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Machine learning and registration for automatic seed localization in 3D US images for prostate brachytherapy

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Abstract

Purpose: New radiation therapy protocols, in particular adaptive, focal or boost 9 brachytherapy treatments, require determining precisely the position and orientation 10 of the implanted radioactive seeds from real-time ultrasound (US) images. This is nec-11 essary to compare them to the planned one and to adjust automatically the dosimetric 12 plan accordingly for next seeds implantations. The image modality, the small size of 13 the seeds and the artifacts they produce make it a very challenging problem. The 14 objective of the presented work is to set-up and to evaluate a robust and automatic 15 method for seed localization in 3D US images. 16

Methods: The presented method is based on a pre-localization of the needles through 17 which the seeds are injected in the prostate. This pre-localization allows focusing the 18 search on a region of interest (ROI) around the needle tip. Seeds localization starts by 19 binarizing the ROI and removing false positives using respectively a Bayesian classifier 20 and a Support Vector Machine (SVM). This is followed by a registration stage using 21 first an Iterative Closest Point (ICP) for localizing the connected set of seeds (named 22 strand) inserted through a needle, and secondly refining each seed position using Sum 23 of Squared Differences (SSD) as a similarity criterion. ICP registers a geometric model 24 of the strand to the candidate voxels whilst SSD compares an appearance model of a 25 single seed to a subset of the image. The method was evaluated both for 3D images of 26 an Agar-agar phantom and a dataset of clinical 3D images. It was tested on stranded 27 and on loose seeds. 28

Results: Results on phantom and clinical images were compared with a manual localization giving mean errors of 1.09 ± 0.61 mm on phantom image and 1.44 ± 0.45 mm on clinical images. On clinical images, the mean errors of individual seeds orientation was $4.33 \pm 8.51^{\circ}$.

Conclusions: The proposed algorithm for radioactive seed localization is robust, tested on different US images, accurate, giving small mean error values, and returns the 5 cylindrical seeds degrees of freedom.

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Keywords: Prostate brachytherapy, Radioactive seed localization, 3D Ultrasound image,
 Bayesian classifier, support vector machine (SVM), iterative closest point (ICP), Sum of
 squared Differences (SSD)

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63 I. Introduction

Prostate cancer is the 3^{rd} most frequently diagnosed cancer in men worldwide, accounting 64 for 1.27 million new cases in 2018 . Brachytherapy using low dose rate radioactive seeds 65 is an effective treatment for low risk prostate cancer. It aims at delivering a specific and 66 homogeneous radiation dose to the prostate whilst limiting the dose delivered to organs at 67 risk (urethra, rectum and bladder). This requires a planning step determining the number 68 and optimal positions of seeds from pre-operative images: most often transrectal US images. 69 In a typical brachytherapy procedure ¹ parallel needles are inserted into the patient's prostate 70 through the skin of the perineum with the help of a guiding grid named template. Once 71 the needle tip reaches the wanted position, the seeds are released through the needle. Two 72 strategies are possible depending on the type of seeds: stranded seeds are pre-assembled 73 with spacers using connectors and released as a whole for each insertion direction. On the 74 opposite, loose seeds are released one by one, which makes needle retraction more complex 75 and progressive. Needle insertion and seed implantation are performed under the control of 76 transrectal US imaging (generally reconstructed in 3D from translated axial 2D US). 77

In practice, seed implantation is performed manually with some imprecision which re-78 sults from operator variable expertise, prostate motion and deformation, edema, needle 79 deflection, etc. Stranded seeds reduce delivery inaccuracy and seed migration compared to 80 loose seeds. However, in both cases, the brachytherapy procedure may require a planning 81 update, at some stage, taking into account the real position of already implanted seeds. 82 Detecting them most often requires human intervention. In this paper we propose a novel 83 method for automatic seeds localization in 3D US images. Connected to a fast replanning 84 this allows to envision a fully automatic adaptive brachytherapy, that is an intra-operative 85 update of the seeds placement planning, based on the localization and actual dosimetry map 86 of the previously implanted seeds. 87

⁸⁸ Detecting the seeds is a challenging task due to their small volume (cylinder: $\emptyset = 0.8$ ⁸⁹ mm and 5 mm in length for I¹²⁵ seeds) and to the low quality of the US imaging modality.

¹https://www.mayoclinic.org/tests-procedures/prostate-brachytherapy/multimedia/ permanent-prostate-brachytherapy/img-20008710

f_the_art

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I.A. State of the art

The accurate localization of seeds is an active field of research. Several approaches have 91 been proposed operating on various image modalities, like magnetic resonance (MRI), X-ray 92 images (computed tomography CT or fluoroscopy) and ultrasound images (US). Because of 93 its excellent soft-tissue contrast, MRI is essentially used for diagnostic. It could be also used 94 for seed localization post-operatively: Kuo et al. ^{MRI} developed an algorithm based on the blob 95 detection technique using the Laplacian of a Gaussian (LoG). Generally the CT images are 96 used to perform post-implant dosimetry one month after seeds implantation. In this context, 97 N'Guyen et al. CTseedSegmentation proposed an approach to determine seeds position and orientation in CT 98 images using K-means and principal component analysis (PCA) techniques; the method 99 allows to separate seeds grouped in clusters, a situation that may occur with loose seeds. 100 MRI only and CT-MRI fusion-based works are proposed to localize seeds post-operatively 101 nosrati2019postir using Deep Neural Network (DNN) methods for low-dose-rate prostate brachytherapy 102 Whilst CT and MRI may be exploited for pre-operative diagnostic or planning or post-103 operative assessment, they cannot be used for intra-operative control of seed position. A 104 possible intra-operative solution is to obtain the real position from X-ray images acquired 105 with a C-arm as presented in $\frac{Xray}{f}$. However the prostate is not visible in X-ray images. US 106 imaging is thus the effective modality used today to guide brachytherapy as it acquires real-107 times images, which is particularly relevant in the context of moving and deformable soft 108 tissue. 109

In this section we describe some of the few methods proposed in the literature to localize seeds in US images. Because seeds are injected through needles, some seed localization methods start with the needle tip localization. This allows building a ROI to be explored.

