Towards the Clinical Implementation of Online Adaptive Radiation Therapy
for Prostate Cancer

by

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Medical Physics Graduate Program
Duke University

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Dissertation submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy
in the Graduate Program in Medical Physics
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ABSTRACT

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Abstract

The online adaptive radiation therapy for prostate cancer based on re-optimization has been shown to provide better daily target coverage through the treatment course, especially in treatment sessions with large anatomical deformation. However, the clinical implementation of such technique is still limited primarily due to two major challenges: the low efficiency of re-optimization and the lack of online quality assurance technique to verify delivery accuracy. This project aims at developing new techniques and understandings to address these two challenges.

The study was based on retrospective study on patient data following IRB-approved protocol, including both planning Computer Tomography (CT) and daily Cone-Beam Computer Tomography (CBCT) images. The project is divided into three parts. The first two parts address primarily the efficiency challenge; and the third part of this project aims at validating the deliverability of the online re-optimized plans and developing an online delivery monitoring system.

I. Overall implementation scheme. In this part, an evidence-based scheme, named Adaptive Image-Guided Radiation Therapy (AIGRT), was developed to integrate the re-optimization technique with the current IGRT technique. The AIGRT process first searches for a best plan for the daily target from a plan pool, which consists the original CT plan and all previous re-optimized plans. If successful, the selected plan is used for
the daily treatment with translational shifts. Otherwise, the AIGRT invokes re-optimization process of the CT plan for the anatomy-of-the-day, which is added to the plan pool afterwards as a candidate plan for future fractions. The AIGRT scheme is evaluated by comparisons with daily re-optimization and online repositioning techniques based on daily target coverage, Organ-at-Risk (OAR) sparing and implementation efficiency. Simulated treatment courses for 18 patients with re-optimization alone, re-positioning alone and AIGRT shows that AIGRT offers reliable daily target coverage that is highly comparable to re-optimization everyday and significantly improves compared to re-positioning. AIGRT is also seen to provide improved organs-at-risk (OARs) sparing compared to re-positioning. Apart from dosimetric benefits, AIGRT in addition offers an efficient scheme to integrate re-optimization to current re-positioning-based IGRT workflow.

II. Strategies for automatic re-optimization. This part aims at improving the efficiency of re-optimization through automation and strategic selections of optimization parameters. It investigates the strategies for performing fast (~2 min) automatic online re-optimization with a clinical treatment planning system; and explores the performance with different input parameters settings: the DVH objective settings, starting stage and iteration number (in the context of real time planning). Simulated treatments of 10 patients were re-optimized daily for the first week of treatment (5 fractions) using 12 different combinations of optimization strategies. Options for objective settings included
guideline-based RTOG objectives, patient-specific objectives based on anatomy on the planning CT, and daily-CBCT anatomy-based objectives adapted from planning CT objectives. Options for starting stages involved starting re-optimization with and without the original plan’s fluence map. Options for iteration numbers were 50 and 100. The adapted plans were then analysed by statistical modelling, and compared both in terms of dosimetry and delivery efficiency. The results show that all fast online re-optimized plans provide consistent coverage and conformity to the daily target. For OAR sparing however, different planning parameters led to different optimization results. The 3 input parameters, i.e. DVH objectives, starting stages and iteration numbers, contributed to the outcome of optimization nearly independently. Patient-specific objectives generally provided better OAR sparing compared to guideline-based objectives. The benefit in high-dose sparing from incorporating daily anatomy into objective settings was positively correlated with the relative change in OAR volumes from planning CT to daily CBCT. The use of the original plan fluence map as the starting stage reduced OAR dose at the mid-dose region, but increased 17% more monitor units. Only < 2cc differences in OAR V50% / V70Gy / V76Gy were observed between 100 and 50 iterations. Based on these results, it is feasible to perform automatic online re-optimization in ~2 min using a clinical treatment planning system. Selecting optimal sets of input parameters is the key to achieving high quality re-optimized plans, and should
be based on the individual patient’s daily anatomy, delivery efficiency and time allowed for plan adaptation.

III. Delivery accuracy evaluation and monitoring. This part of the project aims at validating the deliverability of the online re-optimized plans and developing an online delivery monitoring system. This system is based on input from Dynamic Machine Information (DMI), which continuously reports actual multi-leaf collimator (MLC) positions and machine monitor units (MUs) at 50ms intervals. Based on these DMI inputs, the QA system performed three levels of monitoring/verification on the plan delivery process: (1) Following each input, actual and expected fluence maps delivered up to the current MLC position were dynamically updated using corresponding MLC positions in the DMI. The difference between actual and expected fluence maps creates a fluence error map (FEM), which is used to assess the delivery accuracy. (2) At each control point, actual MLC positions were verified against the treatment plan for potential errors in data transfer between the treatment planning system (TPS) and the MLC controller. (3) After treatment, delivered dose was reconstructed in the treatment planning system based on DMI data during delivery, and compared to planned dose. FEMs from 210 prostate IMRT beams were evaluated for error magnitude and patterns. In addition, systematic MLC errors of ±0.5 and ±1 mm for both banks were simulated to understand error patterns in resulted FEMs. Applying clinical IMRT QA standard to the online re-optimized plans suggests the deliverability
of online re-optimized plans are similar to regular IMRT plans. Applying the proposed QA system to online re-optimized plans also reveals excellent delivery accuracy: over 99% leaf position differences are < 0.5 mm, and the majority of pixels in FEMs are < 0.5 MU with errors exceeding 0.5 MU primarily located on the edge of the fields. All clinical FEMs observed in this study have positive errors on the left edges, and negative errors on the right. Analysis on a typical FEM reveals positive correlation between the magnitude of fluence errors and the corresponding leaf speed. FEMs of simulated erroneous delivery exhibit distinct patterns for different MLC error magnitudes and directions, indicating the proposed QA system is highly specific in detecting the source of errors. Based on these results, it can be concluded that the proposed online delivery monitoring system is very sensitive to leaf position errors, highly specific of the error types, and therefore meets the purpose for online delivery accuracy verification. Post-treatment dosimetric verification shows minimal difference between planned and actual delivered DVH, further confirming that the online re-optimized plans can be accurately delivered.

In summary, this project addressed two most important challenges for clinical implementation of online ART, efficiency and quality assurance, through innovative system design, technique development and validation with clinical data. The efficiencies of the overall treatment scheme and the re-optimization process have been improved
significantly; and the proposed online quality assurance system is found to be effective in catching and differentiating leaf motion errors.
To

My Son Zichen

Who Has Been the Sweetest Distraction During My Writing
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<tr>
<td>AIGRT</td>
<td>Adaptive Image-Guided Radiation Therapy</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ART</td>
<td>Adaptive Radiation Therapy</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone-Beam Computed Tomography</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CT-Sim</td>
<td>CT Simulation</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>CU</td>
<td>Calibration Unit</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Dynamic Contrast-Enhanced Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>DD</td>
<td>Dose Difference</td>
</tr>
<tr>
<td>DMI</td>
<td>Dynamic Machine Information</td>
</tr>
<tr>
<td>DTA</td>
<td>Distance-to-Agreement</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose-Volume Histogram</td>
</tr>
<tr>
<td>Dxx%</td>
<td>Minimum dose to the hottest xx% of a structure</td>
</tr>
<tr>
<td>EBRT</td>
<td>External Beam Radiation Therapy</td>
</tr>
<tr>
<td>EPI</td>
<td>Electronic Portal Imaging Device</td>
</tr>
<tr>
<td>gEUD</td>
<td>Generalized Equivalent Uniform Dose</td>
</tr>
<tr>
<td>GPU</td>
<td>Graphic Processing Unit</td>
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</table>
ICRU  International Commission on Radiation Units and Measurements
IGRT  Image-Guided Radiation Therapy
IMRT  Intensity Modulated Radiation Therapy
IRB   Institutional Review Board
kV    Kilo-voltage
MLC   Multi-Leaf Collimator
MU    Monitor Unit
MV    Mega-voltage
OAR   Organ-at-Risk
PET   Positron Emission Tomography
PTV   Planning Target Volume
QA    Quality Assurance
RTOG  Radiation Therapy Oncology Group
SAM   Segment Aperture Morphing
SPECT Single Photon Emission Computed Tomography
SV    Seminal Vesicle
SWO   Segment Weight Optimization
TPS   Treatment Planning System
VMAT  Volumetric Modulated Arc Therapy
V$_{xx\%}$  Volume that receives at least $xx\%$ of the prescription dose
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1. Backgrounds

1.1 The Rational Of Adaptive Radiation Therapy

External-Beam Radiation Therapy (EBRT) is among the most commonly used techniques in cancer radiotherapy. In EBRT the radiation is delivered to the tumor region, i.e. target volume, from outside the patient’s body by using several radiation beams from different directions. This configuration is similar to the “cross-firing” concept as all radiation beams are focused on the target. Thus the radiation dose from all beams accumulates inside the body to form a three-dimensional dose distribution, with high dose only covering the entire target volume and reduced dose to the surrounding normal tissues/organs, i.e. organs-at-risk (OARs). The latest technology, intensity modulated radiation therapy (IMRT), further improves the OAR sparing via non-uniform beam delivery. An example of IMRT is shown in Figure 1.
Figure 1: Demonstration of intensity-modulated radiation therapy (IMRT). In this example, 7 beams with different shape and non-uniform intensity converges at the target area. The 2D intensity-modulated photon fluence accumulates to provide a conformal dose distribution around the target region, as the color wash indicating the dose range from high to low.

Such radiation treatment (RT) design is based on the 3-dimensional volumetric images such as computer tomography (CT), magnet resonance image (MRI) to capture the anatomical information about the patient and geometrical relationships of the tumor and OARs; and the functional and molecular images such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) to capture features about the tumor extent and staging. The typical timeline for conventional IMRT treatment process is illustrated in Figure 2. Once IMRT has been
selected to be the treatment technique, a team of radiation oncologist, physicist and dosimetrist work together to design an individualized treatment plan for each patient. This treatment plan is designed based on a snapshot of the patient anatomy during planning CT acquisition, and is then delivered over a course of 30-40 daily treatment sessions, which are commonly referred as *fractions*.

![Image](image.png)

**Figure 2: Timeline for a typical IMRT treatment.**

During the actual daily treatment, the radiation is delivered according to the treatment plan by assuming the daily anatomy remains the same as in initial planning stage. In reality, this assumption may not always be valid due to the daily change in the anatomy, the target shape and position in particular, and therefore may lead to mismatch between delivered dose distribution and the “anatomy-of-the-day” scenario. Such mismatch could result in underdosing the target and/or overdosing the healthy
tissues/organs, which may translate into compromised tumor control and/or increased side effects.

Figure 3: Snapshots of the pelvic anatomy in 11 days from CT simulation to the first 10 fractions of treatment. CTV, the bladder and the rectum are contoured in black, green and red color, respectively.

In general clinical practice, the risk of underdosing daily target is addressed by adding a margin around the true target during treatment planning (ICRU-50, 1993), and designing the dose distribution to conform to the expanded target, termed as planning target volume (PTV). This technique leaves some “headroom” for anatomy variations and patient setup errors, but at the cost of increasing dose to the surrounding normal tissue/organs. The IMRT significantly reduces the excessive dose outside the target by providing more conformal dose distribution to the target. Thus, the concern of underdosing target due to anatomy change is of greater importance with IMRT, since higher dose gradient means less tolerance and consequently higher probability of inadequate daily target coverage.
The Adaptive Radiation Therapy (ART) approaches this issue by changing the fundamental assumption of stationary anatomy in traditional EBRT to variable anatomy, and integrates this concept through the entire treatment course. The principle of ART is to capture the anatomical change, to modify the treatment plan accordingly, and to ensure the optimal target coverage and OAR sparing in both planning and daily treatment.

1.2 Components of ART

The implementation of the ART principle is built upon technical components in three main areas: image guidance, dose verification and plan adaptation.

![Figure 4: Components in adaptive radiation therapy system.](image)
1.2.1 Image Guidance

ART is the advanced stage of image-guided radiation therapy (IGRT). The role of imaging has become increasingly important in nearly every aspect of radiation therapy, from staging, structure contouring, treatment planning, treatment delivery verification to treatment response and assessment (Yoo et al., 2010). In the field of ART, image guidance provides the input information of daily anatomy, enables the visualization of the anatomy-of-the-day, and determines how different the anatomy is from the plan. Image guidance in ART commonly includes two steps: volumetric image acquisition and image registration.

1.2.1.1 Daily Image Acquisition

Daily image acquisition techniques for adaptive radiation therapy have been reported by various groups Court et al. (Court et al., 2003; Court and Dong, 2003; Court et al., 2005b; Court et al., 2006; Kuriyama et al., 2003) reported using CT-on-rails as an in-room daily image acquisition technique for adaptive radiation therapy. By installing a diagnostic quality helical CT scanner that shares the couch with the linear accelerator (linac) on-rails in the treatment room, high quality CT image can be obtained before treatment while keeping patients in the same relative position to the treatment couch. Soon after that, the Cone-Beam CT (CBCT) system integrated to the gantry of the medical linear accelerator (Linac) has also been reported as a component in adaptive radiation therapy (Wu et al., 2008; Lei and Wu, 2010; de la Zerda et al., 2007; Jaffray et al.,
The CBCT for ART enables the patient to be imaged and treated at the same position, which minimizes the uncertainty associated with imaging procedure. Integrated CBCT eliminates the need to rotate the patient and move CT scanner between imaging and treatment, and is therefore more convenient. However, the image quality of current CBCT is generally inferior to helical CT in soft-tissue contrast, CT number consistency and artifacts. Alternatively, the megavoltage CT (MVCT) capability of the Tomotherapy (TomoTherapy, Inc. Madison, WI) treatment unit has also been reported for daily image acquisition and target localization (Langen et al., 2005). The Tomotherapy unit uses the same MV x-ray source mounted in a CT-like gantry for treatment and imaging. It rotates helically around the patient to perform both the imaging and the therapy process (Ruchala et al., 1999).

1.2.1.2 Image Registration Techniques

Image registration is used to determine the difference between planning anatomy and the daily anatomy. It can be categorized into two groups: rigid registration and non-rigid/deformable registration.

Rigid registration matches the daily images to the planning CT via translational (3D) or translational + rotational (6D) transformation, which can then be used to re-position the patient for target alignment. Rigid registration technique offers fast and robust performance in daily-to-planning target alignment, and is therefore widely adopted currently in the clinical practice of IGRT. However, at the presence of
target/organ deformation or tumor shrinkage, rigid registration may not be sufficient to provide the information on the shape and volume variations (Wu et al., 2008).

Deformable registration techniques, on the other hand, allow the voxel-to-voxel mapping between the daily and the planning image sets. Yan et al. (Yan et al., 1999) reported a deformable registration method using biomechanical model of elastic body and demonstrated a framework to construct the cumulative dose distribution in organs during the course of radiation therapy. Coselmon et al. (Coselmon et al., 2004) developed mutual information based CT registration method using thin-plate splines for lung deformation with alignment accuracies of 1.7, 3.1 and 3.6 mm in right-to-left, anterior-posterior and inferior-superior directions. Wang et al.’s study on an accelerated “demons” algorithm showed ~1.5 pixels registration error in simulated CT images and in pelvis phantom cases, and acceptable contour-propagation accuracy in patient study (Wang et al., 2005). Lu et al. (Lu et al., 2006) demonstrated the feasibility using free-form deformation method between kV and MV CT images in ART for “automatic re-contouring, deformable dose accumulation and tumor volume monitoring”. They have also cautioned that “under circumstances where large topological changes present, the intensity-based deformable registration technique may fail”. In a multi-institutional phantom study of several deformable registration algorithms, Kashani et al. (Kashani et al., 2008) found that large registration errors exist at various phantom regions for different techniques compared, and suggested that deformable registration techniques
should be employed cautiously. They observed that for the same type of registration, “different implementations, different users, or different parameter settings”, e.g. imaging modalities, image quality, registration site, can significantly alter the registration result and its accuracy. Therefore before clinical use, any deformable registration technique should be carefully validated within the context of the specific implementation, the clinical environment (modalities, image quality, and sites) and user-defined parameters.

1.2.1.3 Functional Imaging

As the field of radiation oncology progresses to include more biological and functional information into the patient care process, functional imaging modalities, e.g. dynamic contrast-enhanced Magnetic Resonance Imaging (DCE-MRI) and PET, have attracted increasing interests. Some pilot studies have demonstrated unique perspectives and promising results of these imaging modalities in guiding radiation therapy. Cao et al. reported using DCE-MRI to assess factors influencing the clinical outcome of high-grade gliomas after radiation therapy, and found that both vascularity and tumor volume influences the time to progression for these patients (Cao et al., 2008). Craciunescu et al. (Craciunescu et al., 2009) piloted a study using DCE-MRI to predict the treatment response in patients with breast cancer. Mayr et al. reported a study using DCE-MRI to correlate the tumor perfusion pattern change (pre-RT, during early RT and min-RT) and the treatment outcome (Mayr et al., 2010). The results indicated that DCE-
MRI can be used in monitoring tumor radio-responsiveness during RT for guiding adaptive therapy. MRI guidance is also reported by Dimopoulos et al. (Dimopoulos et al., 2009) for being effective in assessing the tumor volume shrinkage during EBRT and brachytherapy for cervical cancer. Schuetz et al. (Schuetz et al., 2010) evaluated repetitive $^{18}$F-fluorooazomycin-arabinoside ($^{18}$FAZA) PET scans to map tumor hypoxia during EBRT and MRI-guided brachytherapy for cervical cancer, and found it feasible but has questionable clinical value in addition to MRI. Fallone et al. (Fallone et al., 2009) reported first on-board MR images acquired concurrently with EBRT with in-house developed MR-linac featuring 0.2 T field strength. The acceptable image quality shows promises of using MR over CT/CBCT in adaptive radiotherapy for better soft-tissue contrast. Geets et al. (Geets et al., 2007) used FDG-PET to monitor tumor volume change during RT treatment, parallel to CT and MRI, and performed adaptive re-planning study based on target delineated from PET, CT and MRI. They found that GTVs delineated with functional imaging modality were always smaller compared to using anatomical imaging; adaptive re-planning, coupled with target delineated from repeated FDG-PET has resulted a 15-40% reduction on the irradiated volumes (V90, V95 and V100) compared to pre-treatment CT. For on-line target localization, Roper et al. (Roper et al., 2009) reported a simulation study exploring the feasibility of an on-board SPECT and found it valuable in localizing < 2 cm tumors with clinical uptake of Technetium-99m in 4 min scan time.
The use of functional imaging modality in adaptive radiation therapy is still in the early stage with many technical challenges and limited research data. Although the additional biological information is promising in principle, more systematic studies are needed to justify the added benefit of functional imaging to current anatomical imaging modalities, and then to facilitate the clinical implementation of these technologies.

