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Uncertainty Visualization: Recent Developments and Future Challenges in Prostate Cancer Radiotherapy Planning

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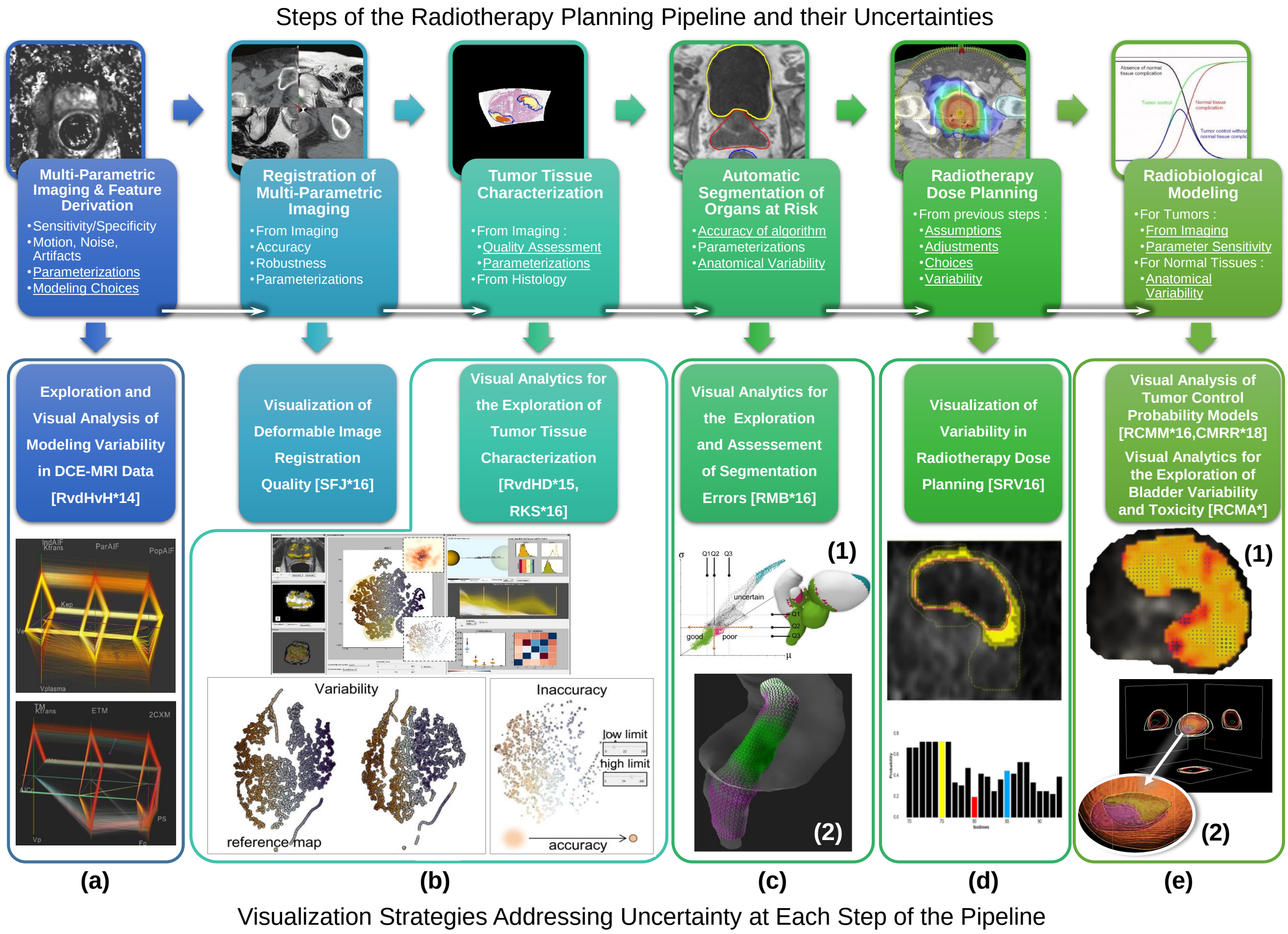

Figure 1: *Schematic depiction of the uncertainty sources at each step of the radiotherapy pipeline, with the visualization strategies designed to address them and to communicate them to the intended clinical users. Underlined text indicates uncertainties tackled in previous work.*

Abstract

Radiotherapy is one of the most common treatment strategy for prostate cancer. Prior to radiotherapy, a complex process consisting of several steps is employed to create an optimal treatment plan. However, all these steps include several sources of uncertainty, which can be detrimental for the successful outcome of the treatment. In this work, we present a number of strategies from the field of Visual Analytics that have been recently designed and implemented, for the visualization of data, processes and uncertainties at each step of the planning pipeline. We additionally document our opinion on topics that have not been yet addressed, and could be interesting directions for future work.

