treatment techniques are used: segmentation and registration. Segmentation aims to extract the gland or sub-gland contours, while registration aims to match different image acquisitions. Review articles, which present a detailed discussion of multimodal prostate image

segmentation techniques and cancer staging, have already been published (Zhu *et al.*, 2006; Ghose *et al.*, 2012a). This section summarizes the most common applications and classifies the techniques employed (table 2).

4.1 Diagnosis and cancer staging

Prostate cancer diagnosis using multimodality imaging aims to detect and map cancers with a focus inside the gland. For this purpose, different imaging modalities and sequences are used to enhance both the specificity and sensitivity of the detection (Alterovitz *et al.*, 2006; Mohamed *et al.*, 2009). For this application, registration is required to place all the images in the same spatial reference. While rigid registration only allows for compensation of the global movements, non-rigid techniques allow for correction of the non-linearity caused by organ deformation.

Segmentation is applied to extract the prostate (Kachouie and Fieguth, 2007; Rafiee *et al.*, 2009; Kirschner *et al.*, 2012) and to describe its zonal anatomy to permit data reduction and the application of different analysis algorithms based on the considered region.

Another application is the automatic or semi-automatic detection and identification of suspicious lesions. As indicated in the introduction section, the most common computer-aided detection methods use multiparametric MR images. The current standard paradigm for using CAD systems is as a second reader. After the radiologist has evaluated the multiple imaging sets, CAD indicates the likelihood that a given suspicious region is malignant. Most of the employed methods are based on using supervised classification and clustering algorithms, such as the Fisher linear discriminant (Chan *et al.* 2003), the Bayesian classifier (Madabhushiet *al.* 2005) or support vectors machines (Voset *al.* 2008, Lopes *et al.* 2011), to group multidimensional voxels into classes. Recently, Tiwari *et al.* (2013) presented a computerized decision support classifier, called semi-supervised multi-kernel graph embedding (SeSMiK-GE), for characterizing high-grade prostate cancer.

4.2 Biopsies

Biopsy remains the gold standard for prostate detection and characterization. TRUS-guided biopsy is currently the standard diagnostic procedure (Narayanan *et al.*, 2008; Baumann *et al.*, 2012; Yang and Fei, 2012; Qiu *et al.*, 2013), and it is used worldwide for detection in the presence of an elevated PSA or an abnormal digital rectal examination. This type of biopsy usually consists of taking 10 to 12 biopsy samples using a transrectally directed

needle, which is visualized using real-time TRUS images of the gland. The cancer burden is expressed as the length of the core involved in cancer (cancer core length (CCL), either in millimeters (mm) or as a percentage of the whole biopsy core), along with the absolute numbers of cores involved. Histological examination is performed by trained pathologists, who characterize each biopsy according to the Gleason grading system (Khouzani and Soltanian-Zadeh, 2003; Zhan *et al.*, 2007a).

In some centers, the procedure is guided using TRUS and MR T2W images (Mitra *et al.*, 2012). In this case, image registration is performed to match the real-time TRUS images to the pre-procedure MR images to guide the biopsy instrument to pre-defined lesions.

In some studies, biomechanical modelling has been applied to simulate tissue interactions with needles to enhance the ultrasound imaging-based guidance (Bauer *et al.* 1999).

4.3 Radical therapies

Conventional radical therapies are composed of radical surgery and radiation therapies (brachytherapy and external beam radiation). Cryotherapy, as well as high-intensity focused ultrasound (HIFU), is also offered in certain centers. These techniques treat the whole prostate regardless of the cancer volume within the prostate, and thus, structures that are in close proximity to the prostate (neurovascular bundles, urinary sphincter, bladder neck and rectum) could become damaged.

In the past few years, some technical refinements have been introduced in radiation therapy (brachytherapy, intensity-modulated radiation therapy (IMRT), and proton therapy as alternatives to external beam radiation) and surgery (laparoscopic and robotic surgery as alternatives to radical prostatectomies).

A. Surgery

The use of conventional imaging modalities, such as TRUS, MR or CT, is limited during surgical procedures. In robotized interventions, biomechanical modelling is used to manage gland motion and tissue deformations (Yan *et al.*, 2009, 2010; Hu *et al.*, 2010; Yan and Kruecker, 2010; Hu *et al.*, 2011).

B. Radiotherapy

Radiotherapy involves two steps: a pre-treatment step consisting of treatment planning with structure definition, dose estimation and ballistics optimization and a treatment delivery step. In both steps, imaging is used (Fenget *et al.*, 2009, 2010; Lu *et al.*, 2011; Acosta *et al.*,

2011). In the first step, CT and MR images are used to delineate the prostate and some organs at risk, such as the bladder and rectum, while in the second step, the challenge is to manage the dose delivery by returning the patient to his planning position and by taking into account motions and deformations (Boubaker *et al.*, 2009). For this case, many techniques have been based on multimodal imaging and registration (Henselet *et al.*, 2007; Zhou *et al.*, 2010; Shi *et al.*, 2011; Zhou *et al.*, 2012).

C. Brachytherapy

This technique aims to treat the prostate by implanting permanent radioactive seeds into the gland or by inserting tiny catheters and then providing a series of radiation treatments through these catheters.

Brachytherapy planning is based on the use of TRUS images that are acquired in the treatment room (Mahdavi *et al.*, 2011). The images are used to define the prostate contours and the positions of the seeds or the catheters. Modelling is often used to account for tissue deformations (Mohamed *et al.*, 2002; Gokselet *et al.*, 2005; Marchalet *et al.*, 2007).

In some cases, pre-procedure planning is performed using CT images. Registration techniques are thus used to update this planning by matching the CT images to the real-time TRUS images (Bharatha *et al.* 2001; Crouch *et al.*, 2007).

4.4 Focal therapies

Focal therapy proposes to treat prostate cancer with a similar approach as that for other solid organ malignancies. That is, the treatment, which is delivered by an energy source, is directed to the area of cancer and to nearby normal tissue to preserve tissue and consequently organ function. By avoiding damage to the whole prostate, damage to the nerves, muscle, urinary sphincter, bladder and rectum can be avoided.

Different energy modalities (e.g., those used in laser therapies, HIFU, and cryotherapy) are currently utilized (Betrouni *et al.*, 2013), and some preliminary results have been published (Makni *et al.*, 2012). In all of these techniques, multimodality imaging of the prostate plays an important role in addressing two main issues: the issue of dosimetric planning to optimize the treatment parameters that will be applied to account for the target volume and the issue of typology and monitoring for real-time evaluation of the treatment and its outcome.

In table 2, we have summarized the previously discussed applications and linked them to the treatment technique used and the prostate modelling methods applied.

5. Conclusion

Analyzing multimodal and multiparametric prostate images is an active research field where organ modelling has been and still continues to be extensively applied. In this review, we have summarized the main steps leading to the construction of a valid prostate model and presented the main clinical applications where this modelling has been applied.

Due to the extensive literature on the topic, a complete description of all the methods and techniques requires a dedicated book. To provide a general overview with a reasonable text length for a scientific paper, we have intentionally focused on the modelling process without deeply discussing the final applications. Table 1 provides a summary of the features and the analysis techniques, while table 2 links these techniques to the clinical applications.

Conflict of interest

The authors declare no conflict of interest.

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