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Quantification and modelling of the geometric and dosimetric uncertainties due to deformable image registration for dose accumulation in proton therapy

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Introduction: Deformable Image Registration (DIR) plays an important role for adaptive proton therapy treatment. Previous works indicated the discrepancies in the accumulated dose for Pencil Beam Scanned (PBS) proton therapy when different DIR algorithms were applied [1,2], due to the presence of geometric uncertainties of the resulting Deformation Vector Fields (DVF). Moreover, the AAPM TG132 report also suggested to quantify the geometric and dosimetric uncertainties of DIRs before radiotherapy application [3]. However, most of the currently available DIR methods do not provide such accuracy measures.

Aims: To propose a workflow able to estimate geometric and dosimetric uncertainties associated with the application of DIR algorithms for adaptive PBS proton therapy.

Methods: The proposed method, as well as its validation, is shown in Figure (a). This study includes seven non-small-cell lung carcinoma (NSCLC) patients, each with a planning (reference) CT and multiple repeated CTs. The 'ground-truth' (GT) dosimetric uncertainties are derived in the first step (shown in the top branch), where the initial plan is recalculated on each fraction CT. The resulting dose distribution is warped back to the reference CT using 5 different DIRs individually (Plastimatch-Bspline, Plastimatch-Demon, Mirada, Raystation-Anaconda, Velocity). From this, the voxel-wise maximum-minimum dose difference (DD) is calculated as the GT dosimetric uncertainty. Moreover, the GT DVF uncertainty is quantified by the voxel-wise difference between the largest and smallest vector. As shown the bottom branch in Figure (a) and more detailed in Figure (b), a patient specific linear uncertainty model is derived by correlating the DVF vector lengths of a reference DIR (e.g. Plastimatch-Bspline) with the GT DVF uncertainty of the first fraction. For successive fractions, only the reference DIR is applied and the uncertainty in DVF is predicted from this model. Consequently, the estimated dosimetric uncertainty (B) can be obtained by multiplying the predicted DVF uncertainty distribution with corresponding fraction dose gradient. This estimation is compared to the GT dose uncertainty (DD), as well as to the estimated dosimetric uncertainty considering the GT DVF uncertainty (A).

Results: Predicted and GT dose uncertainties differ in average 2.3±6.0% over all seven patients (each with six CTs and six structures). Expanding to all non-zero dose voxels inside the body, the dosimetric uncertainty remains within 2.5±8.0% of the GT.

Conclusions: We propose a model based uncertainty prediction framework for quantitatively considering DIR induced dosimetric uncertainties in adaptive proton therapy. The predicted dose uncertainties are within 3% of the ground truth. The proposed workflow is applicable for other applications of DIRs in radiotherapy, such as 4D dose calculations and dose accumulation of combined treatments.

Acknowledgements: This project is funded by Krebsliga Schweiz.

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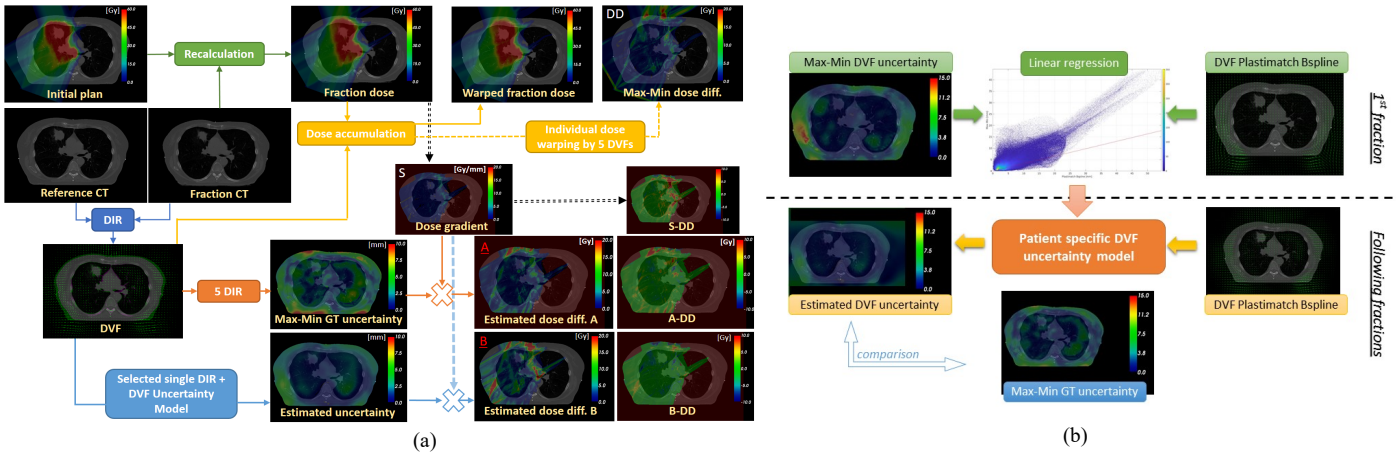

Figures: (a) Proposed workflow, and (b) scheme of the modelling part.