Categories and Subject Descriptors (according to ACM CCS): I.3.8 [Computer Graphics]: Applications—Applications; J.3 [Computer Applications]: Life and Medical Sciences—Life and Medical Sciences

1. Introduction

Radiotherapy is one of the most common treatment approaches for prostate cancer treatment. The basic concept of radiotherapy is that tumors should be irradiated with high ionizing radiation doses, while the surrounding healthy tissues should be preserved [Was15]. In the past decade, radiotherapy technology has managed to offer exceptional flexibility in dose delivery and to minimize the side effects of radiation on the adjacent healthy organs [TOG06]. However, prostate cancer radiotherapy sometimes still results in a number of toxicity-related side effects, especially for the bladder and rectum. With respect to tumor treatment, there is also room for improvement. To this end, a *standardized pipeline* including all available patient- and tumor-specific information has been recently proposed by Raidou et al. [RBV17]. This pipeline is shown in Figure 1.

All steps of the radiotherapy planning pipeline involve several sources of uncertainty. Although some of these uncertainties can be minimized, others cannot be eliminated, and analysis and communication to clinical users is essential. The accumulation and propagation of uncertainties, throughout the entire pipeline, may have an influence on the dose planning, and the final outcome of the planning procedure. In this paper, we analyze different sources of uncertainty from disctinct steps of the pipeline, we provide an overview on conducted work related to each step and we sketch some ideas about challenging – yet, unaddressed – topics for future work.

2. Uncertainty in the Radiotherapy Planning Pipeline

In the pipeline depicted in Figure 1, imaging data of the prostate of the patient are initially acquired, using several modalities. From these, additional features indicative of tissue characteristics may be computed. After registration, tumor tissue characterization takes place to enable the identification of intra-tumor regions, where specific characteristics of each region, such as aggressiveness or resistance to treatment, are derived. The structures surrounding the prostate, which need to be spared during treatment, must be identified as well. This is done during segmentation. Based on all tumor tissue and anatomical information, radiation plans are adequately performed to more effectively treat tumors, without inducing harm to the adjacent healthy organs. After the radiotherapy plan is designed, the eventual response of the tumor to the employed radiotherapy treatment strategy is modeled. From radiobiological modeling, clinical researchers can predict the outcome of the treatment.

An important aspect in the radiotherapy planning pipeline is the uncertainty, which is present at all steps. In literature, there is no unanimous opinion on the definition of uncertainty. According to Griethe et al. [GS06], uncertainty can be defined as *error* – outlier or deviation from a true value, *imprecision* – resolution of a value compared to the needed resolution, *subjectivity* – degree of subjective influence in the data, and *non-specificity* – lack of distinction for objects. In our case, we define uncertainty as *any variation in the dose planning outcome*, which is produced by *an ad-hoc choice or a stochastic process*, at any step of the radiotherapy pipeline.

Although the importance of raising awareness on uncertainty information and its influence on the data has been stressed multiple times, it is still overlooked with serious implications [BWE06, LPSW96]. For example, in radiotherapy treatment planning, the precision and accuracy of the steps of the pipeline can have severe consequences on the treatment outcome. Despite its importance in clinical practice, uncertainty visualization in radiotherapy planning is not a commonly researched topic.

3. Recent Developments in Uncertainty Visualization for Prostate Radiotherapy Planning

Uncertainty visualization is a challenging and popular field [BPK*14, JS03]. Often, uncertainty comes as an additional channel of information, which needs to be visualized on top of other underlying data – increasing the complexity of the view, and decreasing the understanding of implicated information. When approaching an uncertainty visualization problem, the choice of design methods depends on the nature of the uncertainty data, on the uncertainty data type and on the already employed visualizations for the underlying data [GS06]. Uncertainty visualization design is often not easy, as uncertainty tends to dominate over certainty in the data [BOL12]. This results into visualizations where the underlying data are distorted or obscured, while uncertainty is emphasized. Some of the most common design approaches for the visualization of uncertainty are summarized in overview papers [BOL12, BHJ*14, PWL97, RPHL14]. However, a review on uncertainty visualization is out of the scope of this work and we focus only on topics related to radiotherapy. In this section, we provide an overview of uncertainty sources at each step of the pipeline and strategies to address them.