1.2.2 Treatment Adaptation

The treatment adaptation is another major component of ART; it takes the information from the image-guidance as input and mitigates the discrepancies between planned and actual anatomy, aiming for optimal target coverage and OAR sparing. With this goal in mind, many methods and protocols has been developed in research, some of which have already been implemented clinically. These methods can be categorized into four groups:

1.2.2.1 Online Repositioning

Online repositioning is the first stage of ART and has been widely implemented in clinics where IGRT technology is available. The patient position is corrected online using daily images for possible target position change from the planned anatomy, as shown in Figure 5. Different landmarks can be employed to drive the re-alignment of the target volume. Most commercial treatment delivery system offers the online registration of bony structures for patient positioning correction, which is useful when tumor location is relatively stable in reference to the body structures, e.g. intracranial tumors,
but not sufficient for treatment sites such as lung and abdomen. To improve the target localization, fiducial markers implanted in the soft tissue has been used as a surrogate for the target. Chung et al. (Chung et al., 2004) evaluated using fiducial markers to perform on-line target localization and alignment for prostate cancer treatment, which is widely implemented in clinical practice. Jaffray (Jaffray et al., 2002) et al. demonstrated using CBCT with soft-tissue matching to reduce inter-fractional target position uncertainties. This method is also widely implemented in commercial treatment delivery systems and used clinically. Barney et al. (Barney et al., 2010) compared CBCT-based IGRT with fiducial marker-based in prostate cancer treatment and found them to be similar, although fiducial marker-based technique is preferred for efficiency. Wu et al. (Wu et al., 2006a) performed geometric and dosimetric evaluations of on-line re-positioning and demonstrated its effectiveness on reducing the CTV-PTV margin. Shi et al. (Shi et al., 2011) compared manual fiducial marker alignment with automatic soft-tissue match and found the later less reliable for daily target alignment.
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Figure 5: Concept and weakness of online re-positioning. This correction method is very efficient, but may not be able to correct large organ motion/deformations.

Although efficient and widely implemented, online repositioning alone is not capable of correcting dosimetric deficits resulted from daily target/organ deformation, which is commonly seen in prostate and head-and-neck cancer patients. Such changes require the plan to be modified through re-optimization-based techniques.

1.2.2.2 Off-line Re-planning

Yan et al. (Yan et al., 1997) pioneered the study of ART by introducing off-line re-optimization based on the bounding target volume constructed from the first several fractions’ image data, as shown in Figure 6. After the first week’s treatment, the plan can be re-optimized with the bounding target volume and used for subsequent fractions to improve the efficacy of the delivery (Yan et al., 2000). Wu et al. (Wu et al., 2006b)
demonstrated the feasibility of combining off-line re-optimization and dose compensation to safely reduce CTV-PTV margin. Similar offline re-optimization has also been developed and evaluated by other groups of researchers (Birkner et al., 2003; Rehbinder et al., 2004; Wu et al., 2004; de la Zerda et al., 2007; Nijkamp et al., 2008; Nuver et al., 2007). Off-line re-optimization for dose compensation has also been applied with Tomotherapy unit (Mackie et al., 1999; Wu et al., 2002; Welsh et al., 2006). Wu et al. (Wu et al., 2002) proposed using off-line re-optimization to compensate cold-spots in target volume in the next fraction and demonstrated its effectiveness with simulated cases. Welsh et al. (Welsh et al., 2006) demonstrated the clinical implementation concept of compensating underdosed region in the target using dose comparison and Tomotherapy treatment technique in subsequent fractions. Woodford et al. (Woodford et al., 2007) investigated an adaptive radiotherapy planning technique based on daily gross-tumor volume (GTV) changes acquired in daily MV-CT image and found it beneficial to perform adaptive planning for the subsequent fractions if GTV decreases by > 30% during the treatment course. Nijkamp et al. (Nijkamp et al., 2008) at The Netherlands Cancer Institute (NKI) reported their first clinical results on adaptive prostate radiotherapy. They performed off-line re-optimization based on averaged PTV derived from the CBCT data in the first six fractions, and found using this plan for the subsequent fractions to be effective in reducing high dose regions and the dose to the rectum. One important notion of the off-line optimization techniques is that the re-
optimized plan is used for further treatments, not for the current fraction when the daily image was acquired.

**Figure 6:** General concept of offline re-planning method. It improves over daily re-positioning by generating a new plan based on first several fractions’ target motion. The downside of this method is that the irradiating volume (blue dashed line) are often larger than daily target, which can increase the dose to adjacent OARs.

### 1.2.2.3 Online Re-optimization

Since the ultimate goal of ART is to address the daily anatomy change, it is intuitive to develop optimization techniques that can be used online based on daily anatomical structures, *prior to the treatment*, as shown in Figure 7. Court *et al.* (Court *et al.*, 2005b; Court *et al.*, 2006) developed a technique of modifying MLC leaf positions that combines global rigid registration and slice-by-slice 2D registration between planning and daily CT images to account for global shifts and regional deformation of the target,
respectively. They found this technique to be effective in improving target dose uniformity for prostate and head-and-neck cases. Song et al. (Song et al., 2007) also reported the dosimetric evaluation on online correction method based on “MU-MLC” modification. Mohan et al. (Mohan et al., 2005) reported online re-optimization by deforming 2D intensity maps according to the geometric relationship between the intensity maps and projected anatomy in beams-eye-view (BEV), and found it to be able to provide good approximation to the fully-fledged re-planning in a rapid manor. Fu et al. (Fu et al., 2009) developed online MLC leaf position modification techniques based on BEV anatomical structure projections with dosimetric benefits and faster speed. Feng et al. (Feng et al., 2006) reported an effective and fast online plan adaptation method using Direct-Aperture-Deformation that morphs the treatment apertures according to the planning-to-daily deformable registration. Wu et al. (Wu et al., 2008) developed and evaluated a full volumetric online re-optimization algorithm using deformed planning dose distribution and linear programming optimization of the intensity maps, which significantly improves the target coverage and OAR sparing with < 2 min optimization time (Thongphiew et al., 2009). Ahunbay et al. (Ahunbay et al., 2010a) utilized a two-step optimization process called “SAM+SWO” as clinically implementable on-line re-optimization techniques. In this model, the MLC shape and its relevant MU were optimized separately which took a total of 5-10 min for plan adaptation. New
development in GPU-accelerated computing enables to perform full direct-aperture optimization within 4s, as demonstrated by Men et al. (Men et al., 2010).

Figure 7: General concept of online re-optimization. It generates a new plan tailored specifically for the daily anatomy. However, such method requires substantially added cost to the clinical flow.

1.2.2.4 Hybrid Strategies for plan adaptation

Although re-optimization features the optimal target coverage and OAR sparing for a given daily anatomy, both online and offline implementation of such technique involves complicated procedures that adds considerable extra resources burden to the clinic. In the meantime, online repositioning is still the simplest and most widely implemented correction techniques for daily anatomical variations. For rigid target variations or small deformation, online repositioning remains a very effective and efficient method for treatment. However, for cases with significant target deformation, re-optimization based on the new anatomy is optimal for complete target coverage and
ensuring OAR sparing. Therefore to combine on-line repositioning and offline/online re-
optimization will likely to maximize the benefit from both techniques and reduce
redundant re-optimizations. Lei et al. (Lei and Wu, 2010) reported using offline re-
optimization in conjunction with online re-positioning correction is necessary and yields
further margin reductions of 1.4 mm and 2.0 mm for low-risk and intermediate-risk
prostate cancer patients, respectively, while maintains a 99% target volume coverage.

1.2.3 Delivery Verification

Both Yan et al. (Yan et al., 1997; Yan, 2010) and de la Zerda et al. (de la Zerda et al.,
2007) formulated the ART process as a closed-loop system, where dose verification acts
as a feedback chain to provide information on the dosimetric fidelity of the fractionated
treatment process. The dose verification in ART is mainly performed in two fashions:
daily dose verification and cumulative dose analysis.

1.2.3.1 Daily Dose Verification

Daily dose verification calculates the radiation dose of the delivered plan on the
daily image set. This method focuses on the assessing the quality of dose coverage for
each fractionated treatment. The most commonly used method of daily dose verification
is performing dose re-calculation on the daily anatomy with daily delivery information,
acquired during treatment, and compare the daily dose-volume histogram (DVH) to
tractionated planning dose DVH.
Lee et al. (Lee et al., 2008a; Lee et al., 2008b) reported daily dose assessment methods by reconstructing delivered dose with multi-leaf collimator (MLC) Dynalog files and with leaf sequence measured by electronic portal imaging device (EPID). These methods take into consideration the actual MLC positions during the treatment and recalculate the dose in the treatment planning system with the actual measured fluence. Small differences between delivered and planned fluence maps were reported, as well as between delivered and planned dose, except for “discernible differences” in high dose region and maximal dose. Dose reconstructions by Monte Carlo methods have also been reported by various research groups using Linac MLC Dynalog files (Teke et al., 2010) and portal beam measurements (van Elmpt et al., 2006).

1.2.3.2 Cumulative Dose Analysis

Contrary to daily dose verification, cumulative dose analysis focuses on the accumulated dose distribution up to the current fraction. Yan et al. (Yan et al., 1999) developed a model to construct the cumulative dose in a deforming organ of interest using deformable registration techniques based on biomechanical model of the elastic body. Wu et al. (Wu et al., 2006b) utilized this cumulative dose analysis model and developed a weekly dose compensation scheme for the deficit in actual delivered dose. By performing volume-element tracking, the discrepancy in doses delivered to each sub-volume is identified and compensated in future fractions through plan adaptation. O’Daniel et al. (O’Daniel et al., 2007) evaluated the difference between planned and
delivered dose to parotid gland and target using cumulative dose analysis via deformable image registration. Rosu et al. (Rosu et al., 2005) investigated the impact of interpolation methods and grid size on the cumulative dose accuracy via deformable registration. Currently, accurate dose accumulation requires carefully validated deformable registration techniques and complicated workflow. The increased burden and uncertainty in accuracy has been a limiting factor for clinical implementation of cumulative dose analysis, and this needs to be addressed through technology advancement and system integration (Jaffray et al., 2010).

1.3 Current Clinical Applications of ART for Prostate Cancer

Since the early work of ART by Yan et al. (Yan et al., 1997), the advantage of ART has been increasingly explored by physicians and clinical physicists, who have constantly pushed forward the clinical implementation of different ART techniques. The following is a summary of current ART clinical applications for prostate cancer.

The off-line ART technique has been clinically implemented for prostate cancer treatment in some institutions. Due to the nature of being adjacent to the bladder and the rectum, the prostate region can exhibit significant position/volume change inter-fractionally (Xia et al., 2010), especially when treating both prostate and seminal vesicles, which is found to move largely independently (Liang et al., 2009). Xia et al. (Xia et al., 2010) reported one clinical case of concurrent prostate and pelvic lymph nodes treatment with the multiple adaptive plan (MAP) strategy. The MAP generates plans for a number
of potential prostate locations determined using daily image guidance. For each fraction, the patient was treated with the pre-generated plan that closest matched the daily prostate position. Dosimetric analysis indicated that the MAP technique is beneficial for pelvic lymph nodes coverage but is insufficient to provide complete coverage for the prostate. The offline re-optimization technique (Yan et al., 2001; Yan, 2010; Yan et al., 2000) has been clinically implemented at William Beaumont Hospitals (Ghilezan et al., 2010; Yan et al., 2001; Vargas et al., 2005; Harsolia et al., 2007). The outcome analysis on large number of patients (>1000) demonstrates improved biochemical control (Brabbins et al., 2008; Ghilezan et al., 2010) and less normal tissue toxicity (Ghilezan et al., 2010, 2008). Netherlands Cancer Institute (NKI) implemented an off-line adaptive strategy based on planning CT and several repeated CT/CBCT scans but taking into consideration the average position of rectal walls as well (Hoogeman et al., 2005; Nuver et al., 2007). In their reported clinical study with 20 patients, ART protocol was able to reduce PTV volume by avg. 29% and V65Gy for rectum by avg. 19% (Nijkamp et al., 2008).

Clinical implementation of ART with online re-optimization is currently limited due to the extra burden of QA and plan approval associated with modified plans.

1.4 Challenges and Limitations

The development in imaging and re-optimization algorithm has made it possible to personalize radiation therapy and to follow the dynamically changing anatomy
throughout the treatment course. However, fully integrating ART into clinical practice still faces several challenges:

1.4.1 CBCT Image Quality and CT-Number Consistency

For online image guidance, CBCT has been a valuable tool to acquire image with patient in treatment position. However, due to higher scatter and less mechanical stability, the image quality of CBCT is still inferior from planning CT. As one of the key component of many ART systems, deformable registration relies heavily on the quality of CBCT images to provide accurate result. In prostate cases where low contrast soft-tissue dominates, high soft-tissue contrast and low artifacts are essential for producing acceptable deformation accuracy. In addition, the CT number in CBCT images has small but noticeable difference from planning CT for same materials (Yang et al., 2007; Yoo and Yin, 2006). This inconsistency could result in differences between dose calculated on CT and CBCT due to inhomogeneity correction. Although dedicated calibration curve may reduce the inconsistency to acceptable level (Yang et al., 2007; Yoo and Yin, 2006), additional effort is required to generate and maintain the calibration curves for each CBCT unit, especially for centers with multiple CBCTs.

1.4.2 Clinical Resource Management

The main obstacle limiting ART from wide clinical implementation is the time management challenge. Many components in proposed ART process require considerably increased cost to time and staff resources compared to current IGRT
technique, and are therefore difficult to be integrated into clinical flow for each patient. These added costs to recourses come from daily structure contouring, re-optimization, patient-specific quality assurance (QA) and plan evaluation and approval. The key to address this challenge is through improving computational speed and automation. Recent development in these components has shown great promises to increase the efficiency. Automatic contour propagation through deformable registration can be performed by commercially available tools such as VelocityAI (Velocity Medical Solutions, Atlanta, GA). GPU accelerated deformable registration engine developed by Gu et al (Gu et al., 2010) is capable of finishing registration within 7-11s. Fast re-optimization algorithm with linear programming(Wu et al., 2008), two-step “SAM+SWO” algorithm (Ahunbay et al., 2010a), and GPU acceleration (Men et al., 2010) reduces the time of re-optimization to 1-2 min, < 6 min, and 3.8s respectively. Advanced QA technique employing MLC and Monte Carlo technology has also been reported by Teke et al.(Teke et al., 2010). It is envisioned that near real-time online ART is possible in the near future through combination and continuous development of these technologies.

1.4.3 System Integration

For ART to become standard clinical practice in radiation therapy, unified and seamless integration of all ART components into treatment planning system (TPS) and clinical record and verify system (R&V) is essential. This requires close collaboration
between researchers and vendors. Until then, extreme cautions should be placed in the clinical deployment of ART techniques, to minimize mistakes and ensure patient safety.
2. Project focus and the overall structure

This project focuses on proof-of-concept studies facilitating the clinical implementation of on-line adaptive radiation therapy (ART) for prostate cancer through innovative sub-system design, and improvement on the integration and efficiency of multiple sub-systems. The clinical focus of this project is to respond to inter-fractional anatomical changes and ensure accurate daily dose delivery to the target-of-the-day. Because of the emphasis on daily dose accuracy, this online ART technique is most likely to benefit treatment regimes that focus more on daily dose, such as hypofractionated treatments (Miles and Lee, 2008) and prostate Stereotactic Body Radiation Therapy (SBRT) (Lee, 2009). Several recent hypofractionated prostate treatment and SBRT protocol delivers the entire treatment in 5-20 fractions (Madsen et al., 2007; King et al., 2009; Li et al., 2012a; RTOG, 2012a; Miles and Lee, 2008; Martin et al., 2006; Ritter et al., 2006; Soete et al., 2006; Tsuji et al., 2005), as opposed to 35-38 fractions in conventional prostate IMRT. Treatment regimens like these require very accurate daily dose delivery to achieve tumor control and reduce the risk of elevated toxicity, and therefore would be more likely benefit from the online re-optimization-based ART techniques developed in this study.

As mentioned in the background section, on-line ART in general provides improved daily target coverage and OAR sparing compared to currently IGRT techniques. It has however not yet been fully implemented in the clinic due to it being
time- and staff-resource-expensive, as well as the lack of delivery monitoring technique that is suitable of online ART application. This project aims at overcoming these important technical limitations on the efficiency and quality assurance of on-line ART, and pushing it towards clinical implementation.