2 **Automated registration of single 2D histological brain slices with 3D digital atlas in rodents**

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Introduction: Histology is the gold standard to study the spatial distribution of biomarkers of interest, especially within brain. Interpretation of brain-related data requires precise information about the anatomical location of those biomarkers. Therefore, registering histological data on digital atlases becomes a necessity for automated quantification. However, it is a tedious, if not impossible task to perform manually. Depending on the context, the number of used sections can dramatically change: a large number of sections that allows the 3D volume reconstruction, several slices to target a specific region, some slices among the brain, or even a single slice. Although 3D-3D registration methods are performing well when volume reconstruction is possible [1], mapping a single 2D slice to a 3D atlas remains challenging. Recently, a paper proposed a user-friendly interface to manually perform a 2D-2D linear registration [2]; another used histogram of oriented gradient norm to automatically register a group of about thirty slices to a corresponding template [3]. Even if some efforts are done to make the corresponding registration task easier, no automated method has addressed this issue yet.

Aims: We propose a robust method to automatically identify, within a 3D atlas, the most similar slice corresponding to a single individual slice.

Methods: We investigated an exhaustive and exploratory approach, based on linear 2D-2D co-registrations. Clarified mouse brains, digitized in 3D by a light sheet scanner [4] can be considered as multiple 2D sections to be mapped to a template. This gave us the opportunity to explore any incidence and to explore any possible mapping. We chose the mouse Allen Brain Atlas [5], more specifically its associated anatomical template, as the reference for registration with the autofluorescence channel from clarified virtual 2D sections. 2D slice-to-slice rigid registration was performed between each slice of each volume, based on BlockMatching techniques. Normalized Mutual Information (NMI) [6] was used as a similarity metric for each slice-to-slice comparison, generating an exploratory cartography. Calculations were distributed through Soma-workflow library of BrainVISA software [7] on specific multiple processing infrastructures for high-performance computing. An expert carried out slice-to-slice pairing between the two volumes, considered as a succession of independent 2D slices, in order to evaluate the section distance error.

Results: The NMI generated cartography included 180.000 co-registrations computed in parallel on 4.224 microprocessors, and represented over 75.000 hours of computation. This cartography demonstrated coherent results confirming that rigid registration is determinant to identify the considered slice location in the 3D template.

Conclusions: Cartography-related information allowed us to identify a way to quickly find a robust linear transformation of the corresponding atlas-based section for single histological section studies. Ongoing work consists in producing the same cartography with affine co-registration, and taking into account possible oblique incidence of the histological section to quantify and integrate registration error in our framework.

Acknowledgements: This work was granted access to the HPC resources of TGCC under the allocation 2019-(A0040310374) made by the GENCI.

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3 Deep learning based automatic 3D MR-US image registration for the spine

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Introduction: Ultrasound (US) imaging provides several advantages compared to other modalities such as real time volumetric imaging, cost-effectiveness and non-invasiveness. Currently, US image interpretation still requires skilled operators most of the times, making it unsuitable for applications such as real time guidance in surgery. For this reason, automatic registration algorithms between US and MRI, especially in 3D, are clinically not available and there are only few examples reported in literature [1][2][3]. Recently, a convolutional neural network (Voxelmorph) has been introduced for 3D MR volumes (mono-modality) automatic fusion. In our proof of concept work, we extended this approach to multi modal applications, between 3D US and MRI volumes of a spine phantom.

Aims: Automatic volumetric image registration between US and MRI modalities of the same region of interest (thoracic spine region) in a phantom.

Methods: 3D MR and US volumes of a spine phantom were acquired in the same configuration and conditions using a Siemens Magnetom Prisma 3T and a Philips VL 13-5 3D US transducer with a Philips EPIQ 7 system. The phantom consisted of a collection of thoracic vertebrae (T1-T12) aligned along a physiological curvature using a deformable support and positioned in a plastic container filled with water (to allow MRI scanning and to minimize US acoustic coupling errors). One MRI scan was performed of the whole spine, while several US scans were performed due to the limited field of view of this modality. In the registration process, the MRI volume was used as the 'atlas' or fixed image, and 40 US volumes were used as the 'moving' images. Since the bony structures in the spine are not deformable, only rigid rotation translation has been investigated. Voxelmorph is an unsupervised algorithm which matches image pairs through a deformation field parametrized through a convolutional neural network. The model is trained by optimizing a loss function using only the training set of image pairs and the deformation field generated by the algorithm, penalizing spatial and appearance differences between the image pairs. Manual registrations will be performed for the image pairs in the test set by an experienced sonographer to validate the algorithm results. The norm of the difference vectors of the translation and rotation values obtained by the algorithm and the expert will be used to quantify the algorithm performance compared to an expert.

Results: Figure 1 shows a possible outcome from the registration using the trained model on the spine phantom (T8 vertebra).The expected norm of the difference vectors of the translations and rotation values generated by the automated approach and the expert registration are expected to be within the clinical standard of 5mm and around 5 degrees, respectively.

Conclusions: The expected registration accuracy values is promising for possible future translation into clinical applications, for example for real time volumetric guidance for spine surgery. Further development including the introduction of increasingly more complex anatomical features to mimic realistic scenarios is necessary and it will possibly require the use of a deformable registration approach.