Multi-Parametric Imaging and Feature Derivation — The purpose of the first part of the pipeline is to obtain images needed for radiotherapy planning, from a multitude of medical imaging sequences [HCE*07]. Imaging modalities employed in prostate cancer research include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Diffusion-Weighted Imaging (DWI), Dynamic-Contrast Enhanced MR Imaging (DCE-MRI) and, optionally, MR Spectroscopy (MRS). All these imaging acquisitions are accompanied by uncertainty – mainly due to resolution, distortion at interfaces between tissues, noise, or artifacts inherent in each scanning procedure. Motion artifacts, such as patient motion during acquisition, involuntary rectal motion or due to bladder filling, are also significant. Additionally, these modalities differ in sensitivity and specificity for tumor detection and characterization. For example, MRI has high sensitivity and poor specificity for tumor identification. Parameterizations or modeling choices are also noteworthy sources of uncertainty. Of particular interest is the selection of pharmacokinetic models for the derivation of features, indicative of tissue characteristics, from DCE-MRI data. Different modeling approaches exist, the selection of which results into repeatability and reproducibility problems.

From the aforementioned sources of uncertainty, the ones related to specificity and sensitivity are often minimized by combining the different imaging modalities [BRC*12, HCE*07]. The others – related to parameterizations and modeling selection – cannot be avoided, and their impact needs to be analyzed and explored. In the present case, we focus on the uncertainty emerging during the derivation of features from DCE-MRI data. For clinical researchers working on pharmacokinetic modeling, it is valuable to investigate how the derived tissue parameters behave with different modeling choices. A visualization application for the interactive exploration and analysis of model-induced variability in pharmacokinetic modeling parameters was proposed [RvdHvH*14]. It offers a single combined exploratory view on different parameters from different modeling alternatives. An example of the use of the tool is shown in Figure 1(a). A related approaches was proposed by Nguyen et al. [NBYR12].

Registration — In the presented radiotherapy planning pipeline, all previously mentioned modalities need to be registered to ensure that they are in the same coordinate system. Potentially available histopathological data also need to be registered. Registration may be accompanied by uncertainty, which may have a strong impact on the remainder of the radiotherapy planning pipeline. Uncertainty in image registration is primarily related to the inherent characteristics of the different imaging modalities that are co-registered. In addition to this, different registration algorithms may bring different types of uncertainty, related to localization accuracy or robustness. In other cases, the lack of objective ground truth in the validation of registration creates the need for manual registrations by experts, which introduces uncertainty from inter-observer variability.

To the best of our knowledge, very few attemps have been made in the past to visualize uncertainty in registration. The most recent work was proposed by Schlachter et al. [SFJ*16], with a framework for the exploration and assessment of deformable image registration. The approach offers several interactive visualizations for the exploration of candidate regions, with the goal of simplifying the local visual assessment of co-registered images. Other approaches were proposed by Smit et al. [SHS*14].

Tumor Tissue Characterization — Tumors are heterogeneous tissues, enclosing multiple regions with distinct characteristics. Incorporating patient-specific intra-tumor tissue information into radiotherapy planning can lead more effective treatment, where distinct intra-tumor tissues are irradiated with adequately selected radiation doses [TOG06]. To perform a non-invasive in-vivo identification and exploration of intra-tumor tissues, clinical researchers need to associate histopathological findings, with features derived from co-registered imaging data, such as DCE-MRI, or DWI data. Uncertainty at this step of the pipeline involves all uncertainties that are being propagated from the imaging or registration step of the pipeline. Uncertainties in the histopathological data are significant, but they can be minimized by, for example, having different observers characterizing the tumor regions.