The project is divided into three stages. In Chapter 3, an overall system of integrating online re-positioning and online re-optimization is designed to improve daily target coverage as well as overall efficiency. In Chapter 4, optimal strategy for fast online fluence re-optimization using a clinical treatment planning system is explored based on optimization objective settings, different starting stages and iteration numbers. In Chapter 5, the delivery accuracy of online automatically re-optimized plan is validated against that of original plan, and a multi-level quality assurance (QA) system for on-line adapted treatment is developed to provide online monitoring of the delivery accuracy and post-treatment dosimetric verifications of daily treatment.
3. Developing an overall scheme for online ART system combining re-positioning and re-optimization

3.1 Introduction

In prostate radiation therapy, inter-fractional variations of the target volume and position due to the change of fillings in nearby organs, i.e. the bladder and the rectum, make delivering uniform dose to the target challenging on a day-to-day basis. The technical development and clinical implementation of image-guided radiation therapy (IGRT) for prostate cancer has enabled on-line reviewing of the daily anatomy, and consequently has created increasing demands for more conformal target coverage as well as better organ/tissue sparing of the daily treatment. Many of the current IGRT techniques focus on target coverage, such as daily match of PTV volumes using on-board cone beam CT (Olivera et al., 2000; Wu et al., 2006a; Court et al., 2006; Feng et al., 2006). To further balance the PTV coverage and OAR sparing, adaptive radiation therapy for prostate cancer treatment was introduced by several groups to re-optimize initial plan based on daily image sets of the first few fractions in an off-line fashion, (Yan et al., 1997; Yan et al., 2000; Wu et al., 2002; Birkner et al., 2003; Rehbinder et al., 2004; Wu et al., 2004; de la Zerda et al., 2007; Ghilezan et al., 2010; Yan, 2010), due to the time constraints of the re-planning process. On-line re-optimization and adaptation approaches, recently proposed by several research groups (Court et al., 2005b; Mohan et al., 2005; Court et al., 2006; Feng et al., 2006; Song et al., 2007; de la Zerda et al., 2007; Wu et al., 2008; Fu et al., 2009; Mestrovic et al., 2009; Ahunbay et al., 2010b), provide high
quality daily treatment by implementing fast re-optimization and/or fast MLC aperture modification to adapt treatment plans based on daily CT or CBCT image. However, extra clinical work, such as quality assurance (QA) effort and plan approval are required for the modified plans, which adds cost of time and machine resources to the clinical implementation. Therefore in current clinical practice, patient re-positioning based on soft-tissue matching is still the most widely used technique to account for interfractional patient anatomy variation, due to its high efficiency. Lei and Wu (Lei and Wu, 2010) investigated a hybrid strategy of offline re-planning and online image guidance using patient geometrical information and analyzed its benefit for margin reduction. However, the efficiency of an on-line implementation is still of great interest as it maximizes the benefits of such a hybrid scheme.

The primary goal of performing online plan re-optimization is to maintain consistent target coverage on a day-to-day basis. However, since the change of patient anatomy varies on a day to day basis, not all fractions require a plan re-optimization to ensure target coverage. The decision of whether a re-optimization is necessary should be based on the evidence that if a previously available plan is inadequate to provide sufficient target coverage for a particular daily anatomy. Moreover, the previously available plan should not be confined to the original treatment plan only, but be expanded to include any on-line re-optimized plan for previous fractions.
The hypothesis of this part of the project is that by combining online re-positioning and re-optimization in an evidence-based way, the necessity of performing an expensive online re-optimization can be reduced while still maintaining excellent target coverage, and therefore improving the overall efficiency of the scheme. Since we focus on the schematic design of the overall system, it is assume that the key components of the system, including daily re-optimization and quality assurance, are readily available. Implementations of these components are studied in subsequent Chapters.

3.2 Methods and Materials

3.2.1 The Original CT plan

Data from 18 prostate cancer patients treated at Duke University Medical Center, Durham, NC, USA, were retrospectively studied. For each patient, a planning CT image set was acquired using a CT simulator (Lightspeed; GE Healthcare Technologies, Waukesha, WI) with 1mm in-plane resolution and 3mm slice thickness. Structures-of-interest (SOIs) were the clinical target volumes (CTV, including the prostate and the seminal vesicles) and organs-at-risk (OARs, including the bladder and the rectum). Femoral heads were also assigned as OARs during original planning but not evaluated in this study. A uniform 5 mm margin was used to construct the PTV from the CTV.

The initial IMRT plan, “Original CT”, was optimized with the treatment planning system (Eclipse™, Varian Medical System, Palo Alto, CA), using seven co-
planar 15MV beams following the clinical conventions for prostate IMRT treatment planning at our institution. The beam angles are 25°, 75°, 130°, 180°, 230°, 285° and 335° for all patients. The primary dose constraints start from the adopted Radiation Therapy Oncology Group (RTOG) protocols based on 76-Gy target prescription dose (Rx) over 38 fractions (Pollack et al., 2006). For this feasibility study, the same prescription dose was used for the entire CTV, i.e. prostate and seminal vesicles. These constraints can easily be met using IMRT planning technique. More stringent secondary dose constraints were set according to institutional template constraints to achieve as much sparing as possible. The dosimetric constraints to the bladder and the rectum were: 70 Gy, 62 Gy and 39 Gy to <20%, 30% and 50% volumes, and 70 Gy, 56 Gy and 39 Gy to <20%, 30% and 50% volumes, respectively. A priority weight for each constraint was also assigned to gain a better control in balancing target coverage and OAR sparing. A trial-and-error scheme was used to manually adjust these constraints and the associated weights during the optimization process. The plans are normalized so that 100% prescription dose covers at least 98% of PTV.

3.2.2 Daily treatment simulation

In addition to the original CT data, 10 daily CBCT images for all 18 patients were acquired using an on-board imaging system (OBI, Varian Medical Systems, Inc., Palo Alto, CA) with the patient in the treatment position, prior to any IGRT corrections. The images were acquired every day during the first week and once a week for the rest of
the treatment course. These daily images were used to simulate 10 treatment fractions for all online IGRT techniques. The CBCT images were reconstructed with voxel size of 1 mm in-plane and 2.5 mm slice thickness. The daily SOIs were delineated by one attending physician, so the contouring was consistent with original IMRT planning. A previous study (Yan et al., 2000) has shown that for prostate IMRT, sufficient CTV coverage can be achieved through the entire treatment by setting the target to the bounding volume constructed based on daily CT images during the first 2 weeks of treatment, i.e. 10 fractions. This implies that 10 daily CTV shape/positions can represent most the treatment scenarios through the course of the treatment. Based on this result, we assume that for subsequent treatment fractions, the CTV coverage is very likely to follow the results of this study based on the simulated 10-fraction treatment courses.

3.2.3 Three simulated treatment arms

Soft-Tissue-Based IGRT (Online Re-positioning). For each CBCT, the current clinical IGRT technique based on the soft tissue target alignment was applied and the delivered plan was named as Soft-Plan plan. For most treatment couches, current clinical IGRT protocol only performs translational corrections. The matching was performed via finding the translations that yielded the maximal overlap between the target (PTV) on CT and the corresponding CTV on the CBCT images, in order to maximize the likelihood of daily CTV being covered by the dose distribution optimized to conform the
PTV on CT. Delivered dose was calculated on the CBCT images within the Eclipse™ treatment planning system.

**Re-Optimization-based IGRT.** The IMRT re-optimization technique was also applied to all CBCT images, generating another set of delivered plan (Re-Plan plan). The Re-Plan plans were generated using daily SOIs contoured on the CBCT images by a single physician. The 5mm PTV margin was also used in re-optimization process (Thongphiew *et al.*, 2009). The re-optimization based IGRT technique representing the most optimal coverage for the daily CBCT anatomy.

**Adaptive IGRT (AIGRT).** The concept of the *AIGRT* explores the advantages of the two IGRT techniques: re-optimization (re-planning) and patient re-positioning, in order to account for the daily anatomical variations at different levels of complexity and utilize IGRT to its optimal efficiency. By applying the re-planning technique through the entire treatment course, the best treatment plan quality is expected since the plan is customized to maximally match with the daily anatomical structures. On the other hand, the patient re-positioning technique is the existing IGRT technique that is intuitive and effective for simple target variations. Therefore in the *AIGRT* implementation the selection of the re-positioning vs. re-optimization for each fraction is anatomy-driven.
Figure 8: The scheme of the AIGRT technique.

Figure 8 illustrates the flowchart of the AIGRT technique. On the treatment day, the CTV is defined on the CBCT. Instead of using only Original CT plan to treat the patient, the daily CTV will be compared with PTV(s) from the plan(s) in the patient specific database. The database consists of the Original CT plan and previously re-optimized plans if exist. If the daily motion/deformation of the target volume can be accounted geometrically by any plan(s) in the database, the best-matching plan will be selected using our automatic algorithm as detailed in the next paragraph and the couch-shift will be applied to the plan to treat the patient for that fraction. If none of the plans
in the database satisfies the coverage criteria, a re-optimized new plan will be created for that treatment fraction and added to the patient plan database as a candidate for future fractions.

Selection between re-positioning and re-optimization techniques in the AIGRT is achieved by an automatic plan selection algorithm based on the patient’s daily structures-of-interest. Let the plan database contain $N$ previous treatment plans (Original CT and re-optimized plans) $P_i, i = 1, 2, \ldots, N$. Each plan dataset contains the beam information (e.g. beam angles and fluence maps) and PTV structure $PTV_i$ according to plan $P_i$. The daily CTV is aligned with all $PTV_i$. The plan $P_i$ that provides sufficient coverage is the plan such that all voxels $j$ in the CTV are in the $PTV_i$ of the plan $P_i$.

$$CTV_j \subseteq T_j(PTV_{i,j})$$

where $T_j(PTV_{i,j})$ represents the transformation (or re-positioning) of the PTV voxel $j$ of the $PTV_i$. In order to spare the dose to the OARs, the overlapping region of the $PTV_i$ and the daily OARs needs to be minimized, which can be done by comparing the PTV-OAR overlapped region. Alternatively, this can be done by selecting the plan $P_i$, with the smallest $PTV_i$ that provides the complete coverage for the daily CTV.

$$i^* = \arg\min_i \frac{PTV_i}{CTV}$$

The delivered plans, from re-positioning or from re-optimization, are named as AIGRT plans.
3.2.4 Treatment plan comparison

In order to assess the efficacy of our AIGRT concept, delivered plans are compared based on the IGRT techniques applied: (1) soft-tissue based re-positioning of all fractions (referred to as Soft-Plan technique); (2) re-optimization of all fractions (referred to as Re-Plan technique) and; (3) the AIGRT technique. The dose distributions and DVHs of the daily CTV, bladder, and rectum for these techniques were calculated and compared.

The target coverage evaluations are based on directly comparing the minimal dose to the hottest 99% target volume (D99%) among three techniques. Such comparisons are performed for CTV (prostate and SV) and for seminal vesicles (SV) alone to assess the performance of these three techniques for different parts of the target.

To evaluate dose delivered to the OARs, volumes that receive 100% prescription dose (V100%) and 65% prescription dose (V65%) are calculated for the bladder and the rectum. Deviation from V100%/V65% of the daily re-optimized plan (Re-Plan plan) is chosen as the evaluation parameter to represent the performance of a plan in achieving OAR sparing for daily anatomy, against the Re-Plan plans which are the most-conformal to daily anatomy. Histogram of such deviations was generated for comparison.

Recently published multi-institution study by Michalski et al. has shown that the volumes of rectum receiving 70 Gy (V70Gy) reported from multiple centers converge at about 20%, indicating that V70Gy at 20% is the likely threshold for late rectal toxicity.
(Michalski et al., 2010). Therefore in this paper, the V70Gy of rectum is specifically compared among three techniques to evaluate the performance as an index of rectal toxicity. Since our original CT plan was based on a prescription dose of 76 Gy with 2 Gy per fraction, 70 Gy translates into 92% prescription dose, which is used to calculate V70Gy in plan DVHs.

The OARs’ V100%/V65%/V70Gy comparison is performed by calculating the difference between the daily V100%/V65%/V70Gy at evaluation, either from Soft-Plan or AIGRT, and the gold standard values from the daily Re-Plan for that particular fraction. The differences of the total 180 cases are then binned into histograms, which are compared between Soft-Plan and AIGRT. By always setting the reference at the optimal V100%/V65%/V70Gy for the particular daily anatomy at evaluation, the influence by the daily variance of OARs’ shapes and position is removed.

For a particular fraction of treatment, if our AIGRT algorithm does not select re-positioning technique, it suggests that no plan in the patient-specific plan pool is capable of providing satisfactory coverage for the daily target volume, and plan re-optimization is needed. The re-optimization produces the most conformal daily plans; however, it requires additional efforts, e.g. quality assurance and plan approval, to the clinical flow. On the other hand, re-using previously delivered plans will have minimal impact on the current clinical flow and is therefore preferred in terms of efficiency. AIGRT improves the efficiency of plan adaptation by re-using existing plans and reducing the number of
fractions that would otherwise require re-optimization to achieve conformal daily treatment. The effectiveness of AIGRT on improving efficiency is evaluated by comparing the number of fractions requiring re-optimization to the total number of fractions requiring adaptation (re-positioning or re-planning). If AIGRT is able to reduce the frequency of re-optimization in the total number of adapted fractions, implementing AIGRT is beneficial in terms of efficiency.

3.3 Results and Discussion

3.3.1 CTV coverage

Figure 9 shows the comparison between mean target DVHs of all 180 plans with standard deviation for three techniques. Only Soft-Plan is observed to have underdosed CTV and SV region. Quantitative analyses are presented below.
Figure 9: Mean DVHs and standard deviation of CTV (a) and SV (b) of all 180 plans. Red bar, blue bar with arrow and green bar with flat cap show the standard deviation of Soft-Plan, Re-Plan and AIGRT DVHs, respectively.

The mean and range of the daily D99% to the CTV of each patient are plotted in Figure 10a. The ranges of 18 patients' mean D99% are: (100.3%-104.1%), (95.2%-104.1%) and (100.0%-104.1%) for the Re-Plan plans, the Soft-Plan plans and the AIGRT plans,
respectively. For the total 180 plans, the ranges of daily D99% of all patients/fractions are: (99.6%-105.1%), (57.8%-104.1%) and (98.7%-104.7%) for the Re-Plan plans, the Soft-Plan plans and the AIGRT plans, respectively. The smaller ranges of daily D99% of AIGRT plans demonstrate highly uniform CTV coverage throughout the treatment fractions for all patients. The consistency of uniform CTV coverage of AIGRT plans is comparable to that of the Re-Plan technique, i.e. the Gold Standard. However, in Soft-Plan plans, large variations in daily CTV dose, i.e. CTV underdosage, is seen for some patients.
Figure 10: D99% of CTV (a) and SV (b) plotted for 18 patients. Markers show the mean value of D99s of all fractions for each patient; bars show the range of D99% for each individual patient.
In addition, D99% of seminal vesicle (SV) was calculated separately to assess
dosimetric coverage of this particular target region. As shown in Figure 10b, the pattern
of D99% variation is similar between CTV and SV for each patient, and the ranges of 18
patients’ mean D99% are: Re-Plan (100.6%-103.9%), Soft-Plan (91.4%-103.9%) and AIGRT
(100.1%-103.9%). For the total 180 plans, the ranges of daily D99% of all
patients/fractions are: Re-Plan (100.0%-105.0%), Soft-Plan (52.31%-104.1%) and AIGRT
(98.3%-105.0%), respectively. Similar to the CTV coverage results, D99% of SV reveals
that AIGRT and Re-Plan are able to delivery uniform dose to the SV throughout the
entire treatment, while Soft-Plan frequently fails to do so.

Statistics in table 1 on D99% for CTV support the indication that AIGRT provides
reliable target coverage (D99% ≥ 98% Prescription) for all patients, as does Re-Plan. On
the contrary, Soft-Plan plans are prone to target underdosage for both CTV and SV.
Table 1 shows the number of plans fails to provide sufficient coverage, i.e. D99% < 98%
prescription dose, for the three techniques. Soft-Plan has 25 and 44 out of 180 plans with
D99% < 98% for CTV and SV respectively, whereas no plan with insufficient coverage to
CTV or SV was seen using Re-Plan or AIGRT.

<table>
<thead>
<tr>
<th>Technique:</th>
<th>Soft-Plan</th>
<th>Re-Plan</th>
<th>AIGRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of plans</td>
<td>180</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td># of plans with D99% &lt; 98% for CTV</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># of plans with D99% &lt; 98% for SV</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
For the 18 patients in this study, seminal vesicles are often under-dosed with current soft-tissue matching technology, due to their displacement caused by bladder and rectum volume changes. As shown Table 1, 44 out of 180 Soft-Plan plans have D99% < 98% prescription dose when SV is evaluated separately, compared to 25 out of 180 if the entire CTV (prostate + SV) is evaluated. This result indicates that the SV part of the CTV is prone to more frequent under-dosage in Soft-Plan plans. With AIGRT technique, uniform daily coverage to the prostate and the seminal vesicles are achieved. Figure 11 shows an example of significant CTV shape change due to displaced seminal vesicles. Soft-Plan fails to provide coverage for the upper part of daily CTV, i.e. seminal vesicles region, whereas AIGRT selects a previous delivered plan that sufficiently covers the daily CTV, although its rectum sparing is slightly inferior compared to Re-Plan.
Figure 11: Plan comparison between Soft-Plan, AIGRT and Re-Plan for OARs sparing in an example case where daily CTV is significantly deformed compared to that in Original CT plan. Soft-Plan plan is generated by shifting the Original CT plan to match soft tissues in daily CBCT image. AIGRT plan is selected by our algorithm from previous plan library. Re-Plan plan is generated by complete re-optimization based on CBCT image. Isodose lines on Soft-Plan, Re-Plan and AIGRT are calculated for each plan using same CBCT image set.

### 3.3.2 OAR sparing

Figure 12 shows the mean OAR DVHs of all 180 plans for three techniques.

*AIGRT* has shown to have lower mean DVH and smaller standard deviation compared to *Soft-Plan*, for both organs. Quantitative analyses are presented below.
Figure 12: Mean DVHs and standard deviation of the bladder (a) and the rectum (b) of all 180 plans. Red bar, blue bar with arrow and green bar with flat cap show the standard deviation of Soft-Plan, Re-Plan and AIGRT DVHs, respectively.

