# Deep learning for online adaptive radiotherapy

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# Summary and Future Work

Adapting a radiotherapy treatment plan to the daily anatomy is a crucial task to ensure adequate irradiation of the target without unnecessary exposure of healthy tissue. This adaptation can be performed by automatically generating contours of the daily anatomy together with fast re-optimization of the treatment plan. These measures can compensate for the daily variation and ensure the delivery of the prescribed dose distribution at small margins and high robustness settings. In this thesis, we focused on developing a deep learning-based methodology for automatic contouring for real-time adaptive radiotherapy either guided by CT or MR imaging modalities. In this chapter, we summarize the previous chapters, discuss overall results found in this thesis, and give potential directions of future research.

## 7.1 Summary

In the first chapter, we introduced adaptive radiotherapy and gave background about automatic contouring methods as well as MR image reconstruction. In Chapter 2, we proposed a contour propagation pipeline that is a hybrid between iterative-based registration and deep learning-based segmentation. The pipeline was trained and evaluated using three datasets and performed better than only using iterative-based methods. In Chapter 3, we proposed an adaptive training mechanism for personalized automatic contour segmentation. This adaptation showed potential for improving the prediction of the daily anatomy based on personalized imaging accumulated over fractions. In Chapter 4, We proposed a 3D adversarial network for joint image registration and segmentation. This work showed that that a discriminator can learn a measure of image alignment to improve registration. In Chapter 5, we further studied joining registration and segmentation in a multi-task learning setting. We showed that training these tasks jointly can substantially improve the network outcome. All the networks in the previous chapters were trained and tested on CT images for adaptive

CT-guided radiotherapy, however this can be generalized for MR-guided radiotherapy by retraining these networks. The remaining problem would be developing a fast MR reconstruction algorithm, which we proposed in Chapter 6.

**Chapter 2** In this chapter, we developed and validated a robust registration pipeline for automatic contour propagation for online adaptive IMPT of prostate cancer using elastix software and deep learning. A 3D CNN network was trained for automatic bladder segmentation of the CT scans. The automatic bladder segmentation alongside the CT scan are jointly optimized to add explicit knowledge about the underlying anatomy to the registration algorithm. We included three datasets. The first was used for training and testing the ConvNet, where the second and the third were used for the evaluation of the proposed pipeline. The propagated contours were validated clinically as well. The segmentation network achieved a DSC of 88% and 82% on the test datasets. The proposed pipeline achieved a MSD of $1.29 \pm 0.39$, $1.48 \pm 1.16$, and $1.49 \pm 0.44$ mm for the prostate, seminal vesicles, and lymph nodes, respectively on the second dataset and a MSD of $2.31 \pm 1.92$ and $1.76 \pm 1.39$ mm for the prostate and seminal vesicles on the third dataset. The automatically propagated contours met the dose coverage constraints in 86%, 91%, and 99% of the cases for the prostate, seminal vesicles, and lymph nodes, respectively. A Conservative Success Rate (CSR) of 80% was obtained, compared to 65% when only using intensity-based registration. With 80% of the automatically generated treatment plans directly usable without manual correction, a substantial improvement in system robustness was reached compared to a previous approach. The proposed method therefore facilitates more precise proton therapy of prostate cancer, potentially leading to fewer treatment related adverse side effects.

**Chapter 3** In this chapter, we leveraged personalized anatomical knowledge accumulated over the treatment sessions, to improve the segmentation accuracy of a pre-trained CNN network, for a specific patient. We investigated a transfer learning approach, where we fine-tuned the baseline CNN model to a specific patient, based on imaging acquired in earlier treatment fractions. The baseline CNN model is trained on a prostate CT dataset from one hospital of 379 patients. This model is then fine-tuned and tested on an independent dataset of another hospital of 18 patients, each having 7 to 10 daily CT scans. For the prostate, seminal vesicles, bladder and rectum, the model fine-tuned on each specific patient achieved a Mean Surface Distance (MSD) of $1.64 \pm 0.43$ mm, $2.38 \pm 2.76$ mm, $2.30 \pm 0.96$ mm, and $1.24 \pm 0.89$ mm, respectively, which was significantly better than the baseline model. The proposed personalized model adaptation is therefore very promising for clinical implementation in the context of adaptive radiotherapy of prostate cancer.