Wei et al. SeedLocalization1 Proposed a workflow composed of 6 iterative instructions. First steps aim 113 to detect the needle, build the ROI and threshold the obtained volume. Then, neighboring 114 candidate voxels, potentially corresponding to seeds, are grouped into clusters. Seeds are 115 localized by detecting the center and the orientation of each cluster using the PCA method. 116 Finally, clusters which dimensions do not correspond to seed dimensions are removed. These 117 steps are repeated until all implanted seeds have been localized. The method was tested 118 on Agar-agar and chicken phantoms with a CT-based ground truth. Such a method may 119 only be used to localize loose seeds since strands dimensions vary with their composition. 120

As pointed by the authors, selecting the threshold may be very challenging since US images
vary a lot from patient to patient.

In a rather similar way, Wen et al. SeedLocalizationNeedle2 detect seeds by computing a ROI using the 123 preoperative dosimetry plan, thresholding using the Otsu method $\frac{0 \pm s_u}{10}$, clustering the voxels 124 and pruning the set of clusters using dimension information. Needle track based on Hough 125 Transform (HT) is used a posteriori to filter the seed detection results. The method was 126 evaluated on a commercial tissue equivalent phantom. However, the information deduced 127 from the preoperative dosimetry plan may be inaccurate to construct the ROI. Indeed, as the 128 inserted needle may deviate from the target, seeds may be released away from the planned 129 positions. The challenges of real clinical images are also underlined by the authors. 130

Based on a DNN, Holupka et al. determine the position of the seeds from two 131 dimensional transaxial transrectal US clinical images. A common DNN, called DetectNet 132 was trained using 950 US images and tested on 90 validation US images. The network 133 was trained from a data base of 2D clinical images manually segmented. The results on 10 134 patients were compared with the corresponding positions in CT images to obtain an average 135 error of 2.29 mm. However, CT images were acquired one to three months after the day 136 of the implant where prostate gland may inflate causing seeds positions displacement. To 137 compensate this, obtained seeds positions were transformed according to an empirical scaling 138 factor representing the prostate shape change. 139

Deep learning was also used by Golshan et al. ^{golshan2020automatic}/^{golshan2020automatic}/_{2.} The same type of engineered neural 140 network (CNN) was applied to locate the needle and its implanted stranded seeds. The 141 learning phase is based on rather small number of 3D images of anonymous patients: 13 142 images containing 238 seeds. It was carried out with patches, which are 3D cubic sub-143 regions of the ultrasound images, representing models for a 'seed' region and of a 'non seed' 144 region. Localization results were compared with an expert manual localization on ultrasound 145 images giving $F_{1-score} = 0,7$ (seed considered as true positive when its localization error is 146 smaller than 2.5 mm). 147

Dehghan et al. recently proposed a solution ^{EMenhanced} detection based on electromagnetic (EM) needle tracking, which allowed recording of seed dropping locations. A 3D US volume was obtained after each injection. Then, successive registered volumes were subtracted to obtain a difference volume. There, seed candidates were detected using their

extended reverberations as a signature. Finally, false positive seeds were removed by com-152 paring their locations with the expected location which corresponds to the seed dropping 153 locations. However, the transfer to clinical routine of EM tracking (and associated needle 154 modification) is not straightforward. 155

Table Table summarizes the presented methods. Most of them do not allow for a fully 156 automatic binarization. Methods also differ regarding the number of localization parameters 157 that are determined. Ideally, the complete pose of a cylindrical seed requires 5 parameters 158 $(x, y, z, \theta_x, \theta_y)$. Given the cylindrical shape of the seed, θ_z is meaningless and an arbitrary 159 value can be chosen. Many methods consider only the position of the seed (3 parameters) 160 and this may be sufficient when dose calculation relies on very simple 1D model (the seed is 161 considered as a point source and the delivered dose is spherical). However, since very long 162 rivard2004update the American Association of Physicists in Medicine (AAPM) recommends the use of 2D 163 dose models for cylindrical seeds. Taking full benefit of such models requires knowing the 164 orientation of the seed. Collins Fekete et al. ^[collins2014quantifying] 165 errors may have in impact on the dose delivered to organs at risks. Moreover adaptive 166 brachytherapy involves more complex dose models requiring a full localization of the seed. 167 Finally, published methods differ in their level of evaluation. Whilst, all the methods cited in 168 table <u>tab_state_of_the_art</u> table <u>to CT</u> based ground truth, most of them are limited to phantom experiments. 169 Only the deep learning-based methods present results on real patient images. 170

In this paper, we aim at determining the 5 pose parameters of stranded seeds. An initial 171 stage consists in localizing the needle before seed insertion to reduce the ROI to the relevant 172 region (see \S **i.**A.). In order to adapt to local variations in the image and to the patient, we 173 propose an automatic thresholding method based on Bayesian classification (see § 1.8.1.). 174 False positive voxels, that may be selected by thresholding, then detected and removed using 175 SVM classifier (§ II.B.2.). As presented in § II.B.3., binary images are first processed using 176 planning information to localize stranded seeds in the ROI as a whole. In a second stage 177 explained in section II.B.4., individual seeds are precisely localized by locally comparing the 178 grey level of the original image to a seed 3D US image template. The approach was evaluated 179 on two experimental setups: a phantom experiment allowed us to compare our localization 180 method of dummy seeds in an Agar-agar phantom to a a reference manual segmentation 181 $\left(\frac{\text{sec:phantom}_experiments}{1.C.1.} \right)$. The method was also tested on routine clinical images and also compared to a 182 reference manual segmentation (§ 1.C.2.). The associated results are presented in section 183

sec:Phantdsecimageniresliltsages

¹⁸⁵ II. Materials and Methods

Seeds localization begins with a needle detection which is an essential step to build the ROI where seeds are released. First, we introduce the employed method to localize a needle in 3D US images which we previously developed. Then we explain the seed localization method modeled by the workflow of Fig. ^{fig:workflow}