Table 2 shows the averages and ranges of V100%/V65% of the bladder and the rectum, as well as the relative/absolute V70Gy volumes for the rectum. On average, AIGRT plans feature smaller high dose volume (V100%) and median dose volume.
(V65%) to the bladder and the rectum, in comparison with soft-tissue matching, as most of the highest values highlighted in red are found with Soft-Plan plans. Similar to V100%/V65%, the average rectum V70Gy are lower for AIGRT plans than for Soft-Plan plans, by 2.8% or 3.1 cc. The relative V70Gy for Re-Plan plans and AIGRT plans are 15.3% and 19.1%, respectively; whereas for Soft-Plan plans, the average is 21.9%, indicating Soft-Plan has slightly higher V70Gy compared to AIGRT, although the difference might not be clinically significant. In addition to the averaged values, Soft-Plan plans exhibit larger standard deviations and ranges compared to the Re-Plan and the AIGRT plans, indicating larger variance of daily dose to OARs for some patients.

Table 2: OAR sparing. Mean values and ranges are shown for daily V100%, V65% of bladder and rectum and relative/absolute V70Gy for rectum, for all 180 plans generated by three techniques: Re-Plan, Soft-Plan and AIGRT. Highest values in average and upper range among three techniques are highlighted in bold red.

<table>
<thead>
<tr>
<th></th>
<th>Re-Plan</th>
<th>Soft-Plan</th>
<th>AIGRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bladder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V100%</td>
<td>11.7±4.2% (3.1%~22.4%)</td>
<td><strong>17.3±8.9% (2.7%~48.8%)</strong></td>
<td>13.6±6.1% (2.5%~32.6%)</td>
</tr>
<tr>
<td>V65%</td>
<td>37.5±11.4% (12.4%~63.7%)</td>
<td><strong>44.7±16.3% (13.0%~84.8%)</strong></td>
<td>39.9±13.5% (12.5%~71.7%)</td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V100%</td>
<td>8.0±2.9% (1.7%~19.3%)</td>
<td><strong>13.7±7.6% (1.1%~34.6%)</strong></td>
<td>11.2±5.5% (1.1%~31.8%)</td>
</tr>
<tr>
<td>V65%</td>
<td>37.1±7.3% (16.1%~54.1%)</td>
<td><strong>45.6±11.0% (15.6%~66.7%)</strong></td>
<td>42.3±9.7% (18.6%~66.7%)</td>
</tr>
<tr>
<td>V70Gy (Per.)</td>
<td>15.3±4.2% (5.3%~29.6%)</td>
<td><strong>21.9±8.9% (3.5%~42.8%)</strong></td>
<td>19.1±6.8% (4.2%~40.9%)</td>
</tr>
<tr>
<td>V70Gy (Abs.)</td>
<td>12.7±6.5cc (2.8cc~31.9cc)</td>
<td><strong>18.7±13.0cc (2.4cc~71.0cc)</strong></td>
<td>15.6±8.6cc (3.0cc~50.0cc)</td>
</tr>
</tbody>
</table>
Figure 13 evaluates the AIGRT technique over soft-tissue matching for OAR sparing. In this comparison, re-optimized (Re-Plan) plans based on daily anatomy are used as reference since they are the most conformal plans for the daily structures. If a plan, either Soft-Plan or AIGRT, provides the same level of OAR sparing, i.e. the same V100%/V65%/V70Gy as Re-Plan, the deviation would be centered at zero. The deviations in V100%/V65%/V70Gy may be due to daily variations of OARs’ position, volume, shape, or the combination of these factors. Negative variations imply lower OAR volumes receiving V100%/V65%/V70Gy compared to the most-conformal daily Re-Plan, i.e. better OAR sparing, whereas positive variations imply increased OAR volumes receiving high V100%/V65%/V70Gy, i.e. worse OAR sparing, relative to daily Re-Plan.

As seen in Figure 13 (a)–(f), the histograms for Soft-Plan are skewed toward the positive side and have more spread compared to those for AIGRT, indicating higher dose to OARs in average and larger variations from reference plans. In the meantime, less positive variations of daily V100%/V65%/V70Gy are seen for AIGRT, compared with data from Soft-Plan, suggesting that AIGRT technique reduces the frequency and severity of over-dosing OARs. Overall, our results on OAR dose-volume analysis indicate that AIGRT generally provides better daily OAR sparing throughout treatment courses.
Figure 13: Histograms of the variations from the most-conformal Re-Plan for (a) Bladder V100%, (b) Rectum V100%, (c) Bladder V65%, (d) Rectum 65%, (e) Rectum V70Gy in absolute volume cc, and (f) Rectum V70Gy in % volume. Green dotted bar: AIGRT; red shaded bar: Soft-Plan. For each labeled value on the horizontal axis, the corresponding bin extends to ±2.5% or ±2.5 cc from that value.
Results shown in Table 2 and Figure 13 indicate that the advantage of AIGRT over Soft-Plan is not confined in CTV coverage. AIGRT plans achieve better OAR sparing in comparison with Soft-Plan plans. For the example shown in Figure 11, in the Soft-Plan plan, due to the changes of the bladder (green contour) and rectum (yellow contour), large volumes of these two OARs are included in 100% isodose lines. In the Re-Plan plan, such shift and deformation are fully compensated by complete re-optimization, and OARs are best spared. In AIGRT plan, although no new plan was generated, OARs sparing is significantly improved compared to that in the Soft-Plan plan.

In Figure 11, AIGRT and Soft-Plan are compared against most-conformal Re-Plans. Ideally Re-Plans should represent the best CTV coverage and OAR sparing. However, frequencies shown on the negative part of the horizontal axis indicate that for some fractions, Soft-Plan achieves lower V100%/V65%/V70Gy, i.e. better OAR sparing, than the reference Re-Plan technique. Analysis shows small fraction (~13%) of Soft-Plan plan achieves lower V100%/V65%/V70Gy than Re-Plan and AIGRT technique. It needs to be cautioned that such cases are often associated with target (CTV) being underdosed, i.e. the false sparing of OAR at the cost of compromised CTV coverage, as shown in Figure 14a. The majority of AIGRT plans feature better CTV coverage, comparable to Soft-Plan plans (as illustrated in Figure 2), as well as lower high/median dose to bladder and/or rectum, as shown in Figure 14b.
Figure 14: (a) One example case showing false OAR sparing associated with CTV underdose (D99% = 92% Rx) in Soft-Plan. AIGRT and Re-Plan DVHs are close to each other for both CTV and OARs. (b) The representative of majority plans: AIGRT provides CTV coverage very close to Re-Plan, yet still spares bladder and rectum more than Soft-Plan.

3.3.3 The efficiency of AIGRT

Figure 15 illustrates the efficiency of AIGRT implementation on reducing the frequency of re-optimization. Total length of red and blue bars shows the percentage of
fractions requiring plan adaptation for each patient, either through re-positioning the previous daily plan or daily re-optimization. For patient #4 and #9, Original CT plan is capable of providing satisfactory coverage over all fractions, so no plan adaptation is needed. The blue bar corresponds to the actual frequency of re-optimization (re-planning) and the red bar corresponds to the opportunity of re-using the previously daily plans via re-positioning in the AIGRT technique. Therefore, the red bars also indicate that AIGRT technique significantly lowered the re-planning frequency by (43±23) % across all patients, which gives AIGRT the advantage in efficiency, as it tries to remove the redundancy of re-optimization for similar geometry change or deformation by re-using the plans in the patient-specific plan pool.
Figure 15: Frequency reduction on re-planning with AIGRT. Total length of red and blue bars shows the frequency of plan adaptation for each patient. Blue bars show the actual frequency of re-planning in a treatment course, and red bars show the reduction on re-planning frequency due to the re-use of previous daily plans in the AIGRT technique. For patient # 4 and # 9, Original CT plan is capable to provide satisfactory coverage over all fractions, so no plan adaptation is needed.

Additionally, the efficiency of implementing AIGRT can be assessed by the percentage of patients requiring re-optimization for a given fraction. Figure 16 illustrates the reduction of need to re-plan a patient as fraction number increases. At the end of the 10-fraction, only ~10% patients need re-optimization to ensure complete CTV coverage, the rest can be treated with existing plans selected by AIGRT algorithm. Similarly, Yan et al. found that using bounding volume of CTVs over first 10 fractions as planning volume is sufficient to provide reliable CTV coverage in subsequent fractions (Yan et al.,
Therefore, we believe the similar efficiency benefit could also be expected when implementing AIGRT in a conventional 38-fraction IMRT.

![Figure 16: Percentage of patients treated with same-day re-optimized plan for a particular fraction number from 1 to 10.](image)

**Figure 16**: Percentage of patients treated with same-day re-optimized plan for a particular fraction number from 1 to 10.

### 3.3.4 Further Discussions

The results of this study suggest AIGRT technique provides higher quality for target coverage and better OAR sparing compared with the soft-tissue based re-positioning technique. Daily target dose, D99%, of AIGRT plans is very unlikely to fall below clinical dosimetric requirement, making it highly comparable to complete re-planning and substantially better than currently soft-tissue matching technique. In addition, the AIGRT technique significantly reduces the frequency of re-optimization required to provide complete daily target coverage, therefore improves the overall
efficiency of plan adaptation. In this study, uniform 5 mm CTV to PTV margin is used for both original CT plans and Re-Plan plans. If a different margin is used, the frequency of necessary re-optimization would change, e.g. larger margin would allow more daily CTV to be encapsulated by previous PTVs at the cost of possibly less OAR sparing, and vice versa. Future studies would include investigations on possible margin reduction or non-uniform margin design that may be better suited for this implementation scheme.

The dose calculations for daily plans are based on the corresponding CBCT images. Due to the difference in the CT numbers between CBCT and CT images (Yoo and Yin, 2006), dose calculation uncertainty may rise, especially from the inhomogeneity correction process (Papanikolaou et al., 2004). However, according to a previous study at our institution, such uncertainty is relatively small: the MU/cGy differences for most phantom cases were less than 1%, and the isodose lines from calculations on two modalities agree well (Yoo and Yin, 2006). Yang et al also reported that dose calculated on CBCT agrees with the planning CT to within 1%, and concluded that CBCT can be directly used in dose calculation in prostate site (Yang et al., 2007). Therefore in this study, the uncertainty associated with calculating dose on CBCT image set is assumed to be small. For dosimetric evaluation, the dose distributions for the three techniques are calculated on the same image set of each fraction, therefore the uncertainty is consistent for all techniques and its influence is effectively removed when the DVHs are compared in parallel. Further, changes in the rectal gas fillings could also affect the dose
distribution due to the heterogeneity of electron densities, which currently is only considered in the daily dose calculation process, not the plan selection process. In future work attention should be given to dramatic bladder/rectum filling variations during the plan selection process.

In this feasibility study, the QA process for re-optimized plans in AIGRT scheme in Figure 8 is only included for the completeness of the proposed clinical flow and not thoroughly investigated. To suite the clinical implementation of AIGRT, the desired QA technique would be efficient and automatic, allowing to be performed with patient on the table.

This study focuses on the overall design of the clinical implementation scheme that takes advantages of combining re-positioning and re-optimization techniques to fulfill different clinical needs on daily basis, and shows that the AIGRT scheme can be beneficial for both the dosimetry and efficiency. In this part of the project, the time management for each component in AIGRT, i.e. contouring, plan selection, re-optimization, and QA, is not considered at this proof-of-concept stage; however the full clinical implementation of AIGRT indeed requires each component in the AIGRT to be accomplished in a timely manner. The efficiency of re-optimization and development of QA methods are addressed in the following chapters.
3.4 Conclusion

The online ART technique (AIGRT) combining re-positioning and re-optimization was compared against current soft-tissue matching technique and re-optimization technique for 18 patients. Results demonstrated that it is beneficial to implement such a technique clinically. For target coverage, AIGRT achieves highly uniform CTV coverage comparable to Re-Plan throughout the simulated treatment course, but requires significantly fewer re-optimization processes. At the meantime, OAR sparing is improved over Soft-Plan, although not identical to Re-Plan. As a proof-of-concept, this technique improves the overall efficiency of plan adaptation and has the potential of being integrated into clinical flow. Thus, AIGRT can be a valuable and efficient technique for image-guided prostate radiotherapy with precise daily dose delivery. If the plan selection algorithm is integrated into the commercial treatment planning system, the AIGRT technique will be easily implementable into the clinical workflow.
4. Strategies for automatic online treatment plan re-optimization using clinical treatment planning system: a planning parameters study

4.1 Introduction

In Chapter 3 a novel scheme for the clinical implementation of online ART for prostate cancer has been developed and evaluated. It is shown this scheme is capable of providing reliable target coverage and improved OAR sparing with significantly reduced re-optimization necessity. However, for those fractions that does require online re-optimizations, it is essential to perform such a complicated task in a fast, automatic and robust manner based on daily anatomical structures acquired prior to the treatment.

Several research groups have developed such algorithms that aim for fast online adaptation/re-optimization. Mohan et al. (Mohan et al., 2005) developed an online adaptation technique that deforms 2D intensity maps according to the geometric relationship between the intensity maps and projected anatomy in beams-eye-view (BEV), and found that it provided adapted plans that approximate well with the fully-fledged re-planning in a rapid manner. Fu et al. (Fu et al., 2009) also looked at BEV anatomical structure projections and developed a MLC leaf-position modification technique with dosimetric benefits and increased speed. Feng et al. (Feng et al., 2006) reported an online plan adaptation technique (Direct-Aperture-Deformation) that morphs the treatment apertures based on the deformable registration between planning and daily images. These techniques adjusted the original fluence map or aperture based
on daily anatomy, but did not involve plan re-optimization. Ahunbay et al. (Ahunbay et al., 2010a) developed a two-step “SAM+SWO” online re-optimization technique that optimizes the MLC shape and the beams MU separately. This process can be finished within 5 min but is not applicable to fluence-based optimization and dynamic MLC delivery. New development in GPU-accelerated computing enables performing full direct-aperture optimization within 4s, as demonstrated by Men et al. (Men et al., 2010) We have previously developed and evaluated a proof-of-concept system with full volumetric online re-optimization algorithm combining deformable registration between planning and daily images and linear goal programming optimization using CPLEX (IBM ILOG, Armonk, NY) (Wu et al., 2008), which significantly improved the target coverage and OAR sparing with less than 2 minutes of optimization time (Thongphiew et al., 2009). To facilitate clinical implementation of fast online plan re-optimization, the final adapted plan needs to be re-optimized on an FDA-approved commercial treatment planning system (TPS). In this study, the Eclipse™ (Varian Medical Systems, Palo Alto, CA) TPS was used.

A normal IMRT treatment planning process in general includes structure contouring, beam angle and isocenter selection, iterative fluence map optimization, and dose calculation. Different from a fully-fledged IMRT planning, the online re-optimization only redesigns the fluence maps of individual beams, and keeps the rest beam parameters, e.g. beam angle, energy, the same as the original plan. Therefore in
online re-optimization scenarios, the primary planning input parameters are limited to
the DVH objectives for anatomical structures, optimization starting stages, and iteration
numbers, which are the primary focus of this study. Based on these input parameters,
the Eclipse™ TPS will first call the Dose Volume Optimizer™ to iteratively solve for an
optimal set of 2D fluence maps using DVH-based objective functions and a gradient
method(Fogliata et al., 2007; Varian Medical Systems, 2008). The typical iteration number
for this particular optimizer to converge for prostate cases is ~75. This number might
change with improved optimization methods in the future, and will be different in TPS’
by other vendors. Once a satisfactory set of fluence map is reached, the Leaf Motion
Calculator will be called to generate leaf motions that will deliver a certain fluence map
based on the physical properties of the Multi-Leaf Collimator (MLC) used on a specific
treatment machine(Varian Medical Systems, 2008). This leaf motion will then be
executed by the treatment machine to deliver the planned dose.

Currently the efficiency of plan optimization is partially limited by the trial-and-
error process, during which the planner manually adjusts the optimization objectives
back and forth on the fly, to achieve complete target coverage and at the same time spare
critical structures as much as possible. Although manually adjusting optimization
parameters by the planner has the potential to offer good plan quality, this trial-and-
error process is time-consuming: a manual prostate IMRT planning normally takes 15-30
min to finish, which makes the current plan optimization strategy impractical for online
re-optimization application. In addition, the plan quality using this manual adjustment strategy is highly dependent on the experience of the planner, which could vary between different planners (Nelms et al., 2012).

To achieve online re-optimization with a fluence-map-based TPS, the process needs to be automated and completed within a reasonably short time. To achieve this, the DVH objectives and starting stages need to be automatically determined before entering the optimization. The iteration number should be fixed to ensure convergence and time efficiency. This also eliminates the time-consuming trial-and-error process while requiring minimal change to the current clinical flow, by making the initial inputs, or strategies, for the re-optimization critically important.

The purpose of this study is to investigate the feasibility and strategy for online plan re-optimization to be automatically executed within ~2 min, while providing consistently high target conformity and controlled OAR sparing. The study explores different options for DVH objective settings, starting stage and iteration number in the context of fast online plan re-optimization and demonstrates how these factors contribute to the outcome of the online optimization.

The hypotheses are that (1) the full target coverage can be retained with ~2 min re-optimization; and that (2) objectives containing patient-specific and daily anatomical information offers benefit to OAR sparing.
4.2 Materials and methods

4.2.1 Materials

The data used in this retrospective IRB-approved study was obtained from 10 patients with intermediate-risk prostate cancer. Each patient had one planning CT volume dataset, taken on the simulation day prior to treatment. In addition, each patient also had 5 daily cone-beam CT (CBCT) images obtained during the first week of radiotherapy. Planning target volume (PTV) was defined as CTV plus a 5 mm uniform margin. The initial IMRT plan, referred to as the Original CT plan, was manually optimized using seven co-planar 15MV beams. The plans were normalized so that 100% of the prescription dose covered at least 95% of the planning target volume (PTV).

The 5 CBCT image sets were used to simulate the first week of adaptive treatment. For each daily CBCT, structures including the CTV, the bladder and the rectum were contoured by the same attending physician to ensure consistency.