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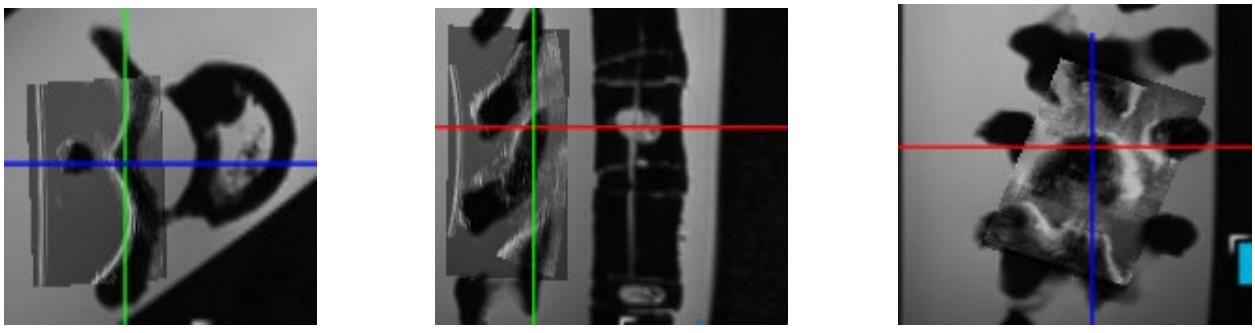

(a) (b) (c)

Figure 1: Registered MR-US spine phantom (T8 vertebra) volumes along the transverse (a), sagittal (b), and coronal (c) planes.

4 Web-based Registration Tools Based on ITKElastix

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Introduction: Registration is frequently needed for many image analysis purposes. Not all the researchers who need it are equipped with proper software tools. And when they are, maintenance of those tools is a burden they would like to avoid.

Aims: Web-browser based application for 3D image registration.

Methods: We leveraged existing open source tools as much as possible and provided an easy-to-use graphical user interface delivered through a zero-install web page or single-file native executable. We rely primarily on Elastix and ITKWidgets for registration and visualization and Voila for application delivery. Elastix [1] is a toolbox for rigid and nonrigid registration of images. ITKWidgets [2] are interactive Jupyter widgets to visualize images, point sets, and meshes in 2D and 3D. Both Elastix and ITKWidgets are based on the Insight Toolkit [3], an open-source, cross-platform toolkit for N-dimensional scientific image processing, segmentation, and registration. All these tools are tied together in a Jupyter notebook, which has browser-based interface and can be served over the Internet. While the raw notebook provides a hackable interface that registration researchers can customize, Voila [4] packages the web application.

Results: The application is simple and effective since all components are focused on the registration task. Buttons enable selection of a fixed and moving image file. Interactive, 3D visualization is possible on the images prior to registration and after the moving image has been registered and resampled to understand the inputs and registration effectiveness. Registration parameters, such as the type of registration, i.e. rigid, affine, or b-spline, can be selected graphically.

Conclusions: This tool makes registration easier to use for a broad range of researchers and clinicians. New registration methods available in Python can be delivered to end users similarly to increase the impact of registration research on the practice of scientific image analysis.

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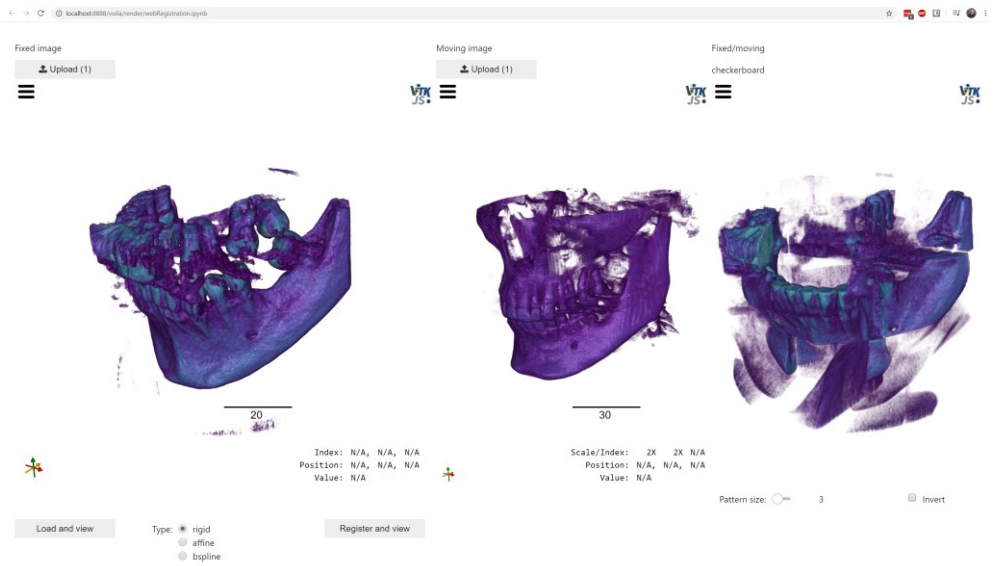

Figure A screenshot of the web application after loading images.