II.A. Needle detection

Needle detection is done using the previous work ^{|ourWork}/₁₀ based on binary Bayesian classification.
We proposed a method to localize needle in 3D US images. Needle voxels within US volumes
are brighter than the other voxels, and form a voxel class selected according to the Bayesian
classifier:

195

edetection

 $\pi_{X_n} P(I(x) = y | X_n) \underset{X_b}{\overset{X_n}{\gtrless}} \pi_{X_b} P(I(x) = y | X_b)$ $\tag{1}$

• X_n = needle voxel class.

- X_b = background (non-needle) voxel class.
- y = I(x) =voxel intensity x.
- π_{X_i} = prior probabilities.
- $P(I(x) = y|X_i) =$ Gaussian probabilities.

Where: a voxel x is classified in X_n if the posterior probability of X_n is larger than that of X_b . The way parameters of the probabilistic model are estimated and a curve representing the needle is fitted to data is fully explained in $\begin{bmatrix} \text{ourWork} \\ \text{fig:needles lolalized} \\ \text{204} \\ \text{tested on anonymized 3D US clinical images. Fig. } \begin{bmatrix} \text{fig:needles lolalized} \\ \text{2 shows a typical result example. In order} \\ \text{to obtain a good estimate of the dropping location of seeds, with respect to the previous} \\ \text{work } \begin{bmatrix} \text{ourWork} \\ \text{fig. needles} \\ \text{fig. needles} \end{bmatrix}$ the last voxel along the curve where

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 $P(X_n \mid I(x)) \le P(X_b \mid I(x)) \tag{2}$ BayesianTip

As shown in Fig. ^{fig:tip}/₅, the detection is successful even for a needle passing through a shadow region, which is a dark region that corresponds to some reflected signals attenuation. Needle detection allows to build the ROI where seeds are supposed to be located. As shown in Fig. ^{fig:References}/₄, the ROI is a parallelepipedic frame which dimensions depend on the length of the released strand supposed to be inside. As explained in § ^{lig:Stranded_seeds_composed}/_{2, strands} compositions and lengths are recoverable from the treatment planning. The next subsection describes the method for seeds localization in the ROI.

²¹⁶ II.B. Seeds localization

The current proposed method has been designed for stranded seeds localization. The workflow shown in Fig. $\frac{\texttt{fig:workflow}}{\texttt{l}}$ contains the main steps and methods used to detect and localize oriented seeds. We detail each step separately in the following subsections. The first typical step for object detection is to separate it from the background.

II.B.1. Thresholding: Binary Bayesian classifier

:Bayesian

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A thresholding step aims to separate seeds voxels from background. The classical method consists in defining a threshold value τ and classifying as follows:

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 $Background = \{x : I(x) < \tau\}$

 $Seeds = \{x : I(x) > \tau\}$

Because of the presence of high intensity artifacts and the high variability of grey levels in US images, defining thresholds for binarization is very challenging. This is why we propose to use a Bayesian classifier to perform binarization without a static threshold definition. In a way similar to needle detection, seeds and background voxels are described through two separated peaks which can be modeled using an additive Gaussian Mixture Model (GMM). The Bayesian classifier^{hy} assigns the most likely class to a given observed feature which is the voxel intensity.

232

$$C_{Bayes}(y) = \underset{X_i}{argmax} \quad P(Cl = X_i \mid I(x) = y)$$
(3) eq:Bayes1

²³³ Where $Cl = \{X_s(Seeds), X_b(Background)\},\$

and I(x) = y is the voxel intensity. According to Bayes theorem:

235

24

$$P(Cl = X_i | I(x) = y) = \frac{\pi_{X_i} P(I(x) = y | Cl = X_i)}{P(I(x) = y)}$$
(4) eq:Bayes2

Where π_{X_i} are the prior probabilities and $P(I(x) = y|X_i)$ are the Gaussian probabilities. The intensities I(x) are independent within each class, which justifies the Bayes theorem application. According to equations $\binom{|eq:Bayes!eq:Bayes2}{5}$ Bayesian classifier assigns to each voxel the class which maximizes $argmax_{X_i} \{\frac{\pi_{X_s} - P(I(x) = y | Cl = X_s)}{P(I(x) = y)}, \frac{\pi_{X_b} - P(I(x) = y | Cl = X_b)}{P(I(x) = y)}\}$. Finally, binary Bayesian classification to be used is summarized as inequalities $\binom{|ineq:Bayes1}{5}$.

$$\pi_{X_s} P(I(x) = y | X_s) \underset{X_b}{\overset{X_s}{\gtrless}} \pi_{X_b} P(I(x) = y | X_b)$$
(5) ineq:Bayes1

Several parameters are required: $\{\pi_{X_i}, \mu_i, \sigma_i\}$ where $i = \{s, b\}$ and μ , σ are the Gaussian 242 parameters. These parameters vary from one stranded seed to another even in the same 243 image. According to a criterion of maximum likelihood, parameters are predicted by ap-244 proaching as much as possible the distribution of seeds volume histogram. This is done via 245 with the well known Expectation-Maximization algorithm (EM algorithm $\stackrel{\text{FB}}{\Longrightarrow}$). EM is applied 246 on a Gaussian mixture model to estimate the unknown parameters by an iterative process, 247 which computes the maximum-likelihood of a given vector of features for each iteration. EM 248 algorithm iterates parameters calculation until their convergence. Fig. <u>5 contains a result</u> 249 example. 250