4.2.2 Re-optimization strategies

During the optimization, the optimizer iteratively minimized the objective function based on 4 key input variables: patient’s anatomical structures-of-interest (including the PTV, the bladder and the rectum), DVH objectives for these structures, starting fluence map and iteration number limit. For online ART application, patient anatomy is a given input, and the iteration number is limited to 50 or 100 iterations, based on the observation that the global objective function reaches plateau in less than
100 iterations. The time required for 100 iterations with our particular setup is \( \sim 2.5 \) min, which fits our expectation on the speed of online re-optimization. The DVH objective and starting fluence map can be specified by the planner and are therefore key parameters of this study. The choice of different options for objective settings and starting stages are built on the idea that these input parameters should be easily obtainable to achieve high efficiency, but also capable of bringing daily anatomy information when needed. Based on this idea, the following options for objective settings and starting stages were obtained, tested and evaluated.

4.2.2.1 Objective setting

On each day of simulated treatment, the plan was re-optimized using the anatomy-of-the-day. The optimization objective for the target was maintained the same for all fractions to offer consistent target coverage: at least 99\% prescription dose (Rx) delivered to 95\% of PTV; at least 98\% Rx delivered to 100\% PTV; no more than 3\% of PTV receives \( > 101\% \) Rx; and PTV hotspot was limited to 102\% Rx.

For OARs, three different sets of objectives were explored in this study for re-optimization, as shown in Figure 17:
**Figure 17: Flowchart of how three sets of objectives are generated based on increasing level of customization.**

RTOG objectives (R), adopted from RTOG protocols (RTOG, 2012b). It is important to note that the DVH objectives were not iteratively adjusted during the optimization process in the context of fast online re-optimization, even though that is what is typically performed during original treatment planning.

CT objectives (C), which were extracted from the Original CT plan DVHs, and thus took into account the original anatomy of a particular patient that was presented on the original planning CT. The volume objectives were sampled at 20%, 40%, 60%, 80%, and 100% of the prescription dose of the Original CT plan DVHs. An additional constraint at 102% Rx was added to control hotspot.

Deformed-CT objectives (D), which were extracted from the DVH of the goal dose distribution for a particular fraction. To generate this goal dose distribution,
deformable registration was first performed between the structures on the planning-CT and the daily-CBCT images using VelocityAI software (Velocity Medical Solutions, Atlanta, GA). This “artificial” dose is referred to as the *goal dose* in this study, and was used to generate the Deformed-CT objectives \(D(Wu et al., 2008)\). Since the deformed dose took into account the daily anatomy, the anatomy variation from the planning CT was inherently reflected in this dose distribution. The deformable registration was firstly evaluated by blended-view comparison methods to ensure reasonable matching between two structure sets. After registration and dose warping, the goal dose is visually inspected by an experience physicist to ensure that it mimics clinically achievable dose distribution, i.e. without unrealistic dose gradient. The goal dose is finally evaluated quantitatively to ensure satisfactory target coverage \((D95\% > 100\%)\) is achieved on the daily anatomy. The goal dose could directly be used in the optimization, which was implemented using linear programming by Wu et al.(Wu et al., 2008). However, to make this concept work in our clinical TPS, consistently with CT objective settings, the 3D goal dose needed to be converted to DVH objectives by sampling the % volumes from the goal DVH at 20\%, 40\%, 60\%, 80\%, and 100\% of the Rx. Similar to CT objectives, an upper constraint at 102\% is added to control hotspots in OARs.

### 4.2.2.2 Starting stages

In addition to objectives, the impact of optimization starting stage and iteration number were also investigated. In this study the starting stage had two options: (i) \(W\),
defined as starting from the original fluence maps in the *Original CT* plan and (ii) WO, defined as the typical starting point for IMRT planning with unit intensity (open beams) in the PTV. It may be intuitive to think that starting with original fluence map will provide a “jump start” for the optimizer and hence better results, but the actual difference between these two starting stages remains to be investigated.

4.2.2.3 Iteration numbers

The iteration number was also divided into two possibilities (i) **50 iterations** and (ii) **100 iterations**. The iteration number is kept low so that the entire optimization process can be finished within ~2 min for online ART purposes. Using our current TPS workstation configuration with 2 Intel Xeon® processors and 24 gigabytes of memory, the optimization time is 1.0 min for 50 iterations, and 2.0 min for 100. Comparison between these two iteration numbers will quantify how much benefit the additional 50 iterations will add to the online re-optimized plan.

In summary, the overall design of the study involved 12 combinations of three input factors, creating a total of 600 re-optimized plans for analysis. The input factors were converted to XML format that can be directly read by the commercial TPS. The re-optimization process include the following steps: (1) duplicating the original CT plan’s beam angles on to a new plan based on daily images; (2) starting a new IMRT optimization with or without original fluence maps; (3) importing DVH objective
template that consists of the input factors; and (4) automatic optimization, followed by
do
calculation and plan normalization.

4.2.3 Dosimetric evaluation and statistical analysis

To evaluate the target coverage quality, the RTOG conformity index ($CI$) was
used. CI is defined as the volume of the target receiving 100% of the prescription dose
divided by the total volume of the target. To evaluate OAR sparing, key DVH
parameters were extracted from the online re-optimized plans. These parameters
included the volume of the bladder receiving at least 50% of the dose ($Bladder\ V_{50\%}$), the
volume of the rectum receiving at least 50% of the dose ($Rectum\ V_{50\%}$), the volume of
the bladder receiving 76 Gy ($Bladder\ V_{76\text{ Gy}}$) and the volume of the rectum receiving 70
Gy ($Rectum\ V_{70\text{ Gy}}$)(Michalski et al., 2010). It is important to note that normalized
volumes (%) were used to assess the median dose, whereas absolute volumes (cm$^3$) were
used to assess the high dose regions, such that they will be less influenced by the
volume of the daily OAR fluctuation.

In this study, different sets of plans were created using different combinations of
three factors (planning parameters): objective settings, starting states and iteration
number. In order to understand how these three variables affect the DVH of the online
re-optimized plan (i.e. independently or jointly), a three-way factorial Analysis of
Variance (ANOVA) was performed. This three-way factorial ANOVA helps to
determine the most important contributing factors and their combinations that will
result in an optimal and efficient treatment plan re-optimization. In this study there were three options for objective settings, two options for starting stages and two options of iteration number, resulting in twelve total combinations. Therefore the factorial ANOVA model for the purpose of this study was defined as follows:

\[ y_{ijkl} = \mu + \alpha_i + \beta_j + \gamma_k + \delta_{ij} + \epsilon_{jk} + \varepsilon_{ik} + \rho_{ijk} + \epsilon_{ijkl} \]

where \( y_{ijkl} \) is an evaluation parameter of the \( l \)th patient in the \( i \)th objective group, \( j \)th starting fluence group and \( k \)th iteration number group, \( \mu \) represents the underlying mean of all 12 groups of the re-optimized plans taken together; \( \alpha_i \), \( \beta_j \), \( \gamma_k \) represents the effect of the three factors (objective settings, starting stages and iteration number) alone, respectively. \( \delta_{ij} \), \( \varepsilon_{jk} \) and \( \varepsilon_{ik} \) represent the interaction between any two of the three factors; \( \rho_{ijk} \) represents the three-way interactions from all three factors, and finally \( \varepsilon_{ijkl} \) is an error term. To determine the significant parameters and interactions, F-tests were performed for both main and interaction effects with JMP statistical software (SAS Institute Inc. Cary, NC). A \( p \)-value of less than 0.05 indicated significance of a particular factor/interaction at test.

Upon determining the significant factors in the ANOVA model, the options for each factor were explored by comparing aforementioned dosimetric parameters among plans created using each option. In addition to such comparisons, regression analyses were also performed between OAR volumes in the high dose region (i.e. Bladder V76Gy and Rectum V70Gy) and the ratio between daily and planning OAR volume. These
regression analyses answer the question of whether the Deformed-CT objectives would perform better than CT objectives for large changes in volume during the course of treatment. If such a trend does exist, then it would allow us to make different recommendations according to daily OAR volumes. For simplicity, linear regression was used in the analysis, also performed with JMP statistical software.

4.2.4 Delivery efficiency analysis

The plan delivery efficiency was evaluated by the total monitor units (MUs) of all treatment fields for a re-optimized plan under a specific set of optimization option. Since the same prescription dose and dose rate are maintained, a larger total MU indicates a more complex fluence map and prolonged treatment time. This may also translate into a higher probability of intra-fractional patient motion, higher exposure from scatter and leakage radiation, and slower clinical flow.

4.3 Results and discussions

4.3.1 Incorporating daily anatomy information into the Deformed-CT objectives

An example case of a daily goal dose generated from deformable registration is shown in Figure 18. In this case, the significant enlargement of daily rectum compared to the planning rectum has pushed the seminal vesicle region away from planning CT positions. Both the target and the OAR are significantly changed in shape and position, which is evident from the disagreement between the planning dose and daily structure seen in the middle column of Figure 18 with the dose distribution overlaying on the
anatomy using rigid target alignment. In the right column, the deformed planning dose conforms to the changed anatomy because the deformation fields transfer the dose changes accordingly with the anatomical changes. This example demonstrates the effectiveness of generating daily goal dose via deformable registration.

Figure 18: Illustration of the daily goal dose generated via deformable registration. Left column shows the original plan dose on planning CT structures. Middle column shows the dose distribution of original plan on the daily anatomy with rigid registration. Right column shows the original dose propagated to the daily anatomy via deformable registration. White arrows point out that the deformed dose conforms to the daily target very well. Contours: white-PTV, green-bladder, yellow-rectum.

4.3.2 Daily target coverage

Figure 19 demonstrates the daily target coverage result of all 600 re-optimized plans in this study. The histogram of daily D99%, i.e. minimal dose to the hottest 99% of the CTV, shows that all re-optimized plans have D99% within 100% and 105% prescription dose, suggesting that regardless of optimization strategy, the re-
optimization provides excellent target coverage for all fractions/patients. This finding is in accordance with the consistent target objectives used for all plans, and further demonstrates the feasibility of restoring daily target coverage within ~2 min fast re-optimization.

![Histogram of daily CTV D99%](image)

**Figure 19:** Histogram of daily CTV D99% (minimal dose to the hottest 99% of the CTV) of all 600 re-optimized plans created in this study.

### 4.3.3 Effect of three optimization factors on dosimetric parameters

Table 3 shows the F-statistics and p-values of the 3-way ANOVA with full factorial design on the six dosimetric parameters: CI, Global Hotspot, Bladder Mid-Dose, Rectum Mid-Dose, Bladder High-Dose, Rectum High-Dose, as well as one delivery efficiency parameter Total MU. The model provides statistically significant fitting effects \((p < 0.05)\) for all parameters except for the rectum in the high dose region \((p = 0.1194)\).
However, because the high dose region of rectum is of primary interest to us, we continued to include this parameter in our analyses.

### Table 3: Global fitting and F-test results for each evaluation variables on the whole 3-way factorial model.

<table>
<thead>
<tr>
<th></th>
<th>Target Bladder</th>
<th>Rectum</th>
<th>Global Hotspot</th>
<th>Delivery Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI</td>
<td>Mid-Dose</td>
<td>High-Dose</td>
<td>Mid-Dose</td>
</tr>
<tr>
<td><strong>F statistics</strong></td>
<td>7.1121</td>
<td>9.2337</td>
<td>1.8179</td>
<td>67.5175</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.048</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

This section presents whether a joint effect of the three main factors should be considered. Table 4 shows the *p*-values for the effect of each factor on a particular dosimetric parameter (i.e. objective, start and iteration alone), as well as the two-way and three-way interaction of factors. The shade-coding indicates the level of statistical significance of a particular effect. Generally, main effects, i.e. objective, start and iteration independently, have significant effects, as illustrated by the majority of cells having a *p*-value less than 0.05 (lighter shading). However, two-way and three-way interaction of factors generally demonstrate insignificant *p*-values, shown by the dark shading on the majority of cells, with the exception of the two-way interaction between objective and starting stage for the rectum median dose volume. Based on these results, it is reasonable to assume a simplified model consisting of only three isolated factors and neglecting two-way and three-way interactions. In this way, the plans generated with different combinations of factors can be separated according to objectives, starting stages and iteration numbers, and then independently analyzed and compared. The
optimal strategy of re-optimization is then simply the combination of the three best options for each factor.

Table 4: Effect tests result for all three optimization parameters, including stand-alone and interactions of objective, starting stage and iteration. The cells in the table are progressively shaded according to their statistical significance, i.e. the p-values. From top to bottom: individual factor (main effect), two-way interaction, and three-way interaction. Lighter-than-medium shade corresponds to p<0.05, indicating the effect of a certain term in the 3-way factorial ANOVA model is significant.

<table>
<thead>
<tr>
<th></th>
<th>Objective</th>
<th>Start</th>
<th>Iteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>CI</td>
<td>0.1923</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hotspot</td>
<td>D_max</td>
<td>0.0001</td>
<td>0.3372</td>
</tr>
<tr>
<td>Bladder</td>
<td>Mid-Dose (%)</td>
<td>0.0250</td>
<td>0.1911</td>
</tr>
<tr>
<td></td>
<td>High-Dose (cc)</td>
<td>0.0715</td>
<td>0.7706</td>
</tr>
<tr>
<td>Rectum</td>
<td>Mid-Dose (%)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>High-Dose (cc)</td>
<td>0.0715</td>
<td>0.7706</td>
</tr>
<tr>
<td>Delivery Eff.</td>
<td>Total MU</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Obj*Start</th>
<th>Obj*Iter</th>
<th>Start*Iter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>CI</td>
<td>0.3757</td>
<td>0.6638</td>
</tr>
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<td>Hotspot</td>
<td>D_max</td>
<td>0.2448</td>
<td>0.9689</td>
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<td>Bladder</td>
<td>Mid-Dose (%)</td>
<td>0.1411</td>
<td>0.7415</td>
</tr>
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<td></td>
<td>High-Dose (cc)</td>
<td>0.9716</td>
<td>0.9908</td>
</tr>
<tr>
<td>Rectum</td>
<td>Mid-Dose (%)</td>
<td>0.0001</td>
<td>0.1106</td>
</tr>
<tr>
<td></td>
<td>High-Dose (cc)</td>
<td>0.9547</td>
<td>0.9293</td>
</tr>
<tr>
<td>Delivery Eff.</td>
<td>Total MU</td>
<td>0.0001</td>
<td>0.0604</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Obj<em>Start</em>Iter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>CI</td>
</tr>
<tr>
<td>Hotspot</td>
<td>D_max</td>
</tr>
<tr>
<td>Bladder</td>
<td>Mid-Dose (%)</td>
</tr>
<tr>
<td></td>
<td>High-Dose (cc)</td>
</tr>
<tr>
<td>Rectum</td>
<td>Mid-Dose (%)</td>
</tr>
<tr>
<td></td>
<td>High-Dose (cc)</td>
</tr>
<tr>
<td>Delivery Eff.</td>
<td>Total MU</td>
</tr>
</tbody>
</table>

Colorbar p-value: < 0.0001 to 0.5
Figure 20: Comparison of boxplots, mean diamonds and histograms of (a) three objectives for different dosimetric parameters. C: CT objectives, D: Deformed-CT objectives, R: RTOG objectives; (b) two starting stages for different dosimetric parameters. W: starting with original intensity map; WO: starting without original intensity map, from unity fluence; and (c) two iteration numbers, 50 and 100, for different dosimetric parameters. Green diamonds indicate one-way ANOVA result: if two diamonds do not overlap vertically, then the two groups are significantly different from each other, and vice versa.
4.3.4 Optimal dosimetric options per input factor

Figure 20(a) shows the dosimetric comparisons between plans generated using the 3 different objective settings: C, D, and R, short for CT, Deformed-CT and RTOG, respectively. Across all dosimetric parameters it is evident that at least one of the mean diamonds (green diamonds superimposed with boxplots) of C, D or R does not overlap with the other two, indicating that the means of C, D, and R plans are significantly different from each other ($p < 0.05$). Qualitative comparison can also be made from boxplots and histogram comparisons. For CI, the three sets of objectives perform similarly. R has lower global hotspots compared to C and D, which is the result of less necessary modulation to achieve relatively looser objectives. For the mid-dose region in both rectum and bladder, R has the highest mean of all three groups, whereas C and D have means and distributions that are similar to each other. For the high-dose region of both OARs, R still has the highest mean, but C and D objectives perform differently between the bladder and the rectum: C results in a lower mean compared to D for Bladder V76Gy, but results in a higher mean for Rectum V70Gy.

Figure 20(b) next compares the same six dosimetric parameters, but between plans generated using 2 different starting fluence stages: W (from original plan’s fluence) and WO (unit fluence). The mean diamonds of W and WO do not overlap across all parameters, with the exception of rectum V70Gy. This indicates that the mean volumes for CIs, V50% of both OARs and Bladder V76Gy are not equivalent between plans.
generated using the two starting stages. The overlapping mean values for Rectum V70Gy indicates that there is no statistically significant difference between W and WO for this particular parameter. Qualitative comparisons can again be made from boxplots and histogram comparisons. Starting with (W) and without (WO) the original fluence results in similar CI (avg. difference < 0.03) and hotspots (avg. difference < 0.3%). For the median dose of both OARs, W has a lower mean (5% for the bladder and 15% for the rectum) compared to WO, as well as a less skewed distribution. For Bladder V76Gy, W has a slightly higher mean (0.5cc) compared to WO, whereas for Rectum V70Gy, the difference is not statistically significant.