For the exploration and analysis of the characteristics of distinct intra-tumor regions, a user-guided exploratory tool [RvdHD*15, RKS*16] has been proposed. In this approach, a 2D t-SNE embedding [MH08] of the imaging-derived features is used to reveal potential intra-tumor regions with consistent high-dimensional characteristics. Additional multiple linked interactive views provide functionality for the user-driven exploration and analysis of the local structure of the tumor tissue feature space, enabling linking to patient anatomy and clinical reference data. A user-in-the-loop approach is followed to incorporate the knowledge of expert users. The incorporation of uncertainty into the proposed approach is done in two ways. The quality assessment of the employed images can be incorporated into the t-SNE embedding, as an additional encoding of quality metrics, such as the Goodness of Fit (GoF) or Akaike Criterion (AIC). The parameterizations or modeling choices produce one t-SNE embedding each, which can be easily compared side-by-side, given a finite number of choices. An example of the tool is shown in Figure 1(b).

Segmentation — The segmentation step of the radiotherapy planning pipeline aims at constructing models of the prostate and the organs at risk, such as the rectum and the bladder [EPW*11,BSS*12]. The results of this step are highly dependent on the selected segmentation method and its eventual parameter settings. Segmentation can be either performed manually, semi-automatically, or automatically. Manual segmentation by experts is time consuming, but it can also create inter-observer variability, posing critical questions concerning reproducibility and accuracy. Therefore, automatic methods are preferred. Still, these methods might not be able to account for all cases and may perform sub-optimally. In such cases, it is required to predict anatomic regions and circumstances under which, they are more prone to inaccuracies. The main source of uncertainty in segmentation relates to the characteristics of the selected algorithm, its eventual parameterizations and also its applicability to the different structures that need to be segmented. A second source relates to the fact that pelvic organs are flexible, soft tissue structures with large variability in shape, size and imaging intensity, where organ motion is also common.

We focus on these two sources of uncertainty in two distinct approaches. For the first one, a visual analytics approach for the prediction of the performance of a statistical shape modeling segmentation algorithm, helping algorithm developers to understand their results was introduced [RMB*16]. This approach supports the exploration and assessment of errors of pelvic organ segmentations starting from a cohort of patients. Also, it enables drilling down to individual subjects, for a more personalized exploration and assessment of segmentation errors. An example of the use of this web-based tool is shown in Figure 1(c.1). The second source is addressed with a web-based framework, which enables easy exploration and detailed analysis of shape variability, facilitating segmentation experts to generate hypotheses in relation to the performance of their algorithms, within a cohort of patients [RBGR18]. This approach allows developers of the algorithms to quickly identify inaccurately segmented organs, and to deliberate about the relation of shape variability to anatomical features and segmentation quality. This framework is depicted in Figure 1(c.2). Related approaches include the work of Saad et al. [SMH10], Torsney et al. [TWSM*11] and Smit et al. [SLK*17].

Radiotherapy Dose Planning — After segmentation, a simulation of the treatment planning is performed in dedicated software. Our focus at this step of the pipeline is not on the actual dose planning procedure, but on the incorporation of variability in planning, which can be induced as a result of assumptions, adjustments, or choices in the previous steps of the pipeline.

It is valuable for clinical researchers to understand and evaluate the sensitivity of the treatment plan to the previous steps of the pipeline. In that way, they can assess whether different choices in the planning pipeline have an impact on the final treatment planning and be aware of this, when designing their treatment plans. A visualization design to address the exploration and analysis of variability in an ensemble of radiotherapy dose plans was introduced [SRV16]. First, an analysis based on the radiotherapy dose iso-contours across different dose plans resulting from different assumptions is performed. Secondly, the analysis is also conducted directly at a voxel level, for obtaining more granular details. An example of the use of the tool is shown in Figure 1(d), for the exploration of the variability of the produced dose planning iso-contours.

Radiobiological Modeling — Clinical practice aims at choosing the most effective radiotherapy strategy, based on clinical knowledge and guidelines. However, clinical research aims at thoroughly evaluating all possible treatment alternatives. For this purpose, radiobiological modeling is used. This involves two aspects: Tumor Control Probability (TCP) modeling and Normal Tissue Complication Probability (NTCP) modeling. TCP models are statistical models that quantify the probability that a tumor is effectively treated, given a radiation dose. NTCP models are statistical models that quantify the probability that normal tissue around the tumor is harmed, given a radiation dose. Different sources of uncertainty are present in both models.