251 II.B.2. False positive voxels removal: Support Vector Machine (SVM)

ve_removal

It naturally happens that some background voxels are assigned as seed voxels. In order to remove these false positives, we propose to apply an additional discriminator: Support Vector Machine (SVM), a learning classifier. In the case of binary classification, a SVM maximizes the margin between classes C^1 of false positive voxels and C^2 of true positive voxels $(C^1 \bigcup C^2 = X_s)$. It aims to find the hyperplane that separates classes optimally. In the linear case, the main equation to establish the hyperplane equation is:

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$$h(x) = w^T x + w_0 \tag{6}$$

where $x = (x_1, ..., x_N)$ is the input vector which contains voxel features, w is the normal vector to the hyperplane and w_0 is the offset of the hyperplane from the origin along the normal vector w. Finally the last parameters (w^T and w_0) determine the classifier as follows:

$$x \mapsto sign(w^T . x + w_0) \tag{7}$$

The input vector x is assigned to the appropriate class regarding to the sign of $(w^T \cdot x + w_0)$. 264 It represents the position of x with respect to the hyperplane. As mentioned previously, the 265 input vector x represents the input voxel to be classified. It contains the voxel features. Clas-266 sification results depend on the selected features. Based on the specificity of brachytherapy 267 application, we propose to use two gradient-based features: indeed, stranded seeds injection 268 in the prostate follows the \vec{Z} axis of the 3D US image, so the intensity change of seeds 269 voxels according to \overrightarrow{X} and \overrightarrow{Y} could have high value, contrarily to others outliers voxels 270 (Fig. 5). The gradient magnitude $(|G_x|, |G_y|)$ along \overrightarrow{X} and \overrightarrow{Y} provide a good discriminative 271 representation as shown in Fig. $\overset{\text{fig:hyperplane}}{\mathbf{5}} (x_1, x_2) = (G_x, G_y), \{G_x, G_y\}$ are the gradi-272 ent magnitudes. The gradient magnitudes are computed from the original US image. The 273 Sequential Minimal Optimization (SMO $\frac{SMO}{19}$ algorithm is used to compute the hyperplane 274 equation parameters (w^T, w_0) . It transforms the problem of parameters prediction into the 275 dual problem: 276

277
$$h(x) = w^T x + w_0 = \sum_{i=1}^N \alpha_i y^{(i)} < x^{(i)}, x > + w_0$$
(8)

278 where

• $(x^{(i)}, y^{(i)}) = \text{training data.}$

•
$$y^{(i)} = \{-1 \text{ if } x^{(i)} \in C^1, 1 \text{ if } x^{(i)} \in C^2\}.$$

• $\alpha \in \Re^N = \text{Lagrange multipliers.}$

• N =the training data length.

For training the SVM, we chose three ROI containing different stranded seeds compositions and different artifacts locations for which we calculated and labelled the features $(|G_x|, |G_y|)$. SMO was trained on the fusion of these three datasets to return the best separative hyperplane which maximizes the distance at the nearest data point of each group. A typical SVM discrimination result is shown in Fig. $\frac{fig:firstTwoSteps}{5}$.

sec:ICP

II.B.3. Global stranded seeds localization

At this stage, strand voxels have been computed using a succession of two classifiers. As 289 proposed in the workflow (of Fig. $\frac{\text{fig:workflow}}{1}$, the next step aims at localizing each strand considered 290 as a whole within selected voxels. This is done by rigidly registering a geometric model of 291 the stranded seeds to the seed voxels detected in the previous stets, represented by their cen-292 ters. This is performed using the Iterative Closest Point (ICP) algorithm $\frac{|ICP|}{20}$. One objective 293 is to transform the 3D voxels already selected into a set of connected cylinders. A second 294 very important objective is to distinguish seeds from spacers connecting them since their US 295 appearance is very similar (Fig. $\frac{fig:firstTwoSteps}{b}$). Based on the treatment planning, we construct the 296 model of the strand injected through each needle. This model, which is a set of 3D surface 297 points, describes the succession of cylinders that represent radioactive seeds linked through 298 $\frac{fig:StrandedSeeds}{7$ shows two real strands and their corresponding models. We propose to spacers. Fig. 299 employ ICP to superimpose the two sets of 3D points. ICP requires a suitable initialization 300 of the relative position of data to be rigidly registered. Since the closest known position of 301 the strand to be localized is the needle tip, the model is initialized at needle tip coordinates 302 (obtained as specified in II.A.) and is aligned with the insertion direction. It allows to find 303 the optimal transformation representing the location of the strand as a whole: 304

³⁰⁵ $T_{Strand} = \{\theta_x^{Strand}, \theta_y^{Strand}, t_x^{Strand}, t_z^{Strand}\}, \text{ where } \{\theta_x^{Strand}, \theta_y^{Strand}\}$ ³⁰⁶ and $\{t_x^{Strand}, t_y^{Strand}, t_z^{Strand}\}$ are respectively the rotations and the translations applied on ³⁰⁷ the strand relatively to the ROI frame $\{\overrightarrow{X}, \overrightarrow{Y}, \overrightarrow{Z}\}$ (Fig. 4). Given the cylindrical shape of ³⁰⁸ the strands, it is impossible to determine the rotation around its \overrightarrow{Z} axis. This information ³⁰⁹ is meaningless and an arbitrary value can be given.