Similar comparisons were made between the effects of two iteration length (100 and 50) on the mean of CI, hotspot, Bladder V50%, Rectum V50%, Bladder V76Gy and Rectum V70Gy. Figure 20(c) displays the mean diamonds, box plots and distributions for the generated plans. The differences between these two groups are statistically significant for all dosimetric parameters, as indicated by non-overlapping green diamonds. For all parameters, plans with 100 iterations result in slightly lower means as compared with 50 iterations. However, the magnitude of differences is very small and the distribution of data in the two groups is very similar.
Table 5 summarizes the results of quantitative comparison between options for each factor, i.e. determining which option is optimal for objectives, starting stage and iteration number. The numbers listed in each cell are the means for a group of plans using a particular option. For dosimetric parameters with difference > 2%/2cc, light-to-dark shades are assigned corresponding to the low-to-high ranking of group means. Pair comparisons that have either no statistical significance or < 2%/2cc difference are assigned with white backgrounds instead of a shaded background. The objectives result in large difference in terms of OAR sparing: CT objectives shows somewhat better OAR sparing in mid-dose volume than Deformed-CT with a mean difference <2.5%. However for the high-dose volumes CT and Deformed-CT objectives perform differently between the bladder and the rectum: CT results in lower mean compared to Deformed-CT for Bladder V76Gy but results in a higher mean for Rectum V70Gy. For starting stage comparison, starting with the Original CT plan fluences (W) demonstrates lower means compared to starting from open beam (WO), primarily in the mid-dose volume of OARs. As for iteration number, the difference between 100 and 50 iterations is in general small across all parameters.
Table 5: Summary of comparison within the three factors of the models (objectives, starting stage and iteration). Numbers shown are the means of each group. Only parameters with a >2%/2cc difference is shown in bold and shaded. Shading corresponds to the ranking of group means: light-to-dark indicating low-to-high in mean values.

<table>
<thead>
<tr>
<th>Objective</th>
<th>CT</th>
<th>Deformed-CT</th>
<th>RTOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>W</td>
<td>WO</td>
<td></td>
</tr>
<tr>
<td>Iteration</td>
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<td></td>
</tr>
<tr>
<td>Ranking</td>
<td></td>
<td>Medium</td>
<td>Low</td>
</tr>
</tbody>
</table>

4.3.5 Objective selection based on daily organ volume variations

Results from Figure 20 and Table 5 show that the preference between C and D is not yet clear from OAR high dose volumes, which is of great importance in preventing complications from radiation. To answer this question, another dimension, the daily-to-planning volume ratio of the two OARs, is added to further break down the data. Figure 21 displays the regression analysis on the OAR high-dose region and daily-to-planning
OAR volume ratio. The horizontal axis is the natural logarithm of the ratio of the daily volume (on CBCT) and the corresponding planning CT volume (quantification of the change in daily OAR volume with respect to the planning CT OAR volume). Natural log was taken to transform the data and give a better linear fit. The vertical axis is the difference in rectum V70Gy and bladder V76Gy between plans generated using objectives C and D per case (quantification of the difference in OAR high-dose volumes between the two objective settings). Positive values on the vertical axis indicate that C irradiates a greater volume of the structure with high dose as compared to D, and is therefore inferior for that particular case. The Pearson’s correlation coefficients ($r$) between C-D differences and natural log of volume ratio are 0.7158 and 0.7075, respectively for bladder V76Gy and rectum V70Gy. ANOVA tests for both regression models show $p$-values < 0.0001, indicating both regression models offer statistically significant predictions on the difference between C and D based on daily volume variation. Therefore, the choice between using C objectives or D objectives should be made based on the volume variation of the daily OAR relative to that in the planning CT.

More specifically, for the rectum, the regression plot demonstrates that D becomes more superior than C when substantial enlargement of the rectum occurs. This is because when the rectum is significantly enlarged, Deformed-CT objectives are more stringent than CT objectives due to the less fractional volume occupied by the high dose region (refer to Figure 18). This daily anatomical feature is then provided to the optimizer via
Deformed-CT objectives instructing it to further reduce irradiated volumes of the rectum. For the bladder, when substantial shrinkage of the bladder occurs, CT objectives are more stringent than Deformed-CT, resulting in lower V76Gy for plans using CT objectives compared to those using Deformed-CT objectives. Although beneficial by looking at the bladder’s V76Gy alone, this extra “push” on the bladder sparing by the over-stringent objectives might not be realistic for the daily anatomy, and could result in trade-offs with the sparing of the other OAR, as shown in the discussions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure21.png}
\caption{Regression analyses on the volume difference between using objectives C and D and the corresponding daily-to-planning-CT OAR volume change. Horizontal axis shows the OAR volume change in natural log scale. Vertical axis shows the difference between C and D in cc: positive value indicates D is better for a particular plan, and negative indicates C is better. Dashed lines are 95% confidence limit of individual predicted values by the fit.}
\end{figure}

Another observation from the regression result is that the two OARs exhibit different trends of volume changes. The rectum volume changes are in general evenly
spread between enlarging and shrinking, however large relative changes are mostly
enlargement rather than shrinkage, as shown by the higher number of dots located > 1
than < -1 on the horizontal axis. The volume changes of bladder however are mostly
shrinkage, as illustrated by the non-symmetric distribution with respect to 0 on the
horizontal axis. Majority of daily bladders shrink compared to the one on the planning
CT. These trend differences between the two OARs are in accordance with our clinical
management instructions. At our institution, the patients are instructed to be treated
with a full bladder and empty rectum. Patients tend to abide by the instructions better at
CT-simulation. During daily treatment, the bladder is more likely to shrink compared to
the full bladder at CT-Sim because of less control of the bladder filling, either caused by
willingness or physiological difficulties in holding a full bladder, or machine delays
causing voiding before treatment. Since the patient comes to the CT-Sim with an empty
rectum, large subsequent changes in rectum volume are more likely to be toward
enlargement due to filling rather than shrinkage, although small changes do occur in
both directions. Figure 22 shows the organ volume variations in greater details.
Figure 22 Organ volume variation for all 10 patients and 5 fractions each. Grey “+” shows the corresponding volume in the planning CT.

An example of the advantage of using Deformed-CT objectives over CT objectives in the presence of a significantly enlarged daily rectum is shown in Figure 23. This is the same case shown in Figure 18, where the daily rectum is significantly larger than the planning rectum. In this case, the CT objectives become excessively loose for the daily anatomy, and therefore result in inferior OAR sparing compared to the Deformed-CT objectives.
Figure 23 Dose comparison between automatically re-optimized plans using CT objectives (left, square) and Deformed-CT objectives (right, triangle). Deformed-CT objectives carry the information of significantly enlarged rectum to the optimizer, and therefore achieved better rectum sparing compared to the CT objectives. This is evident in both DVH and isodose comparisons (white arrows).
4.3.6 Delivery efficiency comparison

Figure 24: Comparison of boxplots, mean diamonds and histograms for delivery efficiency in total MU.

Figure 24 shows the comparison of total MU between different options for three factors. Among different objective settings, RTOG has lower total MU compared to the other two. This is expected since the RTOG objectives are generally loose and therefore require less modulation of the fluence maps, which are also associated with inferior dosimetric performance as seen above. Most worthy of noting is the MU difference between two starting stages, namely with original fluence map (W) and from unit
fluence (WO). It is evident from Figure 24 that re-optimization starting with the original plan’s fluence map (W) has significantly higher total MU compared with those started from open beams (WO). Pair-wise comparison shows an increase of $122 \pm 65$ MU from W to WO with the rest of the conditions being equal. Although W demonstrated some dosimetric advantages in the mid-dose region of OARs, as recalled from Figure 20(b) and Table 5, the increase of MUs is substantial.

**4.3.7 Discussion**

Previously the development of online ART led by X Allen Li (Ahunbay *et al.*, 2010a) using SAM+SWO, and by Lei Dong (Court *et al.*, 2005a) using MLC leaf position shifting both uses segment-based step-and-shoot delivery. This work is developed on a clinical fluence-based treatment planning system, and therefore is a valuable addition to the overall knowledge of online plan re-optimization for ART. It provides a systematic investigation on how input parameters affect the output of online plan re-optimization. Such understanding is important in that it provides necessary information on choosing the optimal combination of parameters for online ART application scenario. The work led by Steve B Jiang utilized GPU-accelerated re-optimization substantially increase the efficiency of both aperture- and fluence-based plan optimization (Men *et al.*, 2009; Men *et al.*, 2010), and will offer further benefit if implemented in our current TPS.

The results of this study provide a deeper understanding on how input parameters affect each dosimetric quantifier separately, so that the clinicians will be
aware of the benefit and trade-offs associated with choosing a specific strategy. In a real clinical situation, the strategy should be determined based on a global picture that balances all dosimetric parameters. Combining all parameters evaluated in this study, for most cases using original CT objectives, starting from unit fluence and limiting the optimization to 50 iterations is in general favored for better balance between quality and delivery efficiency. For cases with larger organ volume change from CT-Sim, Deformed-CT offer extra benefit. It is important to note that there is no globally optimal solution for all cases, and a clinical decision needs to be made on a case-by-case basis, with the help of knowledge presented in this study.

In this study it is assumed that the daily contours are already available within a reasonable time after daily imaging, either by automated segmentation, or propagated via deformable registration. In reality these components takes additional time, and the research community has been actively working on methods to improve the efficiency and effectiveness of these important components other than optimization itself. It has been reported that for prostate cancer online re-planning purposes, delineating prostate, the rectum and the bladder on the daily image set can be achieved within 2 min(Ahunbay et al., 2008). Improvement on these important components, along with the optimal strategies for re-optimization, will eventually make the whole process better suited for clinical workflow.
In this study a 5 mm CTV-to-PTV margin was used for both the Original CT plan and re-optimized plans. Thongphiew et al. (Thongphiew et al., 2009) reported that for prostate + seminal vesicle treatment, 5mm CTV-to-PTV margin combined with daily re-positioning resulted CTV D99 < 98% prescription dose in 14 out of 30 fractions simulated. We have also shown in a previous study (Li et al., 2011) that without online re-optimization and relying only on re-positioning based IGRT, the target coverage of prostate + SV treatment can often be less than adequate, especially for SV. Based on these results, we proposed the online re-optimization technique to regain target coverage. Another benefit of online re-optimization is to help reducing treatment margin, and is currently being investigated. However, it should be noted that even with fully conformal online re-optimized plan, margin is still needed for intrafractional target motion. A study by Melancon et al. (Melancon et al., 2007) using pre- and post-treatment CT-on-rail has shown even with daily re-plan, the margin needed for complete SV coverage should be larger than 3 mm due to intrafractional motion. Based on this recommendation and the tolerance for IGRT system intrinsic position errors, a 5 mm margin for online re-optimization is generous but reasonable. In the meantime, this study investigates the optimization strategy given a defined target, regardless of the margin. Therefore the methods used in this study can be applied to cases with margins other than 5 mm and still help understanding the optimization process. A cumulative dose analysis over the entire treatment course, suggested by several previous studies
(Liang et al., 2009; Liu and Wu, 2011), will further help evaluating the benefit of such re-optimization technique, and is currently being investigated.

This study focuses on the variation between plans generated by different strategies instead of comparing DVH endpoints of each plan itself against clinical standard. However all DVH endpoints values are reported and their distribution presented for the readers. The evaluation on the CTV D99% shows excellent target coverage in all re-optimized plans, which is the primary goal of performing online plan re-optimization. A more detailed evaluation on the plan quality is necessary before applying the re-optimized plans clinically, and physician’s case-by-case evaluation and approval is required before delivery the re-optimized plans. We have proposed a tool to assist this plan quality evaluation process by predicting the achievable DVH using patient anatomical information and machine learning (Zhu et al., 2011), and will continue to evaluate the quality of re-optimized plans both subjectively and objectively.

In this study, the one-fits-all objective was adopted from RTOG guidelines: 15%, 25%, 35%, and 50% of the bladder must receive less than 80 Gy, 75 Gy, 70 Gy, 65 Gy, respectively; and 15%, 25%, 35%, and 50% of the rectum receive less than 75 Gy, 70 Gy, 65 Gy and 60 Gy, respectively. It should be noted that this objective choice was used to provide an institution-independent baseline, instead of representing actual planning objective templates used in the clinic. At our institution the original plans were optimized starting with a more stringent secondary DVH objective set followed by
iterative adjustments to reduce the dose to OARs as much as possible. Since the guideline specifies the minimal OAR sparing required for a plan to qualify for RTOG clinical trials, it represents the minimally acceptable OAR sparing in the clinic. In actual re-optimizations, the RTOG objectives are almost always exceeded due to the existence of other penalty terms in the objective function, e.g. normal tissue objectives. This is in accordance with our dosimetry findings in that (a) all of our plans meet the minimal clinical requirement in terms of target coverage and OAR sparing, and (b) the guideline-based objectives contribute little to the outcome of the optimization. A possible alternative to using RTOG objectives is using the average of all CT objectives as a population based objective. Given a large sample size, such an objective can indeed represent the average quality of plan of a certain institution. However in our case, the number of patients was limited, and the target DVHs in the original CT plans of all patients have quite a large variation, and thus an average of all CT plans would provide limited information on the population-based reference DVH. Increasing the patient sample size is likely to provide a better estimate for the population DVH, but is outside the scope of the current study. Other options for objective settings and starting stages may also be possible, and their pros and cons can also be evaluated using analyses methods presented in this study.

The goal dose distribution generated in this study using deformable registration technique incorporates the daily anatomy information. However, generating daily-
anatomy-based objectives is not limited to this particular method, and can be performed with other techniques that estimate the daily dose distribution/DVH based on anatomical information. For example, Zhu et al. (Zhu et al., 2011) developed a knowledge-based system to estimate the achievable DVH for a fraction based on modeling the correlation between DVH and anatomical features using a database of previous expert plans. Such an estimated DVH could also be used to provide daily objectives.

Figure 25 Illustration of the trade-offs of using CT objectives on a fraction with significantly shrunk bladder but similar rectum. Black arrows show the direction of DVH changing from CT to Deformed-CT objectives.
It should be noted that although the regression analyses show that when the bladder significantly shrinks, CT objectives achieve somewhat better bladder sparing as compared to CT, caution should be taken when using CT objectives due to other potential trade-offs that may arise as a result of the over-stringent CT objective. Figure 25 shows such a case with the daily bladder being 71% smaller than the planning bladder, while the daily rectum is only 4% larger than the planning rectum. In this case the CT objectives for the bladder become over-stringent due to the significantly reduced bladder volume. DVH indicates that although the bladder DVH is reduced using CT objectives compared to Deformed-CT, this gain comes with costs to other dosimetric parameters: the hotspot was increased; and larger fraction of rectum received high dose. In this example, the optimizer under CT objectives somewhat sacrificed target hotspot and sparing of rectum while trying to meet the overly stringent bladder objectives, which is not optimally balanced for the given daily anatomy. To the contrary, Deformed-CT objectives take into account that a higher percentage of volume of the bladder will be in the bladder-PTV overlap region when the daily bladder is significantly smaller than on the planning CT, and adjusts the objectives accordingly. Therefore, Deformed-CT objectives offer a better balance between sparing of different OARs and global hotspot.

To deliver the online re-optimized treatment plan, a novel quality assurance (QA) system is required to perform the plan delivery monitoring and verification with
patient in the treatment position. Currently a commercial online ART system, Real-ART (Prowess Inc., Concord, CA) utilizes a four-step QA to validate the delivery accuracy of this ART system (Peng et al., 2011). Other groups have proposed in vivo QA using EPID dosimetry (Mans et al., 2010) and transmission detector arrays (Poppe et al., 2010; Boggula et al., 2011). We have also proposed a method using dynamic machine information to verify fluence and leaf accuracy during delivery, as well as dosimetric accuracy after delivery (Li et al., 2012b), and will be described in greater details in the next chapter.

The daily dose of the re-optimized plans in this study was calculated on the CBCT image sets. The known inconsistency between the CT numbers in daily CBCT and planning CT could result in small but noticeable difference in the calculated dose from the two modalities due to the inhomogeneity correction in the dose calculation algorithm (Yang et al., 2007; Yoo and Yin, 2006). In this study however, all compared plans were calculated on CBCT, and so such a dose difference was consistent for all plans and had little impact on the relative comparison results. In practice, this dose difference can be corrected by cross-calibrating CT-number between each CBCT unit and planning CT (Yang et al., 2007; Yoo and Yin, 2006).

Finally, the results in this study were based on our clinical TPS only. However, the concept of study design and the framework of analyses is platform independent, and can therefore be generalized to other TPS to enhance understanding of how the input factors affect the optimization output for that particular system.
5. Validation and delivery verifications of online re-optimized treatment plans

5.1 Introduction

The first 2 parts of this project demonstrated that the online re-optimization can be executed in a timely manner, and can be efficiently integrated with current IGRT process using the AIGRT scheme. To clinically implement this technique, it is also important to develop a feasible quality assurance (QA) program for the delivery of online re-optimized plans. Such a QA system should be able to validate the automatically re-optimized plan, catch delivery errors, and respond in real-time to large deviations that may impact the quality of the treatment. It should also provide a way to conduct thorough dosimetric evaluation after the treatment using actual delivery parameters.

For regular (non-adaptive) IMRT treatment, a pre-treatment QA is required at most institutions before the 1st treatment begins. Such QA is performed by delivering the actual patient treatment to a detector that is capable of tracking the dose. Several QA devices are available. One popular way to perform pre-treatment QA is using portal dosimetry. Before QA, the treatment planning system calculates what dose should be detected by Electronic Portal Imaging Device (EPID) in calibration units (CU) using the planned parameters and EPID specification. This simulated delivery provides an estimated dose map as the reference. This reference dose map is then compared to the actual dose acquired by EPID during QA delivery. During pre-treatment QA, each beam is delivered to the portal dosimeter (EPID) placed perpendicular to the beam central axis.
at 105 cm source-to-surface-distance (SSD). The QA delivery is performed using the same setting as simulated in treatment planning system. The difference between these two dose maps is characterized by 2D gamma map (Low et al., 1998). Gamma map combines both point dose difference (DD) and distance-to-agreement (DTA) into one single parameter. The former quantifies the dose magnitude difference at a certain point, and the latter quantifies the shifts of the dose profile. At low gradient region, distance to agreement dominates the gamma value, whereas at high gradient region, dose difference will be more pronounced, as shown in Figure 26. Using the equation in Figure 26, it can be easily seen that if the DD and DTA of a certain point is within the tolerance of 3% / 3 mm, the gamma value would be less than 1. Otherwise, if gamma value is higher than 1, it indicates at least one of DD and DTA tolerance is exceeded. The passing criteria of portal dosimetry QA of an IMRT beam is then specified as % of pixels that has gamma value no higher than 1. Currently in our clinic, the commonly used passing criterion at 3% / 3 mm is 90%.
Figure 26: Illustration of the gamma value at different dose profile points. 3%/3mm specifies the tolerance on DD and DTA, respectively. This tolerance can be manually chosen, but commonly 3%/3mm or 4%/4mm.