**Chapter 4** proposed to combine the registration and segmentation tasks in a deep learning setting using adversarial learning. We considered the case in which fixed and moving images as well as their segmentations are available for training, while segmentations are not available during testing; a common scenario in radiotherapy. The proposed framework consists of a 3D end-to-end generator network that estimates the deformation vector field (DVF) between fixed and moving images in an unsupervised fashion and applies this DVF to the moving image and its segmentation. A discriminator network is trained to evaluate how well the moving image and segmentation align with the fixed image and segmentation. The proposed network was trained and evaluated on follow-up prostate CT scans for image-guided radiotherapy, where the planning CT contours are propagated to the daily CT images using the estimated DVF. The proposed GAN network achieved a MSD of $1.13 \pm 0.4$ mm, $1.81 \pm 1.6$ mm, $1.00 \pm 0.3$ mm, $2.21 \pm 1.3$ mm, and $2.29 \pm 2.0$ mm, respectively, which was significantly better than the deep learning baseline model as well as the conventional algorithm. The inference time of the proposed model is 0.6 sec., thus enabling real-time contour propagation necessary for online-adaptive radiotherapy.

In **Chapter 5**, we formulated registration and segmentation jointly via a deep learning-based Multi-Task Learning setting, allowing these tasks to leverage their strengths and mitigate their weaknesses through the sharing of beneficial information. We propose to merge these tasks not only on the loss level, but on the architectural level as well. The study involves two datasets from different manufacturers and institutes. We carried out an extensive quantitative comparison between the quality of the automatically generated contours from different network architectures as well as loss weighting methods. Moreover, we evaluated the quality of the generated deformation vector field (DVF). We show that MTL algorithms outperform their Single-Task Learning (STL) counterparts and achieve better generalization on the independent test set. The best algorithm achieved a mean surface distance of $1.06 \pm 0.3$ mm, $1.27 \pm 0.4$ mm, $0.91 \pm 0.4$ mm, and $1.76 \pm 0.8$ mm on the validation set for the prostate, seminal vesicles, bladder, and rectum, respectively. The high accuracy of the proposed method combined with the fast inference speed, makes it a promising method for automatic re-contouring of follow-up scans for online adaptive radiotherapy.

**Chapter 6** presented a fast MR reconstruction algorithm, which enables the application of the automatic contouring methods proposed in the previous chapters for online adaptive MR-guided radiotherapy. Starting from undersampled k-space data, an iterative learning-based reconstruction scheme inspired by compressed sensing theory is used to reconstruct the images. We developed a novel deep neural network to refine and correct prior reconstruction assumptions given the training data. The proposed network was ranked #1, shared #1, and #3 on respectively the 8x accelerated multi-coil, the 4x multi-coil, and the 4x single-coil tracks in the 2019 fastMRI competition organized by Facebook and New York University (NYU). The average runtimes for the model are 0.5 and 0.3 seconds for the multi-coil and the single-coil data, thus enabling fast reconstruction for MR guided adaptive radiotherapy. This superior performance in terms of reconstruction quality and time makes the model a good candidate for MR guided adaptive radiotherapy.

## 7.2 Discussion and future work

The aim of the work presented in this thesis was to develop and investigate various methods of automatic contouring for adaptive radiotherapy. Despite the fact that all experiments presented in this thesis were validated on prostate CT scans, all proposed methods are generic and can potentially be applied to MR images as well, thus enabling adaptive CT as well as MR guided radiotherapy. So far the remaining technical bottleneck for applying these methods on MRIgRT would be the fast reconstruction of the MR images, which we addressed in the last chapter of the thesis.

In Chapters 4 and 5, we showed that joining segmentation and registration tasks is very beneficial and clinically important, especially for applications where the output from both tasks is required such as for dose accumulation and dose planning. We concluded that the best mechanism to combine both tasks is by modeling these tasks using a cross-stitch network that shares internal parameters across the tasks. Using a cross-stitch network, we were able to achieve superior performance in the order of 1 mm for the mean surface distance of the target organs and OARs. However, on the independent test set, the deep joint method achieved a result in the order of 2 mm. Compared to the performance of the deep joint network in chapter 5, the hybrid method presented in Chapter 2 had a better generalization since it is a non-learnable method and registers image pairs in an iterative manner. However, the hybrid method running time is in the order of minutes while the joint method takes less than a second, which makes it a better candidate for online adaptive radiotherapy. The generalization of the deep joint method could be further improved, however, by deploying one of the following strategies. First, we could re-train the model and include patients similar to the test data distribution. This way one could adapt the general model to, for example, a specific hospital. Second, we could augment the existing training data with realistic deformations instead of random ones, since such random deformations did not show improvement in our earlier experiments. This realistic deformation can be drawn from a generative mechanical model such as the ones presented in [177, 178]. Using such realistic augmentation would help the network to learn various types and scales of deformations that might not be available in the original training dataset. At last, we can adopt a transfer learning strategy similar to the one proposed in Chapter 3, where we proposed to leverage personalized anatomical knowledge accumulated over the treatment sessions. In that chapter, we demonstrated that adapting the model to a specific patient anatomy can improve the performance of the network especially for the organs that do not deform much from the planning scan as shown in Figure 3.1.