³¹⁰ II.B.4. Improvement of individual seeds localization

ientations

After the ICP convergence, the optimal position of the strand model with respect to the binary image information is obtained, where all seeds are well aligned. However, in practice, stranded seeds may not remain straight, as the linkers may break during the insertion. It may result in subsets of linked seeds with different orientations as shown in Fig. b. As seeds mislocations may modify the delivered dose, an additional stage is necessary and consists in refining each seed pose separately. From that stage, spacers are no longer considered. Knowing precisely the pose of each seed would allow to update the dosimetry and replan, when necessary, the positions of the next seeds to be injected. This refinement is an imagebased rigid registration comparing an appearance model of a seed V_m to a subset V_s of the real gray level image. V_s is computed from the location of the strand obtained in $II.B.3..V_m$ was obtained by selecting a clearly visible seed in an image among those of our dataset (Fig. Ii.g.VSS). This appearance model was applied for all localized seeds.

$$T_{seed} = \underset{T}{argmin} \sum_{x,y,z} (V_m(x,y,z) - T(V_s(x,y,z)))^2$$
(9)

The optimal transformation T_{seed} is the one that minimizes the sum of squared differences (SSD) value between the model volume V_m and the seed volume V_s moved according to Twhere $T = \{\theta_x^{Seed}, \theta_y^{Seed}, t_x^{Seed}, t_y^{Seed}\}$. Similarly to the strand, θ_z^{Seed} cannot be determined and is meaningless. Moreover, because seeds, connectors and spacers have similar response and appear as a whole in the $\overrightarrow{Z_{Strand}}$ direction (Fig. [9]), refining $\overrightarrow{Z_{Strand}}$ is impracticable. This is why neither t_z^{Seed} nor θ_z^{Seed} are considered at this stage. θ_z^{Seed} can be arbitrarily chosen and t_z^{Seed} value is kept similar to what was computed in the previous stage.

materials

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II.C. Materials

Phantom experiments

The approach was tested both on phantom image and on clinical images. This section describes the data acquisition and validation protocol for both types of experiments.

periments

334

II.C.1.

Using a proportion of 2.8% of Agar-agar contained in a plastic box (Fig. ^{fig:KOELIS_Trinity_workstation}, we constructed 335 a phantom sufficiently rigid to avoid any movement of released seeds. We created a preop-336 erative dosimetry plan where 8 needles were inserted. Each of them was used to release one 337 strand. The strands composition is given in table 2. The phantom with the implanted seeds 338 was scanned using the 3D side-fire ultrasound probe of the $\text{TRINITY}^{(\mathbb{R})}$ (Koelis, Meylan, 339 France) assistance workstation for prostate interventions shown in Fig. <u>fig:KOELIS_Trinity_workstation</u> IO. 3D images were 340 produced using the probe internal motor moving a linear array transducer on 170° around 341 the probe axis. The center frequency of the transducer was set to 7 MHz, and the capturing 342 depth was set to 80 mm. The size of generated images was 95x95x80 mm, with a voxel size 343 ig:phantom-seed of $0.3125 \times 0.3125 \times 0.3125$ mm. Seeds in the phantom image are as shown in Fig. $\frac{1}{9}$ 344

To measure the error of the presented seed localization method, we compared automatic localization with a manual segmentation considered as a ground truth. We evaluated the precision of the manual segmentation by repeating it at 7 distant times, and obtained a standard deviation of 0.66 mm.

xperiments

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II.C.2. Clinical experiments

The algorithm was also tested on anonymized 3D US images of two patients. Each patient's 350 prostate with the implanted seeds was scanned using a biplane endocavity Z848 TRUS probe 351 within the Medical Flex Focus 500 ultrasound workstation. Its biplane transducer acquired 352 75 axial images of resolution 600x580 and a 3D image was reconstructed with a voxel size 353 of 0.26x0.26x1 mm. The evaluation was also done by comparing the automatic localization 354 with a manual segmentation considered as a ground truth. Because of the very low quality 355 of the images (Fig. 5), we had to select a few strands for which a manual segmentation could 356 be reliably done. 4 stranded seeds were selected from the data of patient 1 containing in total 357 11 seeds. For the image of patient 2, 3 stranded seeds containing 6 seeds were processed. 358 Detailed compositions of stranded seeds are presented in table 3. We have first measured the 359 variability of the manual segmentation by repeatedly segmenting the centers of three seeds 360 in the two images, at 7 distant times. The obtained standard deviation was 0.7 mm. 361

III. Results

ec:results

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After describing the results of our method using the phantom validation protocol, we present the corresponding results on 3D US clinical images. The parameters values used for each US image type are summarized in table 4.

366 ge_results calization

III.A. Phantom image

III.A.1. Global strand localization

The errors on the seed localization are computed as the Euclidean distances between the centers of the automatically detected and manual identified seeds. Fig. $\frac{\text{fig:boxplotPhantom}}{12}$ presents the statistics of these errors before (3.08 ± 1.55 mm) and after (1.55 ± 0.80 mm) global strands ³⁷¹ localization where the unknowns are $(t_x^{Strand}, t_y^{Strand}, t_z^{Strand}, \theta_x^{Strand}, \theta_y^{Strand})$. The errors be-³⁷² fore global strands localization correspond to the distance between the seeds of the strand ³⁷³ model initialized at the needle tip and the ground-truth positions.