Although EPID QA using gamma map analysis method is widely accepted, it is not suitable for the application of online adaptive radiation therapy application. Online ART requires the patient to be in the treatment position from the acquisition of daily image sets to the end of treatment; and traditional pre-treatment QA cannot be delivered with patient on the couch. This challenge calls for a novel method for the plan validation, monitoring and verification that is tailored specifically for online ART application.

Peng et al. (Peng et al., 2011) reported a validation method for their online adaptive radiotherapy system. They first validated the accuracy and deliverability of 22 adapted plans by comparing the pre-treatment QA results on these plans to those of non-adapted plans, and found that the passing rates of adapted and original plans are

\[ \text{Gamma} = \frac{(DD \text{ } 3\%)}{\sqrt{(DD \text{ } 3\%)}^2 + (\text{DTA} \text{ } 3 \text{ mm})^2} \]
nearly the same (99.7±0.4% vs. 99.7±0.6%, respectively.) They also compared the MU from their RealART treatment planning system and from a secondary MU calculation tool called RadCalc™, and found the agreements of original plans and adapted plans does not differ significantly ($p = 0.41$) and are both within 10%. For actual online adaptive patient treatment, a four-step QA procedure for online replanning was proposed in their study, including:

(i) off-line phantom measurement of the original plan before the replanning process,

(ii) online secondary MU calculation check for adapted plans,

(iii) online verification of plan transfer integrity using in-house software, and

(iv) Offline validation of delivery parameters.

However, machine delivery information in step (iii), including MLC positions and delivered fluence, is not checked or monitored at the machine before or during treatment. Also, the ART system proposed by Peng et al is based on aperture conformal and step-and-shoot delivery. In a step-and-shoot delivery, MLC leaves are static during each beam-on; whereas during our dynamic (sliding window) delivery, the leaves are constantly moving. To ensure accuracy and safety in dynamic IMRT delivery, the positions of MLC leaves therefore need to be continuously monitored. The need to provide such online monitoring of delivery accuracy and added challenge unique to
dynamic MLC-based online ART requires the design of a novel QA system for the online
delivery monitoring and dosimetric verification.

Previous work has been done on online MLC position monitoring using MV
imaging (Cho et al., 2009) for dynamic target tracking purpose. Similar method could be
implemented for online ART QA, however the latency associated with image acquisition
and processing (avg. > 272 ms) (Poulsen et al., 2010) makes this method unsuitable for
real-time delivery monitoring. Currently, Dynamic Machine Information (DMI) has been
used as a potential QA candidate by other research groups (Agnew et al., 2012; Teke et
al., 2010; Dinesh Kumar et al., 2006). It provides sub-millimeter accuracy in actual MLC
positions at 50ms temporal resolution, which makes it an excellent input source for
delivery monitoring/verification. The average interval between control points of MLC
movements are 140~250ms, which is 3~5 times the DMI sampling rate. Therefore the
50ms temporal resolution is sufficient for online monitoring purposes.

The motivation of this specific aim is to design and evaluate a QA system
including (1) pre-clinical validation of automatically adapted plans, (2) online delivery
monitoring, and (3) offline dose reconstruction and verification based on DMI.

The hypothesis is that (1) automatically re-optimized plans have similar
deliverability under current QA standard, and (2) the proposed online and offline
delivery verification system are capable of catching potential errors in MLC motion and
their dosimetric consequences.
5.2 Methods and Materials

In this section the methods and materials used in developing and evaluating the online delivery monitoring/verification system is described in details. The materials include patient data specifications and machine information. The methods for developing and evaluating the system are presented in each subsection according to their order in the development timeline. Each section focuses on a specific component corresponding to a step in the QA system. At the end additional analysis methods for the delivery monitoring data are also presented.

5.2.1 Pre-clinical validation of the overall delivery accuracy of online automatically re-optimized plans.

The first step of this QA system is a general pre-clinical validation of the online adapted treatment plans’ deliverability compared to original plans and regular IMRT plans. The deliverability is assessed using traditional portal dosimetry method so that the results are interpretable with current clinical standard. The hypothesis is that automatically online re-optimized plans in general have the similar level of delivery accuracy as original IMRT plans based on current clinical evaluation method and pass criteria.

5 patients with intermediate-risk prostate cancer are randomly selected under the IRB protocols from the 18-patients pool in Chapter 3 and used as the sample in this study. 5 CBCT image sets for each patient are used to simulate a 5-fraction treatment. For each patient, 5 adapted plans are created based on the re-optimization strategies
determined from Chapter 4. These adapted plans will be verified using portal dosimetry and analyzed using gamma map method with 3%/3mm passing criteria. Aside from adapted plans, the original treatment plans for these 5 patients are also subjected to the same portal dosimetry QA process. In addition, the portal dosimetry QA results from 27 regular IMRT plans outside this 5-patient pool are also collected for comparison.

The pixel passing rate of adapted plans is analyzed in three ways:

(a) The histogram of pixel passing rates from all adapted plans is evaluated and compared to the distribution of pixel passing rates from original plans. This examines the similarity in distribution and provides a global perspective of the similarity/difference between the delivery accuracy of original plans and online adapted daily plans.

(b) The passing rate of online adapted plans is compared to another set of regular prostate IMRT treatment plans randomly selected from the clinic, to further rule out the possible sampling bias of original plans from the patient population at our institute;

(c) In addition, the pass rate is also analyzed for each patient to illustrate possible inter-patient differences.

5.2.2 Online delivery monitoring and offline dosimetric verification using Dynamic Machine Information (DMI)

For online ART workflow, a real-time delivery monitoring system should be able to check delivery process, signaling beam-hold in case of catastrophic errors, and record possible errors of MLC movement for future analysis. As discussed in Section 4.1, DMI
is an excellent source for real-time delivery parameters, and is therefore used in this project to perform online delivery monitoring.

The flowchart of this sub-system is shown in Figure 27. It performs three levels of monitoring/verification on the delivery process.

Figure 27: Flowchart of the QA system including 3 levels of monitoring/verification. Level 1 and 2 are performed in near real-time every 50ms.

Level 1: Real-time fluence map check. Upon receiving each DMI input, the system updates the actual and expected fluence maps and calculates the pixel-to-pixel difference between these two (Figure 27), producing a fluence error map (FEM). The fluence map are calculated by the following method: Firstly, the MLC leaf positions are projected to the isocenter plane, from which a binary mask is generated indicating which pixel at the isocenter plane is not blocked by the MLC leaves, i.e. exposed to the radiation field; the incremental MU from one MLC mask to the next is also obtained.
from the two corresponding DMI input, and is used to create an incremental MU map. The pixels that are exposed in two consecutive MLC masks receive the full increment MU that is delivered between two DMIs, whereas if pixels are exposes in only one of the two consecutive MLC masks, they receive half of the incremental MU in a first order approximation. The cumulative MU up to the most recent DMI is then a 2D sum of all previous incremental MU maps. In this way the cumulative fluence map can be rapidly calculated and still provide necessary information about the leaf motions effects on fluence to the first order approximation.

Both actual fluence delivered up to the last DMI input (Figure 28a Left) and fluence error maps (Figure 28a Right) are dynamically displayed in a graphic interface (Figure 28). In addition, the pixel differences are plotted as a histogram view (Figure 28b) to better visualize the magnitude and frequency of those differences. Both magnitude and frequency could be selected as thresholds to signal warnings with preset thresholds.

Level 2: Independent MLC control point check. The first level of fluence check monitors execution of MLC controller’s command with high temporal resolution (50 ms). However, since the expected and actual MLC positions are both from DMI, i.e. the MLC control unit, the first level check cannot identify errors occurred during the data transfer between the treatment planning system (TPS) and the MLC controller. Therefore in Level 2, another independent MLC control point check is implemented to catch potential data transfer errors (Figure 27). At this level, the difference between actual leaf position
and that in TPS (acquired from TPS right before treatment) could also be used to signal warning signs, and is as well visualized by a histogram for both leaf banks (Figure 28c).

Both Level 1 and 2 are designed to be used as online delivery monitoring tool, which can signal warning with a user-specified error tolerance. In addition to warning, the envisioned system is also expected to signal beam-hold in the event of large errors that exceed the tolerance specified by the treatment plan. This mechanism is to prevent damages caused by the failure of MLC position interlock, or by the errors occurred during plan transfer between treatment planning system and treatment console.

Level 3: Off-line dosimetric verification. This part of the QA system provides a dosimetric verification following the delivery of the treatment plan. Delivered dose is reconstructed in the treatment planning system by replacing planned MLC control points with actual control point leaf positions in DMI, and recalculating dose using the same algorithm and image set as the treatment plan. A similar method has been reported by Qian et al for VMAT QA (Qian et al., 2010). By controlling the MLC position as the only variable, the dosimetric impact from MLC movement alone can be isolated and evaluated. Evaluation criteria includes both DVH and isodose lines comparison.
Figure 28: Graphical Interface of the QA system. All graphs are updated in near real-time. (a) Left: delivered fluence up to current DMI snapshot; (a) Right: fluence error map (FEM) with bi-color-labeled pixels whose fluence error exceeding user-specified threshold ($\pm0.5$ MU used here, red indicates at least 0.5 MU hotter, blue indicates at least 0.5 MU colder, compared to expected fluence); (b) magnitude and frequency of fluence errors; (c) magnitude and frequency of leaf position error at control points.

In its current configuration, although DMI is fed to the treatment console workstation in real time, the information is not yet readily available for real-time output to third-party software. However, the content of DMI is stored in Dynamic Log (Dynalog) files of the MLC movement and is available after each treatment. Therefore
DMI and Dynalog files contain identical information, except that the former is real-time and the latter is available post-treatment. In this study, the Dynalog file is played back to simulate a continuous stream of DMI inputs during beam-on. Such inputs include expected/actual leaf positions, the fraction of total MU delivered, the current control point number, beam-on status, and etc. In future, DMI can be available on-line at 50 ms temporal resolution, and this system would readily be used for online monitoring.

The online monitoring and offline dose verification is performed for the same sample of patients and plans used in the pre-clinical validation, i.e. five patients with 1 original CT plan and 5 adapted plans each. The fluence errors, control points position errors and dosimetric errors are recorded and analyzed to:

(1) Better understand the magnitude of errors so that an action threshold can be suggested;

(2) Assess the overall dosimetric inaccuracies associated with the test cases; and

(3) Further understand the cause of fluence errors patterns manifested in the results.

In additional to testing the proposed monitoring system on clinical plan deliveries, MLC position errors were manually introduced to the Dynalog files and used to test the system’s effectiveness in catching errors. Rangel et al. concluded in their simulated study that for prostate plan, the tolerances on MLC leaf position error are 0.5 mm for systematic error and 2 mm for random error. Such tolerances keep the target
gEUD within 2% deviation from planned. The simulation was performed on Varian Millennium 120 MLC and Eclipse™ treatment planning system, as used in this study. (Rangel and Dunscombe, 2009)

Based on their result, similar types of error is introduced to the DMI stream of one adapted plan before online monitoring and dosimetric verification in order to illustrate how this system performs with larger errors. In this study, two types of errors are introduced: systematic and random. The methods and magnitudes of generating errors follow the study by Rangel et al. For systematic error, both positive and negative errors with magnitudes of 0.5 mm and 1 mm are separately introduced to the leading leaf bank and trailing leaf bank. Gaussian random errors are generated by a pseudo random number generator with standard deviation of 1 mm and 2 mm, and introduced to each leaf separately. The leaf positions with error are then used to reconstruct delivered DVH, as described in section 4.2.2.
5.3 Results and Discussion

5.3.1 Portal dosimetry results of online adapted, original and regular IMRT plans

Figure 29: Per-beam portal dosimetry passing rates distribution of three types of treatment plans: Adapted plans using automatic online re-optimization, Original CT plans, and Regular IMRT plans aside from the original CT plans.

Figure 29 compares the per-beam portal dosimetry results among three types of plans. All beams evaluated in this study have portal dosimetry passing rate higher than 90%, meaning that they would all pass the standard clinical patient-specific IMRT QA. The distributions of Original CT plans and Adapted plans are very similar. Statistical analysis using Wilcoxon Rank-Sum Test indicates that there is no statistically significant difference in passing rate between these two types of plans. In addition, the Original and Adapted plans are also compared to 27 randomly selected regular IMRT plans in terms of portal dosimetry passing rate. The results indicate that online Adapted plans in
general has slightly better passing rate compared to regular IMRT plans. The overall difference in distribution is very small.

![Gamma Pass Rate](image)

**Figure 30: Comparison of IMRT QA pass rates of online adapted plans across 5 patients in this study. Both box-plots and histograms are shown.**

Figure 30 shows an additional comparison of portal dosimetry pass rate between different patients. The boxplots and histograms of per-beam portal dosimetry pass rate are similar across different patients, indicating the deliverability of the online adapted treatment plans is consistent and stable. Therefore for the same patient population, the portal dosimetry passing rate is likely to be similar to those studied here.

Results shown above serve as a pre-clinical validation on the overall deliverability of online adapted plans under current clinical IMRT QA standard. The comparisons show that the deliverability of online adapted plans generated in this study is statistically the same as fully-fledged clinical-approved IMRT plans. It is important to note that the purpose of applying IMRT QA to the online adapted plans in this study is solely to see if their portal dosimetry pass rate is different from original or regular IMRT plans. In a real clinic situation, one will not be able to apply IMRT QA on online adapted plans.
plans because patient is in treatment position while the plan is being generated. This challenge leads to the next part of the project.

### 5.3.2 Online fluence error monitoring

The online fluence monitoring module reconstructs in real time the expected and actual fluence maps from DMI inputs. The difference between this pair of fluence maps are caused by deviations of the actual MLC leaf positions from expected positions. Figure 31 shows the fluence error maps at the end of delivery for all fields tested in this study. Because previous results show that the deliverability of online adapted plans are similar to original CT plans, both adapted and original plans are included in the fluence error analysis to increase the sample size. In general, fluence errors are more prominent at edges of fields rather than center. Majority of the errors are within ± 0.5 MU. Another observation is that for the cohort of deliveries test, nearly all error maps exhibit hotter edges on the left and colder edges on the right. This phenomenon will be discussed in detail later in this chapter.
Figure 31: Fluence error maps (FEMs) between expected and actual fluence generated by online fluence monitoring module.

Figure 31 shows a good variation of pixels fluence difference using a ± 0.5 MU scale. Since most pixels have errors within this range, it is intuitive to set 0.5 MU as a cut-off to define pixels that have a relative large error. It should be noted that this cut-off value can be set to other values as well; when set to other values, the following results may be different, but the analysis methods still hold.
Figure 32: Histogram showing the distribution of percentage pixel failure rate using per-beam fluence monitoring and a failing threshold of ± 0.5 MU.

Figure 32 shows the distribution of per-beam online fluence monitoring results. The horizontal axis corresponds to the percentage of pixels that fails to stay within ± 0.5 MU cut-off for a particular beam evaluated. The vertical axis indicates the percentage frequency of beams with certain pixel-wise failing percentage. It is evident that majority of beams has less than 5% pixels with fluence errors exceeding 0.5 MU. The 95 percentile ranking corresponds to 6.3% of pixels exceeding 0.5 MU, which means 95% of the beams evaluated have less than 7% pixels with errors exceeding the threshold. Therefore by setting the warning action threshold at 7%, the online fluence monitoring module is then capable of responding to a beam that is among or larger than the most erroneous 5%
based on our test sample, and alert the user to perform further evaluation on the delivery accuracy of the particular beam.

**5.3.3 Online leaf position error monitoring**

In addition to fluence errors, the proposed online delivery monitoring system also monitors the leaf position errors. There are two levels of position error monitoring in this system, the 1st level is a part of the fluence monitoring and checks actual leaf positions against expected leaf position recorded at each DMI sample. Because such information is already used in reconstructing real-time fluence, monitoring the leaf position inaccuracies at each DMI is not explicitly monitored in the design of the QA system.

The 2nd level of leaf position monitoring compares the actual leaf positions at each control point to those specified by the treatment plan in the TPS. Because the machine delivers the treatment plan following the instructions in the control points, this monitoring serves as an end-to-end check of both the plan transfer integrity between the TPS and the Linac, as well as the accuracy of delivery. Therefore, the monitoring results from level 2 check – the leaf position monitoring at control points – is analyzed in great details.
Figure 33: Illustration of the leaf position value signs for both leaf banks. The leading leaf, or Bank A, extends to the left and retracts to the right. The trailing leaf, or Bank B, extends to the right and retracts to the left. For either bank, extending beyond mid-line yields a negative value, and retracting pass mid-line yields a positive value.

Figure 33 illustrates the sign of leaf positions used in this study per Dynalog user reference manual (Varian Medical Systems, 2011). For both the leading and the trailing leaf banks, extending beyond mid-line (isocenter plane) yields a negative value, and retracting pass mid-line yields a positive value. Therefore negative value indicates an over-extended leaf, which results a smaller leaf opening, and *vice versa*. 
Figure 34: Boxplot of difference between actual leaf positions and the positions specified by control points in the TPS. Horizontal axis shows the leaf pair number. All 210 treatment fields are included in this plot.