Conventional TCP models are linear regression models, based only on statistical knowledge. Recently, novel TCP models started incorporating additional information from imaging modalities, such as DWI [CMvdHR*16]. In this way, patient-specific properties of tumor tissues are included, improving the radiobiological accuracy of TCP modeling. As a consequence, the uncertainties of the modalities are propagated into the TCP models. In addition to this, the modeling step includes parameter assumptions, which are not always crisp choices. Parameter sensitivity analysis of the model is important when predicting the outcome of a specific radiotherapy strategy. This is addressed with a new visual analytics system [RCMM*16] for the exploration and analysis of TCP modeling. With this approach, the – so far – disregarded imaging-induced uncertainty and parameter sensitivity analysis can be incorporated in the workflow of clinical researchers, providing new possibilities for the evaluation of the selected radiotherapy strategies, even in large cohorts of patients [CMRR*18]. A new way of exploration, which enables clinical researchers to start their analysis from the desired outcome and to determine whether there are feasible radiotherapy strategies to achieve it, is also made possible. An example of this tool is shown in Figure 1(e.1).

NTCP modeling involves many aspects. One of it takes into account the natural shape variation of the organs of patients, to predict whether toxicity was induced to the tissue. This is addressed with a novel tool to enable detailed visual exploration and analysis of the impact of bladder shape variation on the accuracy of dose delivery [RCMA*18]. The tool enables the investigation of individual patients and cohorts through the entire treatment process, and it can give indications of RT-induced complications for the patient. Individual patients can be explored and analyzed through the entire treatment period, while inter-patient and temporal exploration, analysis and comparison are also supported. This approach is depicted in Figure 1(e.2).

4. Future Challenges in Uncertainty Visualization for Prostate Radiotherapy Planning

We described a number of approaches that have been recently proposed to address some of the uncertainties at different steps of the radiotherapy pipeline. However, as briefly mentioned in each of the previous subsections, every step of the pipeline involves an innumerable amount of uncertainties. Not all of them have been addressed and, most probably, not all of them can be addressed. Although extensive studies are being conducted with respect to the errors or inaccuracies of the imaging acquisition step, as long as the acquisition procedures are not being *standardized*, uncertainty due to imaging will remain a problem for the entire pipeline.

Through the course of this work, we learnt several lessons, which open new challenges and directions for future work. One of the most important parts of uncertainty in radiotherapy, as well as in every application that involves a pipeline, is related to the *propagation* of uncertainty and its *accumulation* through the different steps. For example, it is important to know how uncertainty propagates from the imaging to the next steps of registration, segmentation and to the final outcome of the pipeline. In the discussed approaches, propagation was only partially addressed.

An additional gain both for users and for visualization experts is that the communication of uncertainty allows the user to *gain confidence* when employing various visualization frameworks. For example, when exploring the uncertainty at a step of the pipeline, it is important to be able to answer "*how sure I am about this result?*", "*how was this uncertainty created?*", "*which previous steps are mainly responsible for this uncertainty?*", and "*if something changes in the previous steps, how much is the uncertainty affected?*". However, answering all these questions requires adequate integration and linking of all pipeline components.

Other challenges for the future should also consider uncertainties that may occur during the actual *delivery* of the treatment. This is necessary, in order to provide a complete overview of the potential inaccuracies in the final dose plan and their potential impact on the treatment and prognosis. At this point, additional non-imaging patient-specific characteristics of the patients (health record data) should also be incorporated in the analysis.

Another point that has not been taken into account is the uncertainty brought into the workflow by the use of the previously introduced *visual analytics* strategies. Visual analytics is known to combine the strengths of automated algorithms with the knowledge and the cognitive abilities of human experts. In most of the previously discussed cases, the focus was on communicating uncertainty due to the employed methods. However, the user of the designed visualizations is responsible for guiding the exploratory and analytical process, for discovering new knowledge in the data, for generating or confirming hypotheses. Therefore, at this point, we may wonder how reproducible and how accurate are the user's results and how we can account for inter-observer variability.

5. Conclusions

In this work, we presented a number of strategies from the field of Visual Analytics that have been designed and implemented recently for the visualization of the data and uncertainty involved at each step of the radiotherapy planning pipeline. We also documented our own experience working in the field, regarding topics that could evolve into interesting future directions.

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