sec:pose

III.A.2. Pose refinement

As described in section §1.B.4., pose refinement relies on a second rigid registration based 375 this time on voxel intensity differences. Fig. $\frac{fig:boxplotPhantom}{12}$ gives the corresponding boxplot before and 376 after seed pose refinement where the unknowns are (t_x^{Seed}, t_y^{Seed}) (more details in figure S-377 1). The global error is measured as the Euclidean distance between the seeds centers. The 378 mean error is 1.09 ± 0.61 mm. It was not possible to refine the orientations of individual 379 seeds implanted in the phantom because strands did not break, and the strand remained 380 perfectly straight. Therefore, we tested pose refinement on phantom data only for t_x^{Strand} , 381 t_y^{Strand} . We simulated orientation errors by rotating the seed volume V_s and studied how 382 well the transformation parameters could be recovered. Seeds of a strand do not deviate a 383 lot compared to loose seeds. Their deviations are mainly between -20° and $+20^{\circ}$ relative 384 to a direction according to an orientation effects study on the post-planning dosimetry of 385 low-dose-rate prostate brachytherapy $\stackrel{|collins2014quantifying}{15}$. Therefore tests were performed between -20° and 386 $+20^{\circ}$. Based on the template grid dimensions where needle holes are located every 5 mm in 387 \vec{X} and \vec{Y} , a natural dimension in \vec{X} and \vec{Y} of $V_{s/m}$ would not exceed ~2x5 mm to ensure 388 that $V_{s/m}$ contain only one seed. The only constraint along \vec{Z} is the seed length. Taking into 389 account the linker, we chose 6 mm as the 3^{rd} dimension of $V_{s/m}$. Given the voxels resolution, 390 we ended with $V_{s/m}$ dimensions of 11.25x10.31x9 mm. The seed appearance within V_m is 391 shown in Fig. ^{fig:orientations}/₁₃. The results of the simulation obtained on two seeds are presented in Fig. 392 $\overrightarrow{I3}$ left column (rotation around $\overrightarrow{X_{Strand}}$) and middle column (rotation around $\overrightarrow{Y_{Strand}}$). Each 393 row corresponds to a seed where the red curve contains the applied angles and the blue curve 394 contains the estimated values. As shown in Fig. $\frac{\text{fig:VS}}{8}$, seed and artifact signal are merged in 395 the transversal plane, contrarily to the sagittal one where the seed is clearly visible. As a 396 rotation around $\overrightarrow{Y_{Strand}}$ corresponds to a motion in the transversal plane, this rotation angle 397 cannot be accurately refined by our method because of the artifacts, as illustrated by Fig. 398 13, middle column. Although the information exists, the estimation of the seed orientations 399 around $\overrightarrow{Y_{Strand}}$ failed with the chosen dimensions of $V_{s/m}$: indeed those dimensions affect 400 the orientations estimation, when they are of the same order of magnitude as the artifacts 401

dimensions. This was confirmed by extending the dimensions of V_s and V_m to 18.75x10.31x9 mm (60x33x29 voxels) instead of 11.25x10.31x6 mm (36x33x19 voxels) and running the same experiments. The simulation results for the rotation around $\overrightarrow{Y_{Strand}}$ with this new $V_{s/m}$ size are shown in Fig. $\overrightarrow{13}$, third column. The mean errors decrease from 7.4° and 19° to 2.55° and 2.44°. It can be concluded that the small cropping of V_s and V_m is problematic because of the artifact extending laterally over the volumes. This will be discussed in section $\overrightarrow{V_{s.}}$



III.B. Clinical images

Fig. $\frac{\text{fig:boxplotpatients}}{14 \text{ presents the localization errors before global strand localization (2.36 <math>\pm$ 1.11 mm), 409 before (1.59 \pm 0.55 mm) and after (1.44 \pm 0.45 mm) individual seeds refinement (more 410 details in figure S-2). The unknown parameters are $(t_x^{Seed}, t_y^{Seed}, \theta_x^{Seed})$. Table $\frac{\texttt{tab_Statistics}}{\texttt{5} \text{ contains}}$ 411 the seeds orientations refinement compared with the manual estimation. As explained in 412 $S^{\text{sec:pose}}_{\text{M.A.2., it was impossible to refine the rotation around }}$ axis. Rotation could be 413 taken into account to some extent if the US images were acquired during seed insertions, but 414 here the US data was acquired post-operatively with all seeds implanted. We will discuss 415 this point in $\S^{\texttt{sec:discussion}}_{V..}$ 416

417 discussion

IV. Discussion

⁴¹⁸ Challenges in seed localization from 3D US images are essentially due to the low quality ⁴¹⁹ of the imaging modality and the small seed volume. Thus, some echogenic structures can ⁴²⁰ mimic seed appearance and some seeds brightness are affected when they are in a shadow ⁴²¹ region. In this paper we aimed to overcome these difficulties by introducing an automatic ⁴²² seed localization using different machine learning and rigid registration algorithms.

An accurate segmentation of candidate seeds voxels is mandatory for the localization of 423 the seeds. To do so, we performed a thresholding using a Bayes classification, followed by a 424 false-positives removal using an SVM. The EM algorithm of the Bayes classification converges 425 to local optima, and therefore requires a careful initialization of the means and variances 426 parameters. How this initialization is handled is fully described in $\frac{\text{ourWork}}{10}$. The same approach 427 was used for seed localization to obtain the adequate initialization values summarized in 428 parameters The following SVM false-positives removal step is a refinement which could not table 429

replace the Bayes Classification step. Indeed, SVM would then be applied to the original gray-level voxels, resulting in a huge amount of input points. This would be computationally expensive (estimation of the gradients of all the non-zero voxels of the US image). Moreover, this would reduce the precision of the estimation, as it would increase the number of points close to the hyperplane.