Figure 34 shows the distribution of differences between actual leaf positions and the positions specified in treatment plan control points exported from the TPS. All 210 treatment fields’ control points’ differences are included in the boxplots, giving a sample size of ~20000. From the figure, it is evident that inactive leaves have no noticeable position difference, indicating a good MLC position calibration. Active trailing leaves have a tendency to over-retract, i.e. actual positions behind expected positions in treatment plan. Such over-retract could also be interpreted as a delayed arrival at control points due to inertia and insufficient leaf speed to reach a certain position, which is further validated by additional analysis. The median difference of trailing leaves is 0.1–0.2 mm, with majority less than 0.5 mm and maximal at 2 mm. No negative position difference is seen for trailing leaves, indicating the absence of leaf over-shoot.
For the leading leaves, both positive and negative differences are found, with approx. -0.1 mm median differences for all active leaves. The distributions of differences are also skewed to the negative side. Using the sign definition in Figure 33, negative difference for leading leaves indicate over-extending, which could also result from delayed arrival at a particular control points. Compared to trailing leaf results, the leading leaves exhibit slightly smaller median inaccuracies and occasional over-shoot, but generally similar pattern of delayed arrival. Since individual leaf position errors has limited implication on the fluence and dose inaccuracy, the empirical error magnitude is not used as a warning threshold at this stage. The information from Level 2 check is used to supplement the fluence map monitoring to provide magnitudes and distributions of errors.

5.3.4 Off-line dosimetric verification of delivered treatment plans

The off-line dosimetric verification utilized the online Dynalog records of actual leaf positions to reconstruct delivered dose incorporating any leaf motion inaccuracies during delivery. Figure 35 shows the difference in DVH between reconstructed dose using Dynalog and planned dose. For a particular point at DVH, if the actual delivered DVH is lower than the planned, a negative value will be observed, and vice versa. The figure contains all DVH from 25 online adapted treatment plans.

For PTV, the difference in dose coverage is minimal, as indicated by the absence of negative values in the 1-100% prescription dose region. There is an increase in the
hotspot volume, especially around 105%. The increase is smaller for higher dose, < 1% in V110%. The magnitude of hotspot, i.e. the toe of the DVH, shows very small increase, as only 4 outliers is found beyond 110% dose, with volume less than 0.5% of PTV.
Figure 35: Differences in DVH of primary structures-of-interest between reconstructed dose from Dynalog record and planned dose using Eclipse™.
The difference of PTV DVH exhibits a global shift towards the higher end by <1% prescription dose. An example case is shown in Figure 36. Such shift might be resulted from the hotter regions seen in Figure 31. Because hotter region is in general larger and higher in magnitude, it surpasses the effects from the colder region when summing multiple beams from different angels, and therefore dominates the influence on the delivered dose.

![Figure 36: Example case showing the typical difference in PTV DVH between planned dose and delivered dose reconstructed based on Dynalog.](image)

DVH differences of the bladder and the rectum between planned and delivered dose is also shown in Figure 35. In general the differences are very small, with nearly all points less than 1% of the organ volume. The rectum exhibits slightly larger difference compared to the bladder, especially in mid-dose region. This might be due to the fact
that the rectum volume is on average smaller than the bladder volume, causing a larger relative difference in the rectum by the same absolute dose differences.

Overall the dosimetric verification of the 25 online adapted treatment plans revealed excellent delivery accuracy. The change to DVHs due to leave motion inaccuracies presented in this set of plan delivery information is very minimal. This result, combined with previous results on online fluence monitoring and leaf position monitoring, confirms the deliverability of automatic online adapted plans to be acceptable.

5.3.5 Monitoring and verification results with manually introduced MLC errors

Figure 37 shows the impact from MLC position errors on the PTV DVH. The introduced errors changed PTV DVH significantly only when the errors to both leaf banks were systematic and of the same sign, e.g. Systematic: 0.5, 0.5. As illustrated in Figure 33, positive shift of the leaf indicates over-retraction, and negative means over-extension. If both banks have positive errors, the leaf opening is then larger than planned, causing the DVH to shift towards higher dose, as seen in Systematic: 0.5, 0.5 and 1, 1; on the contrary, if both leaf banks have negative errors, leaf opening becomes smaller, and therefore DVH shifts towards the lower dose end, as seen in Systematic: -0.5, -0.5 and -1, -1. The deviations of DVH with errors are positively correlated with the magnitude of error introduced: DVH corresponding to 1 mm error is shifted by nearly twice the amount of the DVH with 0.5 mm error. In cases of only random error present,
even with 2 mm standard deviation, the difference in DVH is nearly invisible. These observations are consistent with previous findings reported in Rangel’s paper. In addition, if two leaf banks have opposite sign of errors, the associated DVH change to the PTV is very small and nearly unidentifiable. This can be seen by the overlapping DVHs with the DVH of original plan.

Figure 37: Variation of PTV DVHs caused by introduced errors to the MLC positions during delivery. The DVHs are labeled as: error type: leading bank error in mm, trailing bank error in mm.

Similar observation can be made for DVHs of the bladder and the rectum. Only systematic errors with the same sign for both trailing and leading banks can be identified as different from the original DVH, and with deviation magnitude proportional to the error magnitude. Deliveries with opposite-sign errors and random errors alone are found to have nearly identical DVHs as the original error-free plan.
Figure 38: Variation of bladder DVH (top) and rectum DVH (bottom) caused by introduced errors to the MLC position. The DVHs are labeled as: error type: leading bank error in mm, trailing bank error in mm.

Figure 39 shows the fluence error maps generated by the online monitoring module, as introduced in Figure 28, for various erroneous deliveries of the same beam.
The center image corresponds to error-free delivery, and the outer images correspond to deliveries with manually introduced systematic errors of different magnitude and signs, as shown by dashed lines on the axes. In this case, 0.5 MU is selected as the error display threshold: pixels are labeled red if their fluences are at least 0.5 MU hotter than expected and blue if at least 0.5 MU colder. The numbers in the lower left corner of each fluence error map indicate the percentage of pixels with absolute error larger than 0.5 MU. For cases with same-sign errors for both leaf banks, only one color is seen in the error map: all red if both errors are positive, i.e. both banks are over-retracted, or all blue if both errors are negative, i.e. both banks are over-extended. If both banks are over-retracted, the leaf-opening will be consistently larger than expected at each segment, causing globally hotter fluence map; and if both banks are over-extended, consistently smaller leaf openings will cause globally colder fluence. These findings are also consistent with dosimetric verification results shown in Figure 37.

For cases with opposite-sign errors, their fluence error maps show distinct feature corresponding to the sign of each leaf bank. If leading leaf bank has positive error and trailing bank has negative error, the fluence error map is colder on the left and hotter on the right; if leading bank has negative errors and trailing bank positive, the fluence error map exhibit the opposite pattern: hotter pixels on the left and colder on the right. In addition, percentage of failed pixels is positively correlated with the error amount, even with opposite-sign errors.
Figure 39: Fluence error maps generated by online monitoring module for both error-free delivery (center) and deliveries with introduced systematic errors. Red indicates the pixel fluence at least 0.5 MU hotter than expected; and blue indicate at least 0.5 MU colder. The numbers at the lower left corner of each fluence error map show the percentage of pixels with error larger than 0.5 MU. Notice the distinct error patterns and percentage for each error introduced.

The distinct features that online fluence monitoring results exhibit when processing delivery record with different errors indicates its excellent specificity in differentiating leaf error directions and magnitude. As shown above, such feature is generally not available in regular IMRT QA and retrospective dose reconstruction with DMI record. The unique information provided by the online monitoring module will offer additional and valuable guidance to MLC performance evaluation and fault diagnosis. Although leaf position error histogram can also indicate the general
distribution of errors, it does not provide information for individual leaf or as intuitive as fluence error map in terms of the actual impact from leaf position errors.

5.3.6 Understanding the fluence error pattern.

This section discusses how the fluence error maps shown in Figure 31 are resulted from leaf position errors in Figure 34. As discussed in the previous section, both leaf banks exhibits slight delays in arriving at expected positions at control points. Such delay is the main source of leaf position errors, and therefore is hypothesized to have strong connection with the fluence errors that are seen in Figure 31.

Figure 40: Example of a fluence error map generated by the online monitoring module. Notice the typical hotter left edge and colder right edge that is generally observed for most fluence maps tested.

Figure 40 is an example case of the typical fluence error map. As seen in Figure 31, majority of the fluence maps have hotter edge on the left and colder edge on the right. The corresponding leaf lag for this particular field is visualized in Figure 41. As
expected, majority of leaf position errors are negative, as seen by blue color. The leading leaf exhibits in general less error, with relatively large errors concentrated around control point #40. Majority of the rest of control points have negative errors around 0.1 mm. When a leading leaf experience negative position errors, or delays, it blocks pixels for a longer time, and therefore effectively reduces the MU a certain pixel receives. The trailing leaf exhibits generally higher delays compared to the leading leaf. During the first 60 control points, trailing leaf is constantly behind expected position by 0.1–0.4 mm, and starting from the 70th control points, the magnitude of trailing leaf delay increases to 0.3–0.5 mm. Delayed movements of trailing leaf causes pixels to be exposed in the radiation field for a longer time, and therefore increases the MU that pixels receive.
Figure 41: Fluence error magnitude at each control point. Negative values indicate the actual leaf position is behind the expected position at the corresponding control point.

MLC positions and fluence error maps at selected control points are shown in Figure 42. The control points shown here correspond to key features in Figure 41. From CP1 to CP20, both the trailing leaves and leading leaves have delays, resulting in hotter and colder regions where leaf ends pass, respectively. From CP 20 to CP40, leaf lags causes both hotter and colder regions to grow. At around CP40, leading leaves exhibit large delay, resulting large colder region seen at CP60. However from CP60 to CP80, the colder region generated by leading leaf lag is partially neutralized, due to the over-exposure caused by the trailing leaf delays, as shown in dark blue in Figure 41. At the last control points, most regions that both leaf banks have traveled through have small
scattered random errors, whereas regions that are only affected by one leaf bank exhibit predominantly one side error: regions affected only by leading leaves are colder, and those affected only by trailing leaves are hotter. The common pattern seen in Figure 31, hotter on the left and colder on the right, is therefore caused by delays of both leaf banks; the low-error middle ground results from error-cancellation from two leaf banks.

![Figure 31: MLC positions and fluence error maps at selected control points (CPs) for an example case. The fluence error map threshold is set to a low value of 0.1 MU for better illustration.](image)

Another observation that can be made from Figure 41 is the non-uniform error magnitude: larger error occurred at CP60 – CP97 for trailing leaf bank, and CP30 – CP50 for leading leaf bank. The increased magnitude of error is caused by higher leaf speed.
requirement at those control points range. Figure 43 shows the leaf speed map of the same beam in Figure 41. The leaf speed is calculated from the control point positions and MUs in the treatment plan, and can therefore be considered as the leaf speed requirement that the treatment plan has for the machine. It can be clearly seen that Figure 41 is highly correlated to Figure 43: CP ranges that have larger errors coincide with higher leaf speed. In other words, in regions where higher speed is required, it is more difficult for leaves to meet the requirement; and consequently larger delays occur.

![Figure 43: Leaf speed at each control points calculated from the treatment plan for an example case.](image)

### 5.3.7 Limitations and further discussions

The current implementation of online monitoring relies on the input of DMI. Therefore the accuracy of the monitoring system is directly dependent on the accuracy
of parameters in DMI, most importantly leaf position measurement. The leaf position in DMI is measured by the MLC controller using motor counts, which is then converted to millimeter per MLC specifications. The motor counts are zeroed at the time of MLC initialization with the leaf fully retracted(2011). Therefore accurate leaf initialization and alignment is the key to the accuracy of DMI, and subsequently the monitoring system. If the reported MLC position is deviated from the actual position due to initialization inaccuracies, the accuracy of the monitoring system is affected.

In this proof of concept study, the real-time fluence map calculation does not consider leaf transmission, leaf leakage or the leaf-end penumbra, but uses a simple ray-tracing-like algorithm. This method is chosen to reduce the calculation time, so that the fluence map can be updated before the arrival of the next DMI snapshot. Since both the expected and actual fluence maps are calculated using the same algorithm, i.e. with the same level of simplification, the inaccuracy associated with omitting these parameters exits in both the expected and actual fluence, minimizing its impact on the fluence error map. In addition, because the additional physical parameters act as blurring kernels to the calculated fluence map, omitting them exaggerates the effects of leaf position errors, making the error detection and analysis more sensitive. In future with faster implementation of the system, these physical parameters could be added into the calculation algorithm, and generate more realistic fluence maps. But such work is beyond the scope of this dissertation.
Currently the computation time for generating updated fluence map is less than 2 ms. However, more time is needed to update the graphical display in MATLAB. Up to 70 ms latency is observed for the graphics to update after the new fluence map is calculated. Considering the interval between DMI samples being 50 ms, in order to achieve a true real-time monitoring, the system needs to finish data pre-processing, fluence calculation and graphic updating within 50 ms, before the arrival of the next DMI input. Therefore at the current implementation, the quantitative monitoring is executed in real-time, but visualization is performed at reduced temporal resolution. A faster, more optimized implementation can further improve the efficiency of the system, but is beyond the scope of this study.

The action levels in the current stage of implementation utilize the distribution of the errors observed in a set of good clinical plans, and are set to signal when an error larger than 95% of the test cases occurs. This methods is effective in catching large errors, but is based on limited test case samples. In addition, since the threshold is derived from the fully delivered fluence map, and fluence error occurred earlier in the process of delivery can be washed out later, the system may signal warning during delivery but the final fluence map error may drops to be within the threshold. In such case a false positive occurs. This behavior of the system lowers its specificity, but ensures a high sensitivity in detecting large errors and warning the user. To develop better action levels, a systematic ROC analysis on the fluence map error magnitude/percentage and its
dosimetric impact is required with larger patient sample. It also needs to take into consideration the clinical flow. The proposed system allows user to manually set threshold for both the magnitude and percentage threshold for the warning action, and is therefore flexible to accommodate different needs.

The results presented here are based on Varian Linear Accelerator, MLC and Eclipse™ treatment planning system. However the concept can be applied to other vendors’ hardware and software platforms as well. Tyagi et al. reported a real time dose monitoring and reconstruction tool using Elekta platform (Tyagi et al., 2012), demonstrating the possibility of using DMI-based fluence monitoring on online adapted IMRT plans on Elekta machines.

5.4 Conclusion

Pre-clinical validation indicates that the patient specific QA pass rate of online automatically re-optimized plans is similar to that of the original plans, and is in general high among regular IMRT plans. The online fluence and leaf position monitoring tool show very small discrepancies between planned and actually delivered parameters. Off-line dosimetric verification on online adapted plans indicates excellent agreement between planned dose and reconstructed actual dose. Utilizing online monitoring tools on deliveries with manually introduced errors shows that the system is capable of identifying MLC error types that is not discoverable in dosimetric analysis. Overall, combining pre-clinical validation, online monitoring and off-line verification, the
proposed system is an excellent candidate for treatment QA of online automatically re-
optimized plans, where pre-treatment patient specific QA is not practical.
6. Summary

This project focused on pushing the online adaptive radiation therapy technique for prostate cancer towards the clinical implementation by addressing two most important challenges: efficiency and quality assurance. The first two steps of this project addressed the efficiency challenge, and the third step focused on quality assurance (QA).

The first step answers the questions of how often should online re-optimization be used. The hypothesis was that with novel methods of combining re-optimization with re-positioning, the necessary re-optimization frequency could be reduced while maintaining similar target coverage as if re-optimization were performed for every fraction. To achieve this goal, an evidence-based decision making scheme, named AIGRT, was developed to determine if daily re-optimization is necessary, and the concept of re-using previously available plans was implemented using a patient plan database. The results show that under this scheme, consistent and complete daily target coverage and reduced dose to adjacent healthy organs can be achieved at the same time with significantly reduced re-optimization frequency. Therefore the proposed scheme is an excellent candidate to manage the integration of online re-optimization with current IGRT technique.

The second step addressed how the re-optimizations should be performed in an efficient way. The hypotheses were that the daily target coverage can be retained with ~2 min automatic re-optimization on the daily structure set, and that objectives with
patient-specific and daily anatomy information provide better guidance for the optimizer. To verify these hypotheses, a systematic planning study was performed with varying planning input parameters in terms of DVH objectives, starting stages and iteration number. The findings indicate that the online re-optimizations provide reliable target coverage. Using original CT’s DVH as objective provides good guidance for most of the plans, but for cases with significantly changed OAR volume, objectives incorporating the anatomy-of-the-day offer extra benefit. Staring the re-optimization with original fluence offers some saving in the mid-dose region of OARs, but substantially decreases the plan delivery efficiency. The difference between running the automatic re-optimization for 50 and 100 iterations is generally small. Based on these findings, the clinical team can then make informed decision on which optimization parameter sets to use for online re-optimization on the case-by-case basis.

Another important challenge for the clinical implementation of online ART is the quality assurance of re-optimized plans, which is addressed in the third step of this project. For this part, the hypotheses were (1) the deliverability of online automatically re-optimized plans are similar to regular IMRT plans using current quality assurance standard; and (2) the delivery process can be effectively monitored by utilizing dynamic machine information. To verify the 1st hypothesis, the online automatically re-optimized plans were subject to the same QA standard used currently for clinical IMRT plans, and were found to have similar QA pass rates to the original CT plans and regular IMRT
plans. To provide online QA on delivery accuracy for online re-optimized plans, a three-level delivery monitoring system was developed to take dynamic machine information as inputs, and perform real-time fluence monitoring, leaf position monitoring and post-treatment dosimetric verification. Applying this QA system to the online re-optimized plans demonstrated excellent delivery accuracy, and provided the baseline action threshold. Applying this QA system to plans with manually introduced errors showed that the system has good sensitivity in detecting MLC motion errors, and excellent specificity in determining the underlying error types.

The three steps together provide substantial contribution to addressing the two most important challenges for clinical implementation of online ART – efficiency and QA. The concepts and techniques developed in this project, as well as understandings gained from the results, add valuable knowledge to the online ART research and helpful guidance towards the clinical implementation of online adaptive radiation therapy for prostate cancer.
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