For the organs that deform between sessions such as the rectum and the bladder, the performance of the adapted network did not improve significantly as shown in Table 3.2. This adaptation strategy is effective for any existing model, therefore it can be used to adapt or personalize a pre-shipped model on in-house data without the need to re-train the model from scratch. This would improve model performance over time at a minimal cost while maintaining data privacy. Moreover, by adjusting the transfer learning strategy it can be used for continuously improving model prediction after being corrected by clinical radiologists.

The networks developed in Chapters 2, 3, 4, and 5 focused primarily on automatic contour propagation for prostate CT. These networks, however, can be generalized to MR images for MRIgRT. Various CNN networks with a U-Net variant architecture have already been proposed in literature for MR prostate segmentation [179, 180, 181, 182] as well as other anatomies such as the brain [183, 184, 185] and the heart [186, 187]. Furthermore, similar networks were successfully adopted for MR registration at different anatomical sites [16, 117, 188]. The success of the aforementioned methods that use similar network architecture, makes it very promising our proposed deep joint networks to generalize to MR images of the prostate and potentially for other anatomical sites. In order to validate that hypothesis, we need to conduct a study that involves multiple datasets from different anatomical sites as well as imaging modalities.

For MRIgRT application, the acquisition and reconstruction time of the MR images themselves are still a bottleneck for online MRIgRT application. In Chapter 6, we addressed this problem, where we developed a fast reconstruction algorithm that works for both single-coil and multi-coil MR images. The output from the network was clinically acceptable based on the clinical evaluation performed by radiologists [159]. The outcome of this clinical evaluation makes it very promising and encouraging to be deployed in clinical trials after doing further clinical assessment on different anatomical sites.

In terms of the clinical readiness of the proposed deep joint registration and segmentation network, in Chapter 2 we performed an extensive dosimetric evaluation on the automatically generated contours from the hybrid method. We found that improving the quality of the generated contours in terms of MSD, resulted in a boost of the dosimetric measures in terms of $V_{95}$ and the Conservative Success Rate (CSR) compared to when only using intensity-based registration. Since the cross-stitch network achieved an even better geometric performance, we hypothesize that this improvement would also result in a boost in the corresponding dosimetric measures and we are currently validating this hypothesis.

A promising direction for future research for the joint network is the addition of a third task, potentially being radiotherapy dose plan estimation. Hence, we can generate contours that are consistent with an optimal dose planning. Further studies could also focus on sophisticated MTL network architectures like sluice networks [132] or routing networks [133]. Moreover, we can study how to fuse the contours from the segmentation and registration paths in a smarter way rather than simply selecting one of them based on the validation set. It also worth investigating semi-supervised training techniques [189] in order to improve the generalizability of the proposed networks. For the fast MR reconstruction network, as a future direction, it will be beneficial to better understand how much the network is relying on the priors by adopting interpretable AI techniques such as differentiable image parameterizations for feature visualization [175]. Stronger use of the priors via the loss function is an additional option. Considering the end goal of MRIgRT which is to extract image contours and to subsequently generate a dose planning, it would be interesting to investigate if we can sacrifice image quality without losing segmentation and registration performance, which may even further accelerate the MR imaging, going from minutes to seconds. This could then in the future lead to an almost realtime steering and control modality, which has benefits for more rapidly moving organs like the lungs and heart.

## 7.3 General conclusions

In conclusion, this thesis proposes a deep learning based automatic contouring methodology for real time adaptive radiotherapy. The proposed networks were evaluated on prostate CT images, a commonly used modality for treatment planning, but may be generalized for MR images. Moreover, we proposed a fast MR reconstruction algorithm in order to accelerate MR acquisition so that our models can be used potentially for MR guided adaptive radiotherapy as well. All deep learning methods proposed in this thesis have a runtime of less than a second, thus enabling real-time automatic contouring necessary for online-adaptive radiotherapy.