Regarding seeds localization, it has been shown in § III.A.2. that the orientation around 435 $\overline{Y_{Strand}}$ could not be refined by the image-based local registration because of the US artifacts 436 and the small size of V_s and V_m . An incremental procedure would be a potential solution for 437 extending the volumes of V_s and V_m . For the first released strands, it would be performed 438 without overlaps. Then, taking into account the neighbor potential seeds already detected 439 would allow to enlarge V_m . The incremental procedure could also allow to introduce priors 440 on previously detected seeds to modify this last stage. Of course, this would need further 441 developments and testing. 442

The presented method was evaluated using two different US acquisition devices, on two 443 different types of data (phantom and clinical), resulting in quite different image contents 444 and quality. Despite this variety, only a few of the different parameters used to establish the 445 classification and registration models needed to be tuned: the initialization values for the 446 parameters estimations of the Bayes classification using EM depend on the probe devices, 447 as illustrated by table 4. Neither the SMO initialization values (false-positives removal 448 using an SVM) nor the ICP initialization values (for the global strand registration) had 449 to be adapted. SMO was trained using phantom data, but the estimated hyperplanes for 450 phantom or clinical images are very close, despite the differences in image content, thanks 451 to our choice of features. The only other device-dependent element is the seed appearance 452 model V_m . We selected for each image type the most generic appearance model. Adapting 453 the few device dependent parameters (EM initialization values and V_m model) to new US 454 imaging devices would be quite straightforward although additional pre-clinical experiments 455 would be needed. 456

⁴⁵⁷ Despite the different experimental conditions, such as the probe technologies which ⁴⁵⁸ provide different US images types (2D or 3D), qualities and resolutions, we try to compare ⁴⁵⁹ the current work with the state of the art. Clinical images are used only in the deep learning-⁴⁶⁰ based works (^{PNN}/₁₁ and ^{[20] shan2020automatic}/₁₂). Although very promising, supervised learning requires large amount

of precisely labeled clinical images to show good performance and ability to generalize: this 461 may be a big issue as testify the published papers. The seed locations are determined by 462 a commercial software in CT volume in $\stackrel{\underline{PNN}}{\vdash}$ and by an expert manual identification on US 463 images in $\overset{[colshan2019automatic]}{\cdot}$. Obtained results are within 2.29 mm and 2.5 mm (used to calculate $F1_score$) 464 respectively in $\stackrel{\text{DNN}}{\vdash}$ and $\stackrel{\text{golshan2020automatic}}{\vdash}$. As for us, the mean errors for patients images are 1.52 mm for 465 the 1^{st} patient and 1.36 mm for the 2^{nd} one. These good results need to be confirmed 466 on larger clinical data. Concerning other mentioned methods, different types of phantom 467 images are used (summarized in table I). Seeds localization in phantom images is more 468 accurate than that in a biological tissues images. For example, it is approximately 1.03 mm 469 using Agar-agar phantom and 1.66 mm in chicken phantom ^{SeedLocalization1}. As for us, obtained result on 470 Agar-agar phantom is about 1.09 mm. According to Su et al. $\stackrel{\text{investigation}}{\stackrel{\text{21}}{\rightarrow}}$, a localization error less 471 than 2 mm is customarily considered to be acceptable. They investigated the effects of a 472 seed mislocation on the dosimetry accuracy and showed that an error of 2 mm accounts for 473 less than 5% deviation in the dose delivered to 90% of the prostate volume. Collins Fekete 474 collins2014quantifying to demonstrated that orientation errors may have an impact on the dose delivered et al. 475 to organs at risks. Moreover, new focal treatments appear where a reduced number of 476 seeds are inserted in an hemi-gland or even more locally for instance for a boost secondary 477 al2015dosimetry stresses the importance of sophisticated dose models and treatment. Al-Qaisieh et al. 478 accurate localization of seeds for focal treatments. The presented method could contribute 479 to such longer term applications. 480

As mentioned before, the use of stranded seeds decreases the implantation errors since 481 it brings them together to make a single injection per needle. We tested the algorithm 482 on various strand compositions. N8 of the table 2 released a strand composed just by 483 one seed. Also, the composition of S1 of the table $\frac{\texttt{tab_Statistics}}{3}$ is just one seed. It proves that this 484 method, contrarily to the state of the art methods, could be a solution for both stranded and 485 loose seeds localization. However if loose seeds are clustered the method would fail as the 486 other methods presented in § [I.A.: This question was addressed by N'Guyen et al. for CT 487 images , and we could consider adapting their approach for the case of US images. Most 488 methods of table i focused on loose seeds except the recent deep learning-based method 489 golshan2020automatic which was tested on strands. Loose and stranded seeds localization are two different 490 problems considering the inability to differentiate between spacers and seeds which have 491 similar response and appearance in the US images. 492

The proposed workflow has been specifically designed for stranded seeds localization in US images. It would probably not be directly applicable to other imaging modalities (MRI or CT) but several components of the approach could be generalized to another modality. Combining US information with other intra-operative data such as cone beam computed tomography (CBCT) image could be envisioned but the benefit/complexity ratio has to be carefully evaluated.

Regarding the clinical applicability of the presented method, several protocols can be envisioned. In a first stage, the automatic localization could simply happen when the peripheral seeds have been injected. This would allow re-planning for central seeds. However, ideally, the adaptive planning would be done much more often. In a way very similar to robot-assisted brachytherapy ^[cunha2010toward]/⁵⁰ where the robot generally handles a single needle and requires repeating needle insertion-seeds injection, re-planning could occur before each new needle insertion.

506 V. Conclusion

Adaptive brachytherapy requires an intra-operative update of the seeds placements, for which 507 localizing the seeds is essential. We proposed an image-based solution for the localization 508 (position and orientation estimation) of stranded seeds, which could also be applied to loose 509 seeds. Our validation was performed both on phantom and clinical data, with two different 510 US imaging devices. Our results are encouraging as the position accuracy is in-par with 511 clinical requirements, and the orientation accuracy is improved compared to state of the art. 512 Improvements and more extensive evaluations on clinical images will be needed to further 513 validate the approach. 514

515 VI. Acknowledgments

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tab_state_of_the_art

Table 1: C	Comparative	study	about	${\sf proposed}$	${\sf methods}$	for
seeds local	ization.					

	Problem to solve	Methods	US images	Ground truth
Wei et al.	$\begin{array}{c} \text{Loose seeds} \\ \hline 11zation1 \\ \hline \text{positions} + \text{orientations} \\ \text{in 3D image} \end{array}$	Gray Level Change GLC >T	Agar-agar phantom Chicken phantom	CT images
Wen et al.	Loose seeds alizationNeedle2 positions in 3D image	Otsu ^{Otsu}	Tissue-equivalent ultrasound prostate phantom model 053	CT/Fluoroscopic scan images
Holupka et al.	Loose seeds positions in 2D image	Deep learning	Clinical	CT images
Golshan et al.	Stranded seeds <u>han2020automatic</u> positions in 3D image	Deep learning	Clinical	US images
Dehghan et al. \mathbb{B}	Loose seeds positions in 3D image	US seed detection enhanced by EM-seed track	Yezitronix phantom	CT images
This study	Loose and stranded seeds	Machine learning	Agar-agar phantom	Manual localization
T IIIS Study	positions + orientations in 3D images	methods	Clinical	of the US images

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	1
tranded_seeds_compositions	

tab_Statistics

Table 2: Compositions of stranded seeds released by the needles in the phantom.

Needle	Released stranded seeds composition
N1	Seed + Spacer + Seed
N2	$2 \ge 2 \ge 1 \le 1$
N3	$Seed + 2 \ge Spacer + Seed$
N4	$2 \ge (\text{Seed} + \text{Spacer}) + \text{Seed}$
N5	3 x Seed
N6	$2 \ge 2 \ge$
N7	$2 \ge 2 \ge$
N8	Seed

Table 3: Statistics of localization error on 3D US images of two patients and error of estimated orientations of seeds composing the strands Si; $i \in [1;4]$.

Error of estimated Localization Stranded seeds orientation in degree error in mm composition mean \pm std [min;max] mean \pm std [min;max] Seed + Spacer +S1 12.5 ± 17.03 [1;37]3x Seed 2x Seed S2 $0.5\,\pm\,0.7$ [0;1]Patient 1 Seed + 1.52 ± 0.64 [0.91; 2.64]S3 1.5 ± 2.12 [0;3]2x Spacer+Seed 2x Seed+ S4 4.33 ± 1.52 [3;6]3x Spacer+Seed S1Seed 2 ± 0 [2;2]2x Seed+ S2 1.33 ± 1.52 [0;3]Patient 2 3x Spacer+Seed 1.36 ± 0.22 [1.2;1.82]Seed+ S3 1.5 ± 0.7 [1;2]2x Spacer + Seed

	EM Initialization					SVM		ICP	
	$\mu_{X_{TG}}$	μ_{X_B}	$\sigma_{X_{TG}}$	σ_{X_B}	$\pi_{X_{TG}}$	π_{X_B}	C	tol	threshold ϵ_{ICP}
Phantom image	235	100	3	40	0.05	0.95	0.15	10 e-3	0.01 mm
Clinical images	255	80	8	40	0.2	0.8	0.15	10 e-3	0.01 mm

tab:parameters

⁵⁹⁶ VII. Figures



fig:workflow

 $\ensuremath{\operatorname{Figure}}\xspace$ 1: Workflow for oriented seeds localization.



Figure 2: Detection of needles (green curves) in clinical images using needle detection method $\frac{10}{10}$.

ig:needles lolalized



Figure 3: Needle tip localization example. Successful automatic localization despite a shadow region [3mm-15mm] where the needle's voxels intensities decrease significantly. The blue line corresponds to the first pixel of the needle shaft belonging to the background class (Bayes rule of inequality 2). The end of the needle initially detected is presented by the broken line passing through the red star.

fig:tip



Figure 4: Reference frames and rigid transforms used by the method: global image, ROI, strand and seed references frames - positions of the strand and the individual seeds are encoded using respectively T_{Strand} and T_{Seed} .

fig:References



Figure 5: Sagittal sections of 3D clinical images containing stranded seeds. (a) manual segmentation based on planning information (seeds in red and spacer in green) added to the original image, (b) image after binarization with Bayesian classifier, (c) image after false positive removal with SVM classification.

fig:firstTwoSteps







Figure 7: Two stranded seeds S1,S2 (left) with their model (right). Red cylinders represent radioactive seeds and green ones are for spacers and linkers.

fig:StrandedSeeds



Figure 8: Artifacts in the 3 planes containing the seed in V_m of phantom image. (a) axial plane, (b) sagittal plane, (c) transversal plane. The seed visualized in (d) is perpendicular to the axial plane.



fig:phantom-seed Figure 9: 3D US phantom image showing a needle during releasing stranded seeds.

fig:VS



 $\rm Figure~10:~Experiments$ on Agar-agar phantom contained in a plastic box using the ultrasound probe of the $\rm TRINITY^{(R)}$ (Koelis, Meylan, France) assistance workstation.

nity_workstation



Figure 11: Seed localization result compared with manual identification ground truth at two different viewpoints. The red cylinders correspond to automatic seeds localization and the green cylinders to the ground truth. Names of the strands (cf table 2) are next to them.

fig:resultUSPhantom



Figure 12: Boxplots presenting the distributions of the seeds localization errors in phantom images at the different stages of the method. The boxplots visualize the minimum and maximum scores (blue lower and upper dashes), the first and third quartiles (blue boxes) and median (red dash).

fig:boxplotPhantom

VII.. FIGURES



Figure 13: Estimation of the orientations of two seeds with different volumes dimensions. {Red,Blue} points are respectively the {applied,estimated} angles.

fig:orientations



Figure 14: Boxplots presenting the distributions of the seeds localization errors in clinical images at the different stages